日本人類遺伝学会 第31回大会一般講演要旨

Abstracts of General Contribution, the 31st Annual Meeting of the Japan Society of Human Genetics

A1. Congenital Anomalies of the Urogenital System Observed in Autopsy Cases of Human Fetuses and Newborns. **Yukio SATOW, Naotaka AKIMOTO, Juing-YI LEE, Hiroshi SUMIDA, Naohiko INOUE** (Dept. Geneticopathol., Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima) **and Naomasa OKAMOTO** (Miyazaki Med. Coll., Miyazaki)

Purpose: To describe the frequencies, kinds and associated anomalies of congenital anomalies of the urogenital system observed in human fetuses for using as references in exploring the causative factors.

Subjects and methods: Data of autopsy findings and, if necessary, data of optical microscopy, electron microscopy and chromosomal findings of some 5,000 fetuses and newborns that came to autopsy at the First Department of Pathology, Nagasaki University School of Medicine in the period from 1947 to 1962 and some 5,000 that came to autopsy at the Department of Geneticopathology, Hiroshima University Research Institute for Nuclear Medicine and Biology in the period from 1962 to the present were studied.

Results and discussion: The numbers of autopsy cases were singleton: 10,363 cases, twins: 190 pairs and 76 cases, and triplets: 4 groups and 3 cases. In 8,570 of these cases for whom data were in order, anomalies accounted for 1,290 cases (15.1%), pathologic findings 3,376 cases (39.4%), and no abnormality observed 3,904 cases (45.5%). Of these, 177 were cases with associated anomalies and 247 cases of complicating anomalies of the urogenital system, which were most frequent next to cases of malformation of the central nervous and cardiovascular systems. In substance, the anomalies were hydroureter, horseshoe kidney, polycystic kidney, and renal agenesis, and in the genital system, abnormalities of the penis, uterus and vagina were observed associated with other anomalies. The anomalies were classified by causative factor into cases suggesting abnormality of hereditary nature (5.1%), cases accompanying chromosome aberrations (5.7%) or a syndrome (12.0%), cases of anomalies due to ureteral obstruction (12.6%), cases of solitary renal cyst (12.0%), cases due to physical factors such as original amniogenous malformation (12.0%), and cases of hypoplasia or dysplasia of kidney due to some cause (40.6%).

A2. Two Families with Familial Renal Malformation. Akira MATSUI[1], Jun-ichi NAKO[2], Yutaka SUZUKI[3] (Dept. [1]Pediatr., [2]Obstet. Gynecol., [3]Pathol., Isesaki City Hosp., Gunma), **and Takeshi MATSUDA** (Dept. Anatomy, Toyama Med. Pharmaceut. Univ., Toyama)

Family 1. The propositus was born at 39 weeks of gestational age and her birth weight was 2,200 g. Cyanosis over the entire body was persisted immediately after birth and bilateral pneumothorax was found by scout film of the chest. She had died at 2 hr after birth. By autopsy findings, bilateral kidneys were found to be dysplastic, associated with Potter's type II cystic kidney. The sibling of the propositus was prenatally diagnosed as an agenesis of the right kidney by ultrasonography at the age of 39 weeks of gestational age. Also right kidney was not detected by excretory pyelography at 6 months after birth. He is now one year old and in good health. Ultrasonography of the left kidney at the age of one year revealed mild hypertrophy with longitudinal diameter of 72 mm and antero-posterior diameter of 32 mm. The parents had no abnormalities on ultrasonographic findings of the kidneys.

Family 2. The propositus (paternal grandmother) had died of uremia due to poly-cystic kidney at the age of 50 years. The father, aged 34 years came to our hospital with chief complaint of lumbago and microscopic hematuria. Bilateral polycystic kidney was found by ultrasonography. Several cysts were also found in the liver and pancreas. The first daughter was referred to our hospital for further examination of microscopic hematu-ria. Small cysts with diameter of 5 mm was found by ultrasonography in the right kidney. These three subjects were diagnosed as Potter's type III cystic kidney inherited as an auto-somal dominant trait.

A3. Oculodentodigital dysplasia (ODD) の家系分析 — 2 症例の報告. 吉川清志・楢原幸二・木村俊介・木本 浩 (岡山大・医・小児), **高橋幸雄・伊予田邦昭** (日鋼福山病院・小児). **Pedigree Analysis of Oculodentodigital Dysplasia (ODD): A Report of Two Families.** Kiyoshi KIKKAWA, Kouji NARAHARA, Shunsuke KIMURA, Hiroshi KIMOTO (Dept. Pediatr., Okayama Univ., Okayama), Yukio TAKAHASHI and Kuniaki IYODA (Dept. Pediatr., Nihonkokan Hosp., Fukuyama)

Oculodentodigital dysplasia (ODD) は, 小眼球・小角膜・鼻翼低形成を伴う細く直線的な鼻, 第4·5 指合指症, 歯のエナメル質形成不全を主要症状とする稀な疾患で, 常染色体性優性遺伝疾患と考えられているが, 孤発例も多い. 典型的な 2 症例の家系調査を行い, これまでの報告例と合わせ検討した.

症例 1 および 2 は, 典型的な ODD の症状を備えていた. 症例 1 の父親と症例 2 の母親に第 5 指内湾と直線的な鼻がみられ, X 線検査では第 2～5 趾中節骨低形成あるいは無形成が認められた. 症例 2 の兄にも母親と同様の中節骨異常と第 5 指内湾が認められた. さらに症例 2 の母方叔父と祖

母に第 5 指内湾がみられた.

これまでに報告されている 31 家系 45 症例（男 25 例，女 20 例）の分析結果：1) 性比は 1：0.8，2) 発端者法による分離比は 0.5±0.134，3) 浸透率は発端者の世代で 100%，保因者の世代で 40% であった．また主要症状の出現頻度には差があり，眼・指・歯の異常頻度は 90% 前後であったが，鼻の異常および中節骨異常の頻度は 100% であった.

以上より，ODD は表現度に変異が強い優性遺伝疾患であると考えられた．本家系のように表現度の低い親から ODD 患者が出生する可能性があるため，ODD の恒常的異常と考えられる第 2～5 趾中節骨低形成無形成を検索し遺伝相談に応用すべきである.

A4. Genetic Patterns of Hereditary Dentato-rubral Pallido-Luysian Atrophy. **Kiyotaro KONDO** (Dept. Publ. Health, Hokkaido Univ., Sapporo), **Akihiko NAITO** (Dept. Psych., Niigata Univ., Niigata) **and Norikazu YASUDA** (Dept. Genet., Natl. Inst. Rad. Med., Chiba)

Hereditary dentato-rubral pallido-Luysian atrophy (HDRPLA) is a rare degenerative disease of the stated systems of the brain showing myoclonus and other unique neurological symptoms. HDRPLA is sometimes familial but mode of transmission has been obscure. Thirty-nine families involving 169 cases (16 were autopsied) were analyzed. Clinical onset was aged 0–70, averaging 27.3, with the initial symptoms of epilepsy (54.5%), ataxia (17.2%), mental disorders (11.8%), dementia (9.1%), *etc.* Variable degeneration was noted in the dentate nuclei, cerebellifugal fibers, and the pallido-Luysian system. No parental consanguinity was observed. Affection was independent of sex, and transmitted from the parents. Preliminary analysis with the proband method disclosed an irregular dominant inheritance with a reduced penetrance to about 69%. A complex segregation analysis, applied to the siblings with one affected parent assuming a single ascertainment, supported preliminary results. However, when applied to the siblings with normal parents, the method disclosed some mimic cases mixed with true cases of HDRPLA in these siblings.

A5. Chorionic Villi Sampling: A Study of Aspiration Techniques and Long Term Culture. **T. MIZUNOE, T. KODAMA, N. MIHARU, T. UTSUNOMIYA, N. TOYOTA, M. TAKENAKA, K. UEDA, A. FUJIWARA** (Dept. Obstet. Gynec., Hiroshima Univ. Med. Sch., Hiroshima) **and K. OHAMA** (Dept. Obstet. Gynec., Kure Natl. Hosp., Kure)

Chorionic villi sampling (CVS) has opened up a new field of prenatal diagnosis. Different sampling methods and culture techniques in CVS, however, are adopted by each investigator. The purpose of this study is to establish CVS method using an aspiration catheter newly developed in Univ. Tokyo, and to examine the emergence of polyploid and aneuploid cells during long term cultures with Chang medium. We performed CVS in 28

patients before the elective abortion from 6 to 12 weeks of pregnancy. Chorionic villi were successfully obtained in 26 cases (92.9%), but failed in two cases at 11 weeks of pregnancy. Karyotypic analysis was successful in 23 cases (46,XX:13 cases and 46,XY:10 cases). Karyotypes of them were confirmed to be identical with those of the aborted specimen. Cultures were failed in three cases (11.5%) because of the insufficient volume of CVS specimen (less than 5 mg). Two of the three were 11 weeks of pregnancy. Cultures from CVS specimen were maintained for four weeks in seven cases. Six of them showed 10 to 20% of tetraploid cells. However one case showed a relatively high frequency of tetraploid cells more than 40%. These results indicate that the CVS using a new catheter is recommended to perform before 10 weeks of pregnancy and that a diagnosis of mosaicism should be carefully made in villous cultures with Chang medium.

A6. Prenatal Diagnosis of Hemophilia A Using Fetal Plasma Obtained by Percutaneous Liver Sampling. Akira YOSHIOKA, Toshiharu FUJIWARA, Ichiro TANAKA, Midori SHIMA, Hiromu FUKUI (Dept. Pediatr., Nara Med. Coll., Kashihara), **Masahiko MATSUMOTO** (Dept. Obstet. Gynec., Osaka Munic. Perinat. Cent., Osaka), **Nakamichi SAITO** (Dept. Obstet. Gynec., Kyushu Rosai Hosp., Kitakyushu), **Shinichi MIYAHARA** (Dept. Pathol., Saga Med. Coll., Saga) **and Mitsuhiko KORESAWA** (Dept. Obstet. Gynec., Inst. Clin. Med., Univ. Tsukuba, Ibaraki)

Prenatal diagnosis of hemophilia A in mid-trimester was achieved by means of coagulation and immunoradiometric assays for factor VIII on fetal plasma by ultra-sound guided percutaneous liver sampling using 21–23 G PTC needle. Samples were analyzed from three male fetuses at 50% risk for severe or moderately severe hemophilia A and from 10 control fetuses for whom sampling was carried out to attempt prenatal diagnosis of other genetic disorders. The factor VIII coagulant activity (F.VIII:C) and factor VIII antigen (F.VIII:Ag) values for the control (non-hemophiliac) samples were 24–83 u/dl (mean $\pm$ SD $= 46.6 \pm 17.5$) and 15–55 u/dl (30.1 ± 11.0), respectively. In all 3 cases the samples contained pure fetal blood cells. Normal levels of F.VIII:C and F.VIII:Ag were detected in Cases 1 and 2, and no F.VIII:C and very low F.VIII:Ag in Case 3. Each pregnant woman of Cases 1 and 2 decided to go term and gave birth to a non-hemophilic baby whose F.VIII:C was 90 and 105, respectively. The pregnant of Case 3 decided to her pregnancy terminated. No F.VIII:C could be detected in the plasma of the male abortus. The accuracy and relative safety make prenatal diagnosis of hemophilia A by the techniques we used a valuable option for those families who are motivated to utilize it.

A7. Partial Ornithine Transcarbamylase Deficiency in Female: Diagnosis by Immunohistochemical Method. Kikuya METOKI, Kiyoshi HAYASAKA, Seiichi ISHIGURO, Kuniaki NARISAWA and Keiya TADA (Dept. Pediatr., Tohoku Univ. Sch. Med., Sendai)

Ornithine transcarbamylase (OTC) deficiency is the most frequent disorder of the urea cycle, transmitted as an X-linked trait. Heterozygous females show a wide spectrum of symptoms, depending on the proportion of hepatocytes with functional enzyme. Among them the patients of late onset type developing Reye-like syndrome are difficult to differentiate from Reye syndrome, since the activity of OTC in liver sometimes decreases secondarily in Reye syndrome. We investigated two female patients, a 15 years and a 2 years old girl, both died of severe hyperammonemia. The activities of OTC in liver were 16% and 4% of controls, respectively. There was no change in the kinetic properties of the residual enzyme. Then liver specimens fixed in formalin were stained with anti-OTC antibody by applying the avidin-biotin-peroxidase complex method. This analysis showed clearly that the patients were heterozygotes for OTC deficiency with mosaic distribution of the stained hepatocytes as expected with X-chromosome inactivation. The high proportion of cross reactive materials negative affected males suggests this method is useful for the diagnosis of most female patients. The confirmation of genetic defect in a proband has added significance now that familial analysis can be carried out by restriction fragment length polymorphism linkage studies. This method can be applied retrospectively using even tissue specimens fixed in 10% formalin.

A8. DNA Analysis on Infant Type Glycerol Kinase Deficiency. Tadashi MATSUMOTO, Tatsuro KONDOH, Tsutomu KAMEI, Norio NIIKAWA, Masaaki YOSHIMOTO and Yoshiro TSUJI (Dept. Hum. Genet., Dept. Pediatr., Nagasaki Univ., Nagasaki)

There are 3 types of glycerol kinase deficiency (GKD), *i.e.*, infant type, juvenile type and adult type. Infant type GKD shows congenital adrenal hypoplasia, muscular dystrophy and developmental and mental retardation in addition to GKD. We report the results of a cytogenetic study and a DNA analysis on a patient with infant type GKD. ^{32}P-labeled cloned-DNAs, C7, pERT87-8 and 754, derived from an X chromosome library were used as probes. Genomic DNA extracted from leukocytes of the patients, a sister and his parents were digested by several endonucleases. DNA fragments were analyzed with Southern blot hybridization. When digested by *Pst*I, probe 754 hybridized to a 12 kb fragment in the control, while the patient had a 5.2 kb fragment instead of the 12 kb, indicating a partial deletion of the nuclear DNA sequence. The two fragments seen in the mother, a 12 kb and a 5.2 kb, are derived from a normal X and from a GKD-related

X, respectively. Southern blot analysis with pERT87-8 and *Taq*I revealed negative signal in the patient. Hybridization using C7 as a probe showed the same pattern between the patient and the control. High-resolution GTG-chromosome banding revealed a deletion in Xp21.2 band in the patient. These findings indicate that the deleted DNA sequence of the patient does not include the sequence corresponding to C7 but a part of 754 and whole of pERT87-8.

A9. 毛根による Hunter 症候群保因者検索の判定方法の検討. 中村 仁・祐川和子・折居忠夫 (岐阜大・医・小児). **Studies on Detection of Hunter Heterozygotes.** H. NAKAMURA, K. SUKEGAWA, T. ORII (Dept. Pediatr., Gifu Univ., Gifu)

Hunter 症候群の毛根による保因者検索では，これまで，O 活性の毛根の有無により，保因者であるか否かを判定してきた．これは，毛根は発生学的には数個の細胞から起源していると考えられていることと，Lyon の仮説により女性の X 染色体の一方は胎生初期に不活性化され，その不活性化は非選択的に起こることから，Hunter 症候群保因者の毛根の細胞は，Hunter 症候群の欠損酵素である iduronate sulfatase の欠損している細胞と，正常の活性を有する細胞とから構成されており，一定の割合で，酵素活性をもたない毛根が出現するという理論に基づいて考えられた方法である．それゆえに，正確な判定のためには，O 活性毛根の出現頻度が問題になってくるので，われわれは検索毛根数を増やすことによって，O 活性毛根の出現頻度を高め，検査の信頼度を増す方法をとり，これまで好結果を得てきた．今回は，視点を変え，O 活性毛根以外の毛根の酵素活性値に着目し，その活性値の分布が，2 項分布にあてはまるか否かの検定を試みたところ，5% の危険率で，保因者 40 症例は全例 2 項分布を示し，非保因者 30 症例は全例 2 項分布を示さないという，その方法が，保因者・非保因者を判別する手段となりうると考えられる結果が得られたので，その結果の意義について，考察し報告した．

A10. Red Cell Enzymopathies Found in Our Laboratory. Yoji ISHIDA, Yukari MIURA, Kenji SHINOHARA, Youichi AZUNO, Hiroyuki TANAKA, Toshio KENEKO (3rd Dept. Intern. Med., Yamaguchi Univ. Sch. Med., Ube), **Noboru MATSUMOTO** (Allied Health Sci., Yamaguchi Univ.) **and Naoki UEDA** (Dept. Clin. Pathol., Yamaguchi Pref. Cent. Hosp., Houfu)

We performed the red cell enzyme activity measurements in 88 cases from December 1980 to July 1986. Six cases of 5 families with glucose-6-phosphate dehydrogenase (G6PD) deficiencies and 2 cases of 2 families with pyruvate kinase (PK) deficiencies were found. Biochemical characterization of 4 G6PD variants and 1 PK variant were studied with the methods recommended by WHO scientific group and ICSH. Two new variants in G6PDs were found: One had abnormal parameters such as low G6PD activity, low *K*m (G6P) and *K*m (NADP), high utilization of 2d G6P, gal G6P and deamino NADP, heat unstability and biphasic pH curve. The other had abnormal parameters such as low G6PD activity,

slow moving in electrophoresis. On the other hand, abnormal PK showed low PK activity, high $K_{0.5}$ (PEP), low ATP inhibition and fast moving in electrophoresis. As the parents of this PK patient had no consanguineous marriage, this abnormal PK patient is likely to be compound heterozygote.

A11. Genetic and Clinical Studies on 19 Families with Adenine Phosphoribosyltransferase Deficiencies. **Naoyuki KAMATANI, Shouko KUROSHIMA, Kusuki NISHIOKA and Kiyonobu MIKANAGI** (Inst. Rheum., Tokyo Women's Med. Coll., Tokyo)

Adenine phosphoribosyltransferase (APRT) is a purine enzyme coded for by a gene on chromosome 16. The deficiency of APRT as the cause of 2,8-dihydroxyadenine urolithiasis has been considered to be rare. We have examined blood samples from 19 Japanese families with homozygous APRT deficiencies. In 79% of the families, patients were only partially deficient in APRT activities (Japanese type APRT deficiency). The ages at onset and severity of symptoms were not significantly different between the completely deficient type and Japanese type homozygotes. Family studies have shown that 2 symptomatic and 4 asymptomatic homozygotes existed among siblings of the propositi. Studies on the data as to the incidence of urolithiasis in Japan, and the incidence of 2,8-dihydroxyadenine stones among all urinary stones examined have indicated that 0.00368% of general population in Japan experience this type lithiasis. These data indicate that more than 1% of general population in Japan possess mutant alleles of APRT gene as heterozygotes. Our studies suggested that most of the patients with this disease are left undiagnosed.

A12. Heat Stability of Catalase in the Anemic Blood of Acatalasemic and Hypocatalasemic Mice Injected Phenylhydrazine Hydrochloride Subcutaneously. **Michiko KOGASHIWA and Masana OGATA** (Dept. Publ. Health, Okayama Univ., Okayama)

Acatalasemic (C3H/AnL $C_s^bC_s^b$), hypocatalasemic (C3H/AnL $C_s^aS_s^b$) and normal (C3H/AnL $C_s^aC_s^a$) male mice, were injected with neutralized phenylhydrazine hydrochloride (40 μg/g body weight) subcutaneously, daily for 3 days. Their bloods were taken from orbital vein, 2 days after final injection and analyzed. The thermonal sensitivity of catalase was examined at 2°C intervals from 36°C to 50°C for 10 min. The results were as follows. 1) Ratio of specific catalase activity (PU/gHb) in the anemic blood to that in non-anemic blood of normal, hypocatalasemic and acatalasemic mice was 1.1, 1.6 and 3.4, respectively. 2) Heat stability was expressed as temperature (T_{50}) at which 50% of the catalase activity was lost. And T_{50} value of anemic acatalasemic blood, containing reticulocytes abundantly,

was significantly lower than that of anemic normal blood and T_{50} of anemic hypocatalasemic blood was between them. These data indicate that the heat stability of catalase in the anemic bloods of 3 kinds of mice was decreased in the order of normal, hypocatalasemia and acatalasemia. Similar results to anemic blood were obtained by non-anemic blood of 3 kinds of mice. 3) The T_{50} values of anemic blood showed a little higher than that of non-anemic blood, in 3 kinds of mice.

A13. Changes in the Liver and Blood Catalase Activities and Serum Enzyme Activities of Acatalasemic Mice Administered Ethyl Chlorophenoxyisobutyrate Orally. **Michiko KOGASHIWA and Masana OGATA** (Dept. Publ. Health, Okayama Univ., Okayama)

Acatalasemic and normal mice were administered ethyl chlorophenoxyisobutyrate (CPIB) orally and variation of catalase activity in the liver and blood and those in serum enzyme activities were determined. The results obtained were as follows. 1) Catalase activity in the liver of normal mice administered CPIB significantly increased and the activity was 2.2 times than that before injection. 2) Catalase activity in the blood of normal and acatalasemic mice administered CPIB slightly increased. 3) Liver catalase of acatalasemic mice administered CPIB is more stable for heat than that of control mice, while catalase of normal mice administered CPIB is slightly more stable than that of control mice. 4) Activities of ALP and CHE in the serum of normal mice administered CPIB were significantly increased, and TG concentration in the serum were significantly decreased. Activities of GOT and CHE in the serum of acatalasemic mice administered CPIB were significantly increased and TG concentration were significantly decreased. There were no distinct differences in serum components and enzymes between normal and acatalasemia administered CPIB. 5) Determination of ALP isozymes by electrophoresis on agarose film showed that increased ALP in the serum of normal mice administered CPIB was ALP derived from liver.

A14. Genetic Analysis of LEC Rats with Spontaneous Hepatitis: Establishment of Animal Model for Hepatitis and Liver Cancer. **Michihiro C. YOSHIDA, Ryuichi MASUDA and Motomichi SASAKI** (Chromosome Res. Unit, Fac. Sci., Hokkaido Univ., Sapporo)

A new mutant causing hereditary hepatitis associated with severe jaundice has been discovered in an LEC strain isolated from random-inbred Long-Evans rats. Hepatitis appeared suddenly in adult rats three to four months after birth. The clinical signs of hepatitis are characterized by severe jaundice, subcutaneous bleeding, oliguria, and loss of

body weight. The affected rats showed a high lethality and histological changes of the liver with focal necrosis of enlarged hepatocytes without inflammatory cell response. Genetic tests indicate that at least a single autosomal recessive gene is responsible for the major cause of hepatitis. Furthermore, liver cancer appears in long survived rats after recovery from jaundice as well as a few asymptomatic rats without jaundice. The LEC rats thus provide an animal model useful for the basic and clinical studies of hepatitis and liver cancer, including their pathogenesis, prevention and treatment.

A15. Biochemical Studies on Adult Sibling Gaucher Disease with Severe Neurological Deteriolation. Misao OWADA, Teruo KITAGAWA (Dept. Pediatr., Nihon Univ. Sch. Med., Tokyo), **Eiichiro UYAMA and Toshiro ARAKI** (Dept. Intern. Med., Kumamoto Univ., Kumamoto)

Chronic adult form of Gaucher's disease usually reveals no neurological manifestations. We recently had the opportunity to examine three adult siblings with ocular motor apraxia, corneal opacities, hydrocephalus and valvlar heart disease. Their verbal IQs were normal and death occurred at 3rd to 4th decade of age. Typical Gaucher cells and accumulation of glucocerebroside (Glcer) in the livers and the spleens as well as decreased glucocerebrosidase (Glcer-ase) in the tissues lead us the diagnosis of Gaucher's disease. The present report describes clinical and biochemical findings in the adult siblings with Gaucher's. Lipid analysis in tissues were carried out by Folch's method, and infra-red spectrum and fatty acid composition of isolated Glcer were performed. Glcer-ase activity in the tissues and cultured skin fibroblasts were measured by using [^{3}H]Glcer as a substrate. Glcer content in the liver and spleen of the patients were increased 5- to 10-fold compared with control tissues. These values, however, were about one-fifth of the typical Gaucher's tissues. Glcer-ase activity in the tissue with the patients decreased as much as one-tenth that of normal controls, but the properties of the residual enzyme was not different from that of controls. The pathogenesis of these cases was discussed.

A16. Studies on Leukocyte α-D-Mannosidase in Patients with Mannosidosis. Kenji YONEDA, Hisaomi KAWAI, Yoshihiko NISHIDA, Katsunori TAKEDA, Kenjiro MASUDA, Shiro SAITO (1st Dept. Intern. Med., Sch. Med., Univ. Tokushima, Tokushima) **and Katsuhito ADACHI** (Tokushima Hosp. Natl. Sanatorium, Tokushima)

Isozyme pattern of leukocyte α-D-mannosidase and its activity were examined in two sisters with mannosidosis and their parents. The leukocyte materials were subjected to electrophoresis on cellulose acetate membrane to examine the isozyme pattern of α-D-

mannosidase, and their pH dependent enzyme activities were measured at pH between 3.0 and 7.1. Lysosomal enzymes were also examined in a patient with chromosome 19 trisomy. Electrophoresis of α-D-mannosidase of normal leukocyte revealed isozyme A+B band at pH 3.5 and 4.5, which corresponded to acidic mannosidase, but the activity of isozyme C, neutral mannosidase, could not be found due to its low activity. In the patients with mannosidosis no band of the isozyme was recognized. In their parents the isozyme A+B band could be seen, although enzyme activities were low. The studies of pH dependent enzyme activities in normal subjects showed that the activity of acidic isozyme A+B (at pH 4.3) was much more higher than that of neutral isozyme C (at pH 6.5). In contrast, in the patients with mannosidosis the activities of isozyme A+B were scarcely detected, but isozyme C activity was preserved normally. In their parents isozyme A+B activities showed a value between normal controls and the patients, whereas isozyme C activity was found to be normal. In a patient with chromosome 19 trisomy had normal pattern of predominant A+B, and only the activity of α-D-mannosidase was elevated about 5 times as high as normal upper levels, although the activities of other lysosomal enzymes in leukocyte were within normal limits. The present study indicates that our patients with mannosidosis are the homozygote for gene defect in isozyme A+B, but isozyme C gene is not affected. The parents are thought to be heterozygotes since isozyme A+B activity were deficient to half of normal value. The study of the lysosomal enzyme in a patient with chromosome 19 trisomy suggests that the locus of mannosidase isozyme A+B gene might be located in chromosome 19.

A17. **Clinical and Biochemical Analysis of Zellweger Syndrome and Its Variant Form.** **Yasuyuki SUZUKI, Nobuyuki SHIMOZAWA, Tadao ORII** (Dept. Pediatr., Gifu Univ., Gifu) **and Takashi HASHIMOTO** (Dept. Biochem., Shinshu Univ., Matsumoto)

Zellweger syndrome is a fatal autosomal recessive disease characterized by profound hypotonia, psychomotor retardation, hepatomegaly, multiple renal cortical cysts and absence of peroxisomes. This syndrome is considered to be a prototype of peroxisomal diseases including neonatal and X-linked adrenoleukodystrophy, infantile Refsum disease, rhizomelic type chondrodysplasia punctata, pseudo-Zellweger syndrome and acatalasemia. We have experienced 3 cases of typical Zellweger syndrome and a male case who resembled pseudo-Zellweger syndrome. All cases had a typical face consisting frontal bossing, large fontanellae, low nasal bridge and epicanthic fold. Severe hypotonia, convulsions, psychomotor retardation and horizontal nystagmus were also observed. All patients died within several months of their lives. Peroxisomes were absent in cases with typical Zellweger syndrome, but the patient who resembled pseudo-Zellweger syndrome had peroxisomes as

much as the control. The levels of very-long-chain fatty acids in serum sphingomyelin were increased more than twentyfold. Enzyme activities of peroxisomal β-oxidation system in the autopsied liver were markedly decreased, and immunoblot analysis revealed that proteins of these enzymes were also deficient. But mRNA activities of these enzymes were present. These results indicate that the enzymes of peroxisomal β-oxidation are degraded rapidly once they are synthesized, which leads to the accumulation of very-long-chain fatty acids in these disorders.

A18. Glutaric Aciduria Type I: Two Japanese Patients Detected by the Screening and Their Family Studies. Seiji YAMAGUCHI, Hiroyuki NAGASAWA, Kanji YASUDA, Tadao ORII (Dept. Pediatr., Gifu Univ. Sch. Med., Gifu) **and Keiko SHIKURA** (Div. Pediatr., Juntendo Unic. Izu-Nagaoka Hosp., Shizuoka)

Two Japanese cases of glutartic aciduria type I (GA-I) and investigation of their families are presented.

Case 1 (EN) was a 7-month-old girl. She had complaints such as poor head control, ill temper or irritability. She was diagnosed to be GA-I by the screening of organic aciduria using GC/MS in Gifu University. Case 2 (HT) was a 5-month-old boy. He was born weighing 998 g at 27 weeks of gestation as one of fraternal twins. He had one episode of convulsion at 3 months of age, and was noticed the tendency of a macrocephaly. The cerebral CT findings of both two patients showed unique abnormalities such as marked fluid collection in bilateral frontotemporal resions. Administration of lioresal, GABA analogue, were seemed to be effective against the neurological symptomes, while dietary treatment and carnitine therapy were effective biochemically for the two patients. There were no abnormalities in their family histories. The enzyme activity of glutaryl CoA dehydrogenase in the leucocytes of these two patients and their families were assayed. The enzyme activity revealed no detection in both patients, and intermediate values in four patients and some relatives. The number of patients diagnosed as GA-I may be increased in future by the screening test in Japan.

A19. A Novel Diagnostic Method of Familial Amyloidotic Polyneuropathy Based on Isolation and Identification of a Prealbumin Variant. Tomokazu SUZUKI, Tsutomu AZUMA, Ryuzo MIZUNO, Seiichi TSUJINO, Susumu KISHIMOTO (3rd Dept. Intern Med., Osaka Univ. Hosp., Osaka), **Yoshinao WADA, Akira HAYASHI** (Osaka Med. Cent. Res. Inst. Maternal Child Health, Osaka), **Shu-ichi IKEDA and Nobuo YANAGISAWA** (3rd Dept. Intern. Med., Shinshu Univ. Sch. Med., Matsumoto)

We developed a method for the isolation of a prealbumin variant (30Val→Met) asso-

ciated with familial amyloidotic polyneuropathy (FAP) from plasma. First, prealbumin was isolated from several milliliters of plasma by a two-step procedure: affinity chromatography on a Blue Cellulofine (Seikagakukogyo) column and ion exchange chromatography on a Mono Q column (Pharmacia Fine Chemicals). Then separation of the prealbumin variant from normal prealbumin was achieved by reverse phase high performance liquid chromatography. While prealbumin isolated from the plasma of normal subjects was eluted as a single peak, two sharp peaks were clearly evident on the elution profile of prealbumin isolated from the plasma of FAP patients and preclinical carriers. Secondary ion mass spectrometric analysis of their tryptic digests characterized the primary structure of each peak, identifying a peak with longer retention time as the prealbumin variant. This method was successfully used as a novel diagnostic method of FAP and as a preclinical test for offsprings of patients with FAP.

A20. Genetic Polymorphism of Apolipoprotein E and Hyperlipidemia in Japanese: Frequencies of Apo E5 and Apo E7 in Myocardial Infarction Survivors. **Yasuko YAMANOUCHI,[1] Shigeru TSUCHIYA,[2] Hideomi FIJIWARA,[3] Ryunosuke MIYAZAKI[4] and Hideo HAMAGUCHI[1]** ([1]Dept. Hum. Genet., Inst. masic Med. Sci., [2]Inst. Comm. Med., Univ. Tsukuba, Ibaraki; [3]Tsuchiura-Kyodo Hosp., Tsuchiura; [4]Kudanzaka Hosp., Tokyo)

It has been suggested that apolipoprotein (apo) E5 and apo E7 might be atherogenic. In order to examine whether apo E5 and E7 are associated with myocardial infarction, apo E phenotypes were analyzed for 108 myocardial infarction survivors of Tsuchiura-kyodo Hospital and 134 age-matched subjects who visited the health care center of the same hospital. Apo E phenotypes were analyzed by isoelectric focusing and immunoblotting using 8 M urea–2% NP40 polyacrylamide gel, anti-human apo E goat serum and peroxidase conjugated anti-goat Ig rabbit serum. Apo E5 or E7 was found in about 4% of myocardial infarction survivors and about 5% of controls, suggesting that strong positive association may not be present between myocardial infarction and apo E5 and E7. We have so far found 13 adults with apo E3/5 or apo E3/7. Twelve of them were normolipidemic, indicating that apo E5 and E7 genes do not have dominant effects on hyperlipidemia.

A21. DNA Polymorphisms of Apolipoproteins AI and CIII in Japanese Patients with Myocardial Infarction. **Juichi SATOH,[1] Naoko HATTORI,[1] Hideomi FUJIWARA,[2] Takaaki OKAFUJI[1], Kimiko YAMAKAWA,[1] Yasuko YAMANOUCHI,[1] Tohru SAKUMA,[3] Yukio IWAMURA,[1] Shigeru TSUCHIYA[4] and Hideo HAMAGUCHI[1]** ([1]Inst. Basic Med. Sci., [4]Inst. Comm. Med., Univ. Tsukuba, Ibaraki: [2]Tsuchiura-Kyodo Hosp., Tsuchiura; [3]Tsukuba Med. Cent., Ibaraki)

To search for a linkage marker for the putative deleterious atherogenic gene in the apo AI-CIII-AIV gene complex in Japanese, apo CIII *Sst*-I genotypes and apo AI *Msp*-I genotypes were investigated in 69 Japanese myocardial infarction survivors, using genomic hybridization analysis, and compared with the genotypes in 82 healthy subjects. Unlike the association of the *S2* and *M2* alleles with myocardial infarction found in Caucasians, there were no differences in both the frequencies of the *S2* and *M2* alleles between Japanese myocardial infarction survivors and healthy subjects (*S2*, 0.32 *versus* 0.34; *M2*, 0.44 *versus* 0.40). The individual with the haplotypes *S1-M2*, however, was significantly increased in myocardial infarction survivors compared with the one in healthy subjects (24% *versus* 11%; $p<0.05$). The data suggest that the haplotype *S1-M2* may be a linkage marker for the putative atherogenic gene or may show regional differences in the frequency in Japanese.

A22. DNA Polymorphism of LDL Receptor Gene in Japanese. **Kimiko YAMAKAWA, Takaaki OKAFUJI, Hideo HAMAGUCHI** (Dept. Hum. Genet., Univ. Tsukuba, Ibaraki) **and Yukio IWAMURA** (Dept. Microb., Univ. Tsukuba)

Familial hyperchoresterolemia (FH) is one of the most common genetic disease of humans. Mutations in the gene for low density lipoprotein (LDL) receptor give rise to FH. RFLPs of the LDL receptor gene are useful markers for the genetic analysis and preclinical diagnosis of FH. In order to find RFLPs of the LDL receptor gene in Japanese, we digested DNA samples from 50 unrelated individuals with nine different restriction enzymes (*Pvu*II, *Bam*HI, *Bgl*II, *Eco*RI, *Eco*RV, *Msp*I, *Pst*I, *Taq*I, *Hae*III), and analyzed by the Southern blot hybridization using the LDL receptor cDNA prove pLDLR-3 gifted kindly from Dr. D.W. Russell. RFLPs of 19 kb and 16 kb in *Pvu*II fragments that had been reported by S.E. Humphries *et al.* (1985) and H.H. Hobbs *et al.* (1985), were observed in Japanese people. In a Japanese population, the gene frequencies of the two alleles were 0.895 and 0.105, respectively. Furthermore, one of 57 individuals examined had a variant band of 0.6 kb in *Pvu*II digested DNA fragments. Family study suggested that this band represents a genetic variant. At present, it is not clear whether this variant is polymorphic. We can not detect RFLPs of the LDL receptor gene with other eight kinds of restriction enzymes. Since heterozygosity of RFLP of *Pvu*II is rather low (19%) in Japanese, we need to find another RFLPs of the LDL receptor gene.

A23. Analysis of Familial Amyloidotic Polyneuropathy by DNA Polymorphic Markers. **K. YOSHIOKA, H. FURUYA, H. SASAKI and Y. SAKAKI** (Res. Lab. Genet. Inform., Kyushu Univ., Fukuoka)

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant genetic disorder and molecular analysis showed that one base change from G to A which causes an amino

acid substitution from Val to Met at position 30 of serum prealbumin is tightly linked to the disease. For understanding the genetic basis of FAP families, we assigned the prealbumin gene to the locus 18q11.2-q12.1 using mouse/human hybrid cells and also *in situ* hybridization techniques. We also identified two RFLPs and some other polymorphic base changes associated with the gene, and then, analyzed the haplotype of FAP families of various geographic loci in Japan. Our results showed that FAP families can be divided into two groups based on the haplotype. These results suggested that the Val to Met change which is commonly found in FAP families in Japan is independent by origin and that the amino acid substitution is crucial in FAP.

A24. Use of Minisatellite Core Probe for Detecting RFLPs: Zygosity Determination in Twins. **Kazuyoshi MOTOMURA,[1] Hideo TATEISHI,[1] Isamu NISHISHO,[1] Makoto OKAZAKI,[1] Tetsuro MIKI,[2] Shin-ichiro TAKAI[1] and Takesada MORI[2]** ([1] 2nd Dept. Surg., [2]Dept. Intern. Med. Geriat., Osaka Univ., Osaka)

Hypervariable 'minisatellite' regions which are dispersed in the human genome show restriction fragment length polymorphisms (RFLPs) due to allelic differences in the number of tandem repeats of the core sequence. We report here the use of minisatellite core probe (λ33.15, kindly provided by Dr. Jeffreys) for zygosity determination in 4 twin pairs. In two cases, the twins had identical band patterns suggesting that they are monozygotic. In the remaining two cases, different band patterns indicated dizygosity. These results are in good agreement with the data obtained by analysis with conventional genetic markers. In addition, we are studying whether the minisatellite core probe can detect specific bands in close linkage with disease locus in large families at high risk for multiple endocrine neoplasia type 2 (MEN-2). We are also applying this probe to compare the constitutional and tumor DNA of the MEN-2 patients to detect loss of heterozygosity in tumor DNA which might be responsible for tumorigenesis in this syndrome.

A25. Analysis of HLA-DQ Gene. **Michio YASUNAMI, Akinori KIMURA, Hirotoshi SINAGAWA and Takehiko SASAZUKI** (Dept. Genet., Med. Inst. Bioregul., Kyushu Univ., Fukuoka)

HLA-DQ molecule is regarded to be a human homologue of murine I-A. We cloned and sequenced two different DQβ cDNAs from an HLA-Dw12 homozygote. One clone (pDQβ101) contained 24 nucleotide sequence homologous to the fifth exon ("cytoplasmic" exon) of I-Aβ, the other (pDQβ201) lacked this portion and had longer 3′ untranslated region. Analyses of RNA by Northern blot hybridization and nuclease S1 mapping suggested the existence of alternative splicing of this "cytoplasmic" exon and multiple poly A

addition sites. It was reported that DQβ genes of HLA-Dw3-DQw2 and HLA-Dw4-DQw3 had the aberrant splice acceptor site 5′ to "cytoplasmic" exon (AAG), thus this exon was not expressed in mRNA. Nucleotide sequencing data of DQβ genomic clone (DQβDw12) from the same HLA-Dw12 homozygous individual indicated that the acceptor site was intact (AGG). Restriction enzyme *Ava*II could cleave the intact site (*AGGACC*), but not the aberrant site (AAGACC), so that this base substitution could be detected as *Ava*II RFLP. The *Ava*II RFLP using a DQβ specific probe revealed that the acceptor site is intact in the DQw1 haplotype but not in the DQw2 or DQw3 haplotype.

A26. Exogenous Factors Triggering the Manifestation of Narcolepsy. Akio ASAKA, Yutaka HONDA, Seiichi HARADA, Takeo JUJI, Kazumasa MATSUKI (Dept. Mental Health, Neuropsychiat., Blood Transfus. Cent., Univ. Tokyo Sch. Med., Tokyo)

Patients with narcolepsy all showed positive DR2. This finding indicate that DR2 is a sine qua non, but not *vice versa*, for the development of narcolepsy. Among 185 Japanese narcoleptic patients examined, there were at least 11 cases of unquestionable symptomatic narcolepsy. The major exogenous factors were loss of consciousness, heavy bleeding, and encephalitis which were found in immediate preceding history of the disease. Other genetic and/or environmental studies lead to the conclusion that some predisposing factors or other genetic backgrounds are needed, and that some minor or major exogenous factors, in a biological as well as a psychological sense, are also required as triggering factors for the manifestation of the disease. The mode of inheritance is fitted both a single gene model and a multifactorial inheritance model.

A27. Genetic Polymorphism of MHC Class III Antigens in Healthy Controls and Psoriatic Patients of Four Asian Populations. K. SUZUKI, H. MATSUMOTO (Dept. Legal Med., Osaka Med. Sch., Takatsuki), **T. SASAZUKI, S. MATSUSHITA** (Dept. Genet., Med. Inst. Bioregul., Kyushu Univ. Fukuoka), **P. CHAROENWONGSE** (Chulalongkorn Univ., Bangkok), **R. M. PITCHAPPAN** (Madural Kamaraj Univ., India), **N. M. CONTRACTOR** (Bombay Univ. India), **A. L. LINGAO** (Manila) **and G. J. O'NEILL** (St. Francis Med. Cent., Wichita)

The distribution of MHC class III antigens was compared between unrelated patients with psoriasis vulgaris and healthy controls in four Asian populations: Indian, Filippino, Thai, and Chinese. The class III antigens were typed using electrophoretic procedures. Of the class III antigens detected in this study, C4A6 in the patients was significantly increased in Thai (R.R.=8.6, $\chi^2=8.04$, $p=0.005$) and in India (R.R.=5.9, $\chi^2=18.39$, p=

0.00002). C4B5 and C4B96 were detected only in Chinese psoriatic patients. No significant increase nor decrease of the frequencies of the class III antigens other than C4A6 was estimated in the patient groups. Some rare variants in Factor B (BF) and C2 were observed. Those were BFF025, F035, S03, S045, and S07 in Chinese, BFS07 in Indian, C2BH in Filippino, and C2AIndia in India. Gene duplication in C4A or C4B locus has found to be not so rare event also in the four populations as has been reported thus far.

A28. Genetic Variants of the Complement Components and Diseases. **Katsushi TOKUNAGA,[1] Georg DEWALD,[1] Fujio TAKEUCHI,[2] Yasushi YUKIYAMA,[2] Hidemi NAKAGAWA,[3] Yasumasa ISHIBASHI,[3] and Takeo JUJI[4]** ([1]Dept. Anthropol., [2]Dept. Med. Phys. Ther., [3]Dept. Derm., [4]Blood Transfus. Serv., Univ. Tokyo, Tokyo)

Genetic polymorphisms of the serum complement components (C2, C4, BF, C6, and C7) have been studied in the Japanese patients with several diseases. The results on three diseases, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriasis vulgaris (PV) are presented. SLE: A positive association with the C4A "null" (C4A*Q0) was found ($p<0.005$). C4A*Q0 could be a susceptibility gene, because 1) the same association is also found in Caucasian, and 2) C4 deficient individuals are known to suffer from SLE, while 3) SLE-associated HLA alleles in Japanese are different from those in Caucasian. RA: Strong positive associations with C4A*Q0 and C4B*5 were found ($p<0.001$). The effect of the co-existence of the two C4 alleles on the relative risk was more than additive ($RR=13.5$). Take the associations with HLA alleles into consideration, it is likely that there are at least two high risk haplotypes, HLA-Bw54-C4A3B5-BFS-C2C-DR4 and C4AQ0B1-BFS-C2C. PV: Positive associations with C4A*4 ($p<0.01$) and C4B*2 ($p<0.005$), and a negative one with BF*F ($p<0.01$), which was also reported in Caucasian, were observed. Besides the previously reported haplotypes HLA-Cw6-B13 and Cw6-Bw57-DR7, the haplotype HLA-CX46-Bw46-C4A4B2-BFS-C2C-DRw8 might be a high risk haplotype in Japanese.

A29. Erythrocytic Receptors for the Third Complement Component in Patients with Systemic Lupus Erythematosus. **Tatsuo KAWAGUCHI, Eisuke YOKOTA, Yuji NARITOMI, Yasushi NAITO, Kunihiro TOKIYAMA, Tomohiro KUSABA, Yoshiyuki NIHO** (1st Dept. Med., Kyushu Univ., Fukuoka) **and Takashi IMAMURA** (Dept. Hum. Genet., Natl. Inst. Genet., Mishima)

Erythrocytic receptors for the third complement component (CRl) were measured by the use of an immune-adherence hemagglutination (IAHA) reaction. The erythrocytes

were obtained from 101 patients with definite systemic lupus erythematosus (SLE), 105 relatives of the patients and 169 normal controls in Fukuoka population. Apparently healthy 688 subjects residing in Yonaguni and Hateruma Islands were also studied. The CR1 activities on erythrocyte membranes were deficient in 79% of the patients with SLE in Fukuoka population, as compared with the 22 individuals (13%) among 169 normal controls. Pedigree analysis indicated that the deficiency was determined by an autosomal recessive mode of inheritance, except for 4 families for which an autosomal recessive gene was unlikely to be involved. To clarify the mode of inheritance of defective CR1 activity, we assessed CR1 activities in apparently healthy subjects. Fifty-three individuals (7.7%) among 688 controls in Okinawa population were shown to be defective in CR1. Family study in this population revealed that the deficiency was determined by an autosomal recessive gene. The CR1 activities both in patients with SLE and in healthy individuals, were genetically determined by an autosomal recessive gene. Some acquired factors, such as disease activity of SLE, were thought to involve in the variability of CR1 activities.

A30. 全身性エリテマトーデスの発症にかかわる遺伝要因の解析. 兼岡秀俊・山口雅也・森戸文隆・緋田めぐみ・大田明英・永吉敏郎（佐賀医大・内科）. **Analysis of the Polygenic System Involving in Pathogenesis of Systemic Lupus Erythematosus.** H. KANEOKA, M. YAMAGUCHI, F. MORITO, M. HIIDA, A. OHTA and T. NAGAYOSHI (Dept. Intern. Med., Saga Med. Sch., Saga)

全身性エリテマトーデス (sytemic lupus erythematosus, SLE) は多因子遺伝形質に属する代表的自己免疫疾患であり，複数の遺伝要因の関与が推定されている．われわれは，SLE 発症にかかわる遺伝要因を解析する目的で，さまざまな免疫学的遺伝形質と SLE の関連を検討し，SLE 患者およびその家族において，HLA 抗原系，免疫グロブリンアロタイプ (Gm アロタイプ)，補体第3成分レセプター (CR 1)，リンパ球表面抗原である Lp 1 および Lp 17，および血清タンパク S1 のスコアが高いことを報告してきた．今回は，SLE 多発家系を用いて，これら遺伝要因の SLE 発症に及ぼす影響の差について検討した．2 人以上の SLE 患者を有する 6 家系 7 家族について，HLA, Gm アロタイプ，CR 1, Lp 1, Lp 17, S1 の表現型および遺伝子型を決定した．それぞれの項目について点数を与え，その総点を SLE 発症にかかわる遺伝要因のスコアとし，患者とその家族の間でスコアに差が出るかを検討した．その結果，HLA について，他の項目よりも加重して点数を与えると，患者群と家族群の間のスコア値に有意の差がみられた．従来の報告によると，HLA 抗原系の SLE に対する相対危険度は，むしろ CR 1, Lp 1, Lp 17, S1 より低値である．しかし，今回の成績は，HLA 抗原系は SLE 発症にかかわる多因子の一つとして，penetrance はさほど強くないが，より多くの患者の発症に関与していることを示唆している．

A31. Alzheimer's Disease and Genetic Markers. **Kazuo MIYANAGA and Nobuo KAWAHARA** (Dept. Neuropsychiat., Gunma Univ., Gunma)

In order to investigate the genetic basis of Alzheimer's disease (AD) and senile dementia of Alzheimer type (SDAT), the frequencies of types of various genetic markers such as ABO, Rh, MNSs, P, Lewis, Duffy, Diego, Kidd, Hp, Gc, Gm, Km, PGM1, HLA-A and -B were examined in 21 AD and 24 SDAT patients. The results were as follows: 2) Statistically significant differences were found between AD and controls in the frequencies of types of Rh, P, Kidd and Gc. 2) Statistically significant differences in the frequencies of types of Kidd and HLA-A10 were found between SDAT and controls. 3) No statistically significant differences were found between AD and SDAT in the frequencies of any genetic markers. In conclusion, AD and SDAT might be identical diseases. This study may provide an important approach to determine the loci which are involved in AD and SDAT.

A32. Application of Todai Flushing Screening Test (TFST). **A. ASAKA and K. YAMADA** (Dept. Mental Health, Univ. Tokyo Sch. Med., Tokyo)

Todai (Tokyo University in Japanese) Flushing Screening Test (TFST) was the questionnaire, consisting of 13 subjective symptoms when one drinks, for the discrimination between flusher (ALDH2 deficient individuals) and non-flusher (ALDH2 non-deficient individuals). Two main contributing factor axes were extracted when the scores of TFST from 1,826 University staffs were subjected to factor analysis. The first axis was considered to display signs induced by ALDH such as facial flushing, increased palpitations, and the second axis signs induced by ADH such as dizziness, dyspnea and so on. TFST discriminates the population into 821 flushers and 1,005 non-flushers. The mean of scores of the first and the second axis, in the flushers, were 0.747 ± 0.020 and 0.151 ± 0.036, respectively. These values in the non-flushers were -0.611 ± 0.012 and -0.123 ± 0.012, respectively. Among "cannot drink" population, these values were 0.888 ± 0.166 and 0.724 ± 0.059, respectively, which indicated that the population was strongly sensitive to both ethanol and acetaldehyde. With respect to the population with alcohol dependence, these values were -0.380 ± 0.108 and 0.476 ± 0.285, respectively, which showed low sensitivity to acetaldehyde but high sensitivity to ethanol.

A33. Biochemical and Genetic Studies of Glutathione *S*-Transferase. **Shoji HARADA,[1] Masato ABEI[2] and Naomi TANAKA[2]** ([1]Inst. Comm. Med., [2]Inst. Clin. Med., Univ. Tsukuba, Ibaraki)

The liver glutathion *S*-transferase (GST) isozymes coded by different GST loci (GST1, GST2, GST3) were purified using CM Sephadex-C50, epoxyactivated-Sepharose 6B and

hydroxyapatite. Each isozyme was characterized to study the biochemical and immunological properties. The pI values of GST1 1 and GST1 2 were 6.2 and 6.7, respectively and their M.W. of the subunit was 27,000. GST2 isozymes consist of two different isozymes possessing the pI values of 8.7 and 9.5 and their M.W. of subunit was 26,000. GST3 shows pI value of 4.5 and the M.W. of subunit was 24,500. Using a specific antibody against GST1 isozyme, it was confirmed that the GST1 O may result from gene deletion since the GST1 O made no precipitate against GST1 antibody. Antibodies to GST1, GST2 and GST3 reacted only with GST belonging to the same isozymes. Family studies using lymphocytes indicated that alleles of GST1*1 and GST1*2 are most likely codominant.

A34. A GPT Silent Allele Found in A Case with Acute Hepatitis. **Itsuro NISHIGAKI,[1] Naokazu SHIMIZU,[1,2] Hiroshi KAWASHIMA,[2] Yoshihide FUJIYAMA[2] and Shiro HOSODA[2]** ([1]Kohoku-Sohgo Hosp., [2]2nd Dept. Intern. Med., Shiga Univ. Med. Sci., Shiga)

Cytoplasmic or soluble fraction of glutamic-pyruvic transaminase (sGPT) exhibits genetic polymorphism, by two autosomal codominant alleles, Gpt^1 and Gpt^2. Among enzyme products by these alleles there also exists a quantitative difference. The catalytic activity of the Gpt^1 product is 2–3 times higher than that of Gpt^2. Apart from these characteristics, the existence of a silent allele has so far been predicted by several authors. In the present study, we report on this Gpt^0 allele encountered in a Japanese family. The proband, a 47-year-old female with acute hepatitis, showed a remarkable low value of serum GPT activity, comparing with the elevated value of GOT (GPT 11 U; GOT 1, 170 U) at admission. This relation was exactly alike in cytosol fraction from liver. In red cell lysates the GPT activity was 0.82 U/gHb and a very weak pattern of electrophoresis led to the phenotype GPT 2. This activity value was very low, comparing with that of a normal level in its same phenotype. GPT phenotypes and activities of her family were GPT 1 (2.93) for mother; GPT 2 (0.99) for brother; GPT 1 (8.43) for sister; GPT 1 (2.29), GPT 1 (4.67), and GPT 2 (1.18) for children; GPT 2-1 (6.85) for husband. In their phenotypes there was a discrepancy between the mother and the proband or the brother. Other genetic markers tested showed no such discrepancies among them. This atypical segregation could be explained by the presence of a silent allele which would not participate in determination of the phenotype. Values of below one half of normal activity for supposed heterozygotes of Gpt^0 support well this evidence.

A35. Mitochondrial DNA Polymorphism in Japanese: III. Analysis in Okinawa Population. Satoshi HORAI, Ei MATSUNAGA (Natl. Inst. Genet., Mishima), **Kiyotake HIRAYAMA and Shizuhiro TAKENAKA** (Ryukyu Univ., Okinawa)

The mitochondrial DNA (mtDNA) from 82 Okinawa people were analyzed with 24 restriction enzymes. In the analysis of 15 enzymes that recognize 6 base pairs, 8 enzymes showed at least two different digestion patterns, while remaining 7 enzymes exhibited monomorphic patterns. In the analysis with 9 enzymes that recognize 4 or 5 base pairs 60 different morphs were observed in all, 19 of which were unique in the Okinawa population. Comparisons of the frequencies of each morph for the Okinawa population with those for the mainland Japanese revealed significant differences in frequencies of 10 morphs between the two populations. Based on a comparison of the cleavage map among the Okinawa samples, 39 types of different combinations of the morphs were observed. It is remarkable that only 11 of them have been found in the mainland Japanese while the remaining 28 types were unique in Okinawa. We then estimated the numbers of nucleotide substitution (d) for each pair of these types by the method of Nei and Li (1979). The mean value of d was 0.0016, taking into account the frequency of each type, which is lower than that (0.0026) for the mainland Japanese. A phylogenetic analysis showed that the clustering pattern of the constructed tree for the two populations was essentially similar to each other. The tree constructed on the basis of the combined data for the two populations indicated that the mtDNAs appear to have been already polymorphic even in the founder population of Japan.

A36. Antholopological Study Using HLA Antigen Frequencies as a Genetic Marker. Akemi WAKISAKA,[1] Yoshiki KONOEDA,[2] Shuichi HAWKIN,[1] Akio TAKADA[1] and Miki AIZAWA[1] ([1]Dept. Pathol., Hokkaido Univ., Sapporo; [2]Dept. Surg., Kyorin Univ., Tokyo)

In the 3rd Asia Oceania Histocompatibility Workshop, more than 8,000 peoples from 36 different ethnic groups from all over the world were studied. This is a first trial that HLA antigen frequencies of such a large number of ethnic groups were investigated using the same materials and methods at the same time. Comparisons of the HLA antigen frequencies among these population offered us quite valuable informations for the antholopological studies since HLA antigen is one of the most polymorphic genetic systems in man. According to the geographical distributions of the HLA antigens they were classified into 6 groups; *i.e.* pan ethnic, north Mongoloid, south Mongoloid, Caucasoid, Negroid and Oceanian antigens. Mongoloid antigens are found in only Mongoloids and show clear genetic cline from north to south or from south to north. Caucasoid antigens, which might be originated in Caucasoids and found in Caucasoids with highest frequencies, are

also found in Mongoloids. Frequencies of these antigens among Mongoloids are highest in North Chinese with genetic decline to eastwards and to southwards. These antigen might be brought into North Chinese by horse-riding peoples passing through North-Central Asia then into other Mongoloids. Negroid antigens also show similar distribution but they are observed highest in Negroids. Although some antigens show unexplained distributions, it might be due to genetic drift, the geographical distributions of most HLA antigens reflect the migrations and admixtures of the ethnic group. These data suggest that variations of HLA antigen frequencies are caused by racial migrations rather than the natural selections.

A37. Molecular Phylogenetic Tree of 30 Populations over the World Using HLA Antigens. **Shuuichi HAWKIN, Akemi WAKISAKA, Akio TAKADA, Miki AIZAWA** (Dept. Pathol., Hokkaido Univ., Hokkaido) **and Yoshiki KONOEDA** (Dept. Surg., Kyorin Univ., Tokyo)

HLA antigens of 8,830 people collected from 34 ethnic groups over the world were assigned in the 3rd Asia Oceania Histocompatibility Workshop conference. Out of 34, 30 ethnic groups with enough number of panels were used for genetic study. Using the antigen and gene frequencies provided by central analysis, the genetic distance was calculated by Nei's and Cavalli-Sforza's method. Computer program was developed to draw the molecular phylogenetic tree automatically according to UPG (Unweighted Pair-Group Clustering) and MF (Modified Farris) method. Data obtained were consistent with the general concept that there are 4 major population groups in the world: Caucasoid, Mongoloid, Negroid and Australoid. Caucasoid includes American Caucasoid, European Caucasoid, Australian Caucasoid, Jewish, Mexican, Indian and Iranian. Mongoloid includes Japanese, Chinese, Korean, Thai, Filippino and Malay. Negroid includes African Black, and Australoid includes Australian Aborigine and Papua New Guinean. Populations from neighboring regions had smaller genetic distance than other population of their ethnic groups: Indian from northern part, sourthern part of India and Sourastran, Japanese and Korean, Chinese from northern and sourthern part of China, Filippino and Malay, and Australian Aborigine and Papua Newguinean make one group, respectively. On the other hand, populations from isolated area such as Eskimo, North American Indian, Maori, other Polynesian and Nepalese didn't belong to any ethnic group mentioned above. It might reflect that genetic drift took part and resulted in big genetic distance from other populations. Comparing UPG method and MF method, the former is convenient for making group of populations. However, it sometimes showed unusual big genetic distance between some groups. The latter is more acurate in genetic distance, but sometimes difficult to understand. It is interesting that the genetic distance calculated using HLA antigens

is very high. For example, the Nei's genetic distance between Caucasoid and Mongoloid is 0.224, which is about 10 times bigger than that using ordinary proteins. This suggests the molecular evolutional change of the HLA antigens go extremely fast.

A38. Erythrocyte Acid Phosphatase (ACP1) Variants in Japanese. Chiyoko SATOH, Norio TAKAHASHI, Kazuaki GORIKI, Junko KANEKO, Akiko MIURA, Hideo OMINE, Naomi MASUNARI and Ryuji HAZAMA (RERF, Hiroshima, Nagasaki)

To evaluate genetic effects of atomic bomb radiation, 30 blood proteins of children of survivors and their controls were examined by starch gel electrophoresis and detected protein variants were used as markers for germ cell mutation. This paper describes results of examination of erythrocyte acid phosphatase (ACP1) in hemolysates obtained from 21,761 children of both groups. Electrophoresis was carried out with TEMM buffer, pH 7.4. Allozyme bands were detected with 4-methyl-umbelliferyl phosphate and their activity was assayed at 37°C with *p*-nitrophenyl phosphate. Four kinds of variants similar to type B were detected in 8 children from 7 families. In each of them, a major band was detected at the normal position but a minor band was absent in 2 variants, or faintly stained, or migrated cathodal to the normal position. Five A-like variants were detected in 12 children from 11 families. Only a single band was detected at the position of minor band in 2 variants. In other 3 variants, only a single band was detected at the major band position, or major and minor bands were weakly stained, or migration of major band was normal but that of minor band was abnormal. Since 3 kinds of B-like variants and 4 kinds of A-like variants are activity variants, the former and the latter could be detected only when they were in the heterozygous phenotype with type A and type B, respectively. Family study for 8 variants could be done in 16 families. Genetic nature of variants was confirmed in all of them and no mutation was observed. For 3 activity variants in 3 families, the existence of the same variant in one of parents could only be confirmed by examining characteristics in activity and thermostability.

A39. Genetic Polymorphism of Urinary Pepsinogen PGA (PG 1/PG I) Detected by Immunoblotting. Toshihiro YASUDA and Koichiro KISHI (Dept. Legal Med., Fukui Med. Sch., Fukui)

Genetic polymorphism of PGA in human urine has been reported by several workers. But, the complexities of sample preparations, electrophoresis, and staining procedures yielded a number of conflicting results, leading to various different assumptions regarding a working genetic model. In this study, we present a new technique utilizing polyacryl-

amide gel isoelectric focusing followed by immunoblotting with anti-PGA antibody, which provides a better band resolution. PGA was clearly separable into five fractions, termed I to V in order of decreasing anodal mobility. The most slowly migrating fraction V was composed of F (fast) and/or S (slow) band(s). The population frequencies of the three patterns of fraction V (F, FS and S) and family studies indicated that PGA V is controlled by a pair of alleles, *PGA V*F* and *PGA V*S*, at a single autosomal locus, and that both are codominant. The frequencies of the alleles are 0.07 for *PGA V*F* and 0.93 for *PGA V*S*.

A40. Development of a Simplified Cosmid Cloning System. Masahiro ISHIURA,[1] Hiroshi OHASHI,[1] Nobuyoshi HAZUMI,[1] Tsuyoshi KOIDE,[1] Tsuyoshi UCHIDA[1,2] and Yoshio OKADA[2] ([1]Natl. Inst. Basic Biol., Okazaki; [2]Inst. Mol. Cell. Biol., Suita)

To develop a simplified cosmid cloning system, firstly we have constructed a series of cosmid vectors carrying the two cohesive end sites (cos) of phage lambda arrayed in tandem, which enable us to easily clone genomic DNA fragments up to 50 kb in size by a modified Ish-Horowicz and Burke's procedure, and examined the conditions for cosmid cloning using pDcosAp^r/ori vector and mouse genomic DNA. We have attained cloning efficiencies of 1.7×10^5 to 4.6×10^5 colony forming units (cfu)/μg of 45 kb-sized Sau3A fragments. We examined over 4,000 clones and found that all clones contained insert DNA. Secondly, introducing mammalian selective marker genes into pDcosAp^r/ori vector, we have constructed a series of cosmid vectors which enable us to easily detect and isolate transformant cells when the recombinant DNA are transferred into cultured mammalian cells. Using these vectors, we have constructed several cosmid libraries for mouse, chinese hamster and human DNA, and have isolated several genes including toxin-resistant elongation factor-2 (EF-2) genes from the libraries. Thirdly, recombinant cosmid DNA deletes during propagation in *E. coli* hosts. We have studied the deletion events and have found that recA mutation of the hosts could not block the deletion events but that recB recC sbcB recJ mutation and recB recC sbcB recN mutation could block.

A41. Molecular Cloning of the Lymphocyte Cytosol Polypeptide 1 (LCP1). Ikuko KONDO,[1] Kimiko YAMAKAWA,[1] Hideo HAMAGUCHI,[1] Takafumi NOMA,[2] Ryushin MIZUTA,[2] Hideo TANAKA[3] and Tasuku HONJO[2] ([1]Dept. Hum., Genet., Univ. Tsukuba, Ibaraki; [2]Dept. Med. Chem., Kyoto Univ., Kyoto; [3]Inst. Chem. Techn., Ibaraki)

Lymphocyto cytosol polypeptide 1 (LCP1) is a polymorphic protein detected by two-dimensional gel electrophoresis and exists mainly in lymphocytes. The phenotypes of this

protein is determined by two alleles at an autosomal locus and frequencies of the alleles are 0.94 and 0.06, respectively, in a Japanese population (*Hum. Genet.* 1981). The gene has been assigned to human chromosome 13q14.3 by chromosome deletion mapping and the close linkage between the loci for LCP1 and esterase D is reported previously (*Am. J. Hum. Genet.* 1985). The gene for esterase D is assigned to chromosome 13q14.1 and is a useful genetic marker for preclinical diagnosis of retinoblastoma (RB) and Wilson disease, because genes for these genetic diseases are closely linked to the gene for esterase D. Therefore, the gene for LCP1 is also useful genetic marker for detection of carriers of these genetic diseases. However, heterozygosity of the gene for LCP1 is 11.3%. Then, we have carried out molecular cloning of LCP1 using synthesized oligonucleotides based on five amino acid sequence. We have selected two hybrid clones from 20×10^3 independent genes and have studied restriction map of two clones and sequenced the hybridized region of cDNA clones. However, there was no matched sequence of probes used to the hybrid region of two clones, but 12-mer of sequence of the oligonucleotide was matched to the hybrid sequence. We are further going to analyze these two probes and to isolate LCP1 cDNA clone.

A42. Restriction Fragment Length Polymorphism at *Pst*I Site in the Genomic Gene of Human F_1 Beta Subunit. **Kiyoshi HASEGAWA, Shigeaki MIYABAYASHI, Kuniaki NARISAWA, Keiya TADA** (Dept. Pediatr., Tohoku Univ., Sch. Med., Sendai), **Shigeo OHTA and Yasuo KAGAWA** (Dept. Biochem., Jichi Med. Sch., Tochigi)

ATP synthase (F_0F_1) is a proton-translocating ATPase which is composed of two moieties, F_0 and F_1. It is located in the inner membrane of mitochondria and chloroplast membrane or the plasma membrane of prokaryotic cells. ATP synthesis in oxidative and photosynthetic phosphorylation is catalyzed by the F_1 beta subunit using the energy of proton flux across the membranes. Recently, Ohta and Kagawa have cloned a full-length cDNA for the human F_1 beta subunit (*J. Biochem.* **99**. 135, 1986). We show, here, the restriction fragment length polymorphism (RFLP) in the F_1 beta subunit using the cDNA as a probe. Genomic DNA from 19 Japanese individuals were analyzed by Southern blot hybridization. The RFLP characterized by polymorphic bands at 3.4, 1.8 and 1.6 kilobase pairs (kbp) was detected after complete digestion with *Pst*I. Out of 19 persons, twelve (63%) were homozygous for the 3.4 kbp band and one (5%) was homozygous for the 1.8 and 1.6 kbp bands. The others were heterozygous for these bands. Judging from the restriction map of the cloned genomic gene, the polymorphism is caused by the (dis)appearance of a *Pst*I site in an intron. Mendelian inheritance of the *Pst*I polymorphic bands was shown in one family.

A43. ヒト肝アルギナーゼ cDNA の単離と構造解析. **原口洋吾・滝口正樹・天谷吉宏・蛯名洋介・森　正敬**（熊本大・医・遺伝研），**川本　進**（帝京大・医・細菌），**松田一郎**（熊本大・医・小児）. **Molecular Cloning and Nucleotide Sequence of cDNA for Human Liver Arginase.** Y. HARAGUCHI, M. TAKIGUCHI, Y. AMAYA, Y. EBINA, M. MORI (Inst. Med. Genet., Kumamoto Univ., Kumamoto), S. KAWAMOTO (Dept. Bact., Teikyo Univ., Tokyo) and I. MATSUDA (Dept. Pediatr., Kumamoto Univ., Kumamoto)

アルギナーゼは尿素サイクルの最後の反応を触媒する酵素で，主に肝臓に存在し，約 3.5 万のサブユニット 3～4 個より成る．本酵素が先天的に欠乏するとアルギニン血症をきたす．川本らはすでにラット肝アルギナーゼ cDNA をクローン化し，塩基配列を決定した．今回，ラット酵素の cDNA をプローブとして，ヒト肝アルギナーゼ cDNA のクローニングを行った．ヒト肝 oligo d(T) primed cDNA および random primer cDNA の λgt 11 ライブラリーをスクリーニングし，それぞれ 4 個の陽性クローンを単離した．大腸菌中で発現させ，酵素活性を検出することによりヒト肝アルギナーゼ cDNA と同定した．ジデオキシ法により二重鎖プラスミドを直接鋳型に用いて塩基配列を決定したところ，5′ 非翻訳領域が 56 bp，蛋白翻訳領域が 966 bp (322 アミノ酸)，3′ 非翻訳領域が 423 bp であった．分子量は 34,732 と推定された．ヒト肝アルギナーゼは，ラット肝および酵母のアルギナーゼのアミノ酸配列とそれぞれ 87，41% の相同性を示し，同じ起源であることが示唆された．また，剖検ヒト肝の全 RNA を用いた RNA ブロットによりヒト肝アルギナーゼ mRNA は約 1.6 kb と測定された．今回単離されたすべての cDNA について塩基配列を比較したところ，5 個所において塩基配列の不一致が認められ，すべてアミノ酸の変換を伴っていた．塩基配列多型および複数遺伝子座の存在の可能性が考えられる．

A44. Isolation of the Human Ornithine Transcarbamylase (OTC) Gene and Identification of Restriction Fragment Length Polymorphisms. **Akira HATA,[1,3] Teruhisa TSUZUKI,[1] Kazunori SHIMADA,[1] Masataka MORI[2] and Ichiro MATSUDA[3]** ([1]Dept. Biochem., [2]Inst. Med. Genet., [3]Dept. Pediatr., Kumamoto Univ., Kumamoto)

We isolated over 20 phage clones carrying the OTC gene from two independently constructed human genomic DNA libraries. These clones, classified into 12 different groups, spanned more than 100 kilobase pairs region of the human genomic DNA. Restriction mapping and Southern blot analysis demonstrated that two of the clones cover the 5′- and 3′-end region of the OTC gene, respectively. We sequenced the 5′-end region and found that it covered 665 base pairs of the 5′-flanking region, the complete first exon and a part of the first intron (150 base pairs). In the 5′-flanking region, there were two pairs of putative CAAT and TATA boxes and one enhancer core-like sequence, GTGGAAAG. The first exon contained a coding region for most of the OTC presequence, *i.e.* 26 out of 32 amino acid residues of the presequence, including initiation methionine. Sequence analysis of the 3′-end region revealed the existance of two polyadenylation signallike se-

quences. RFLP analysis using the probes derived from the cloned OTC gene are in progress. Using 5′-end region as a probe, approximately 35% of women are heterozygous for an RFLP characterized by polymorphic bands at 2.0 and 1.1 kb observed after digestion with *Msp*I.

A45. Molecular Cloning of cDNAs for Human Liver Microsomal NADH-Cytochrome b5 Reductase. **Yasushi NAITO,[1] Eisuke YOKOTA,[1] Yoshiyuki HINO,[1] Shuhei ZENNO,[2] Yoshiyuki SAKAKI[2]** ([1]1st Dept. Intern. Med., [2]Res. Lab. Genet. Inform., Kyushu Univ., Fukuoka), **Toshitsugu YUBISUI** (Dept. Biochem., Med. Coll. Oita, Oita) **and Takashi IMAMURA** (Dept. Hum. Genet., Natl. Inst. Genet., Mishima)

Hereditary methemoglobinemia is known to be caused by two types of NADH-cytochrome b5 reductase (Cb5R) deficiency, the erythrocytic type and the generalized type in which Cb5R deficiency is demonstrated not only in red blood cells but also in cells of various other tissues. In erythrocytes Cb5R is a hydrophilic cytoplasmic enzyme and in other tissues it is present as a microsomal membrane binding protein. As the first step for characterization of these two forms of Cb5R and the enzyme deficiency, we screened for cDNAs coding for the liver microsomal Cb5R from a human liver cDNA library using an antibody against the human erythrocytic Cb5R. The nucleotide sequence of the longest cDNA fragment (1,800 base pairs) that was determined contained most of the coding region. The amino acid sequence of the liver microsomal Cb5R deduced from the nucleotide sequence was identical with that of the erythrocytic Cb5R in the 266 residues that constituted the sequence from the 10th residue to the C-terminus. Southern blot analysis of the human genomic DNA using the cDNA fragment as a probe indicated that the Cb5R gene is a single copy per haploid genome. By a blot hybridization analysis of RNAs from the human liver, the bone marrow and the K562 cells, a single band of 2.0 kilobase length was detected by this probe. These data suggest that the two forms of human Cb5R are the results of a posttranslational processing. Southern blot analysis of the genomic DNAs from 3 members of a family with hereditary methemoglobinemia of the erythrocytic Cb5R deficiency revealed that there is no visible deletion in the patient's Cb5R gene region.

A46. 色素性乾皮症A群の遺伝子クローニングに関する研究. **田中亀代次・内田 暁・岡田善雄** (阪大・細胞工学センター). **An Attempt to Isolate the Group A Xeroderma Pigmentosum Gene by DNA Transfection Procedures.** K. TANAKA, T. UCHIDA and Y. OKADA (Inst. Mol. Cell. Biol., Osaka Univ., Osaka)

色素性乾皮症 (XP) A群細胞に, pSV_2gpt とマウスゲノム DNA をコトランスフェクションし, マイコフェノール酸 (MPA) 抵抗性 XP 細胞の約 16 万コロニーより, 紫外線 (UV) 抵抗性クローン 2

つを得た．次に，これらUV抵抗性XP細胞のゲノムDNAとpSV$_2$gptを，再びA群XP細胞にコトランスフェクションし，MPA抵抗性XP細胞50万コロニーより，1つUV抵抗性XP細胞を得た(XRII130)．XRII130にはマウス遺伝子が取捨選択されて存在することが確かめられた．XRII130 DNAを*Bam*HIで切断して作ったファージライブラリーより，XRII130に含まれるマウス遺伝子断片をクローニングした．このクローニングしたマウス遺伝子をプローブにして，XRII130の*Eco*RI部分切断コスミドライブラリーより，XP細胞のDNA修復能を回復させる遺伝子を検索中である．

A47. Molecular Genetic Study of 21-Hydroxylase Deficiency: Gene Conversion Causes the Disease. Fumiki HARADA, Kazutaka URABE, Tomohisa IWANAGA, Akinori KIMURA and Takehiko SASAZUKI (Dept. Genet., Med. Inst. Bioregul., Kyushu Univ., Fukuoka)

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21-OH) deficiency is a monogenic autosomal recessive trait closely linked to HLA. Two genes, 21-OH A and 21-OH B, are localized next to C4A and C4B, respectively in the class III region of HLA. The 21-OH B is functional, whereas the 21-OH A is a pseudogene. We performed Southern blot analysis of the genomic DNA from the Japanese patients with CAH using a 21-OH cDNA (PC21/3C) probe. This analysis revealed that the 3.7 kb *Taq*I fragment and 1.7 kb *Pvu*II fragment which correspond to the 21-OH B were absent in about 30% of the affected haplotypes. However, it was demonstrated that the 10.5 kb *Bgl*II fragment corresponding to the 21-OH B was conserved on the affected haplotypes, suggesting that the absence of both the 3.7 kb *Taq*I fragment and the 1.7 kb *Pvu*II fragment is not due to a deletion of 21-OH B, but due to conversion of 21-OH B into nonfunctional 21-OH A. To obtain direct evidence for the gene conversion, we constructed a genomic library from a patient homozygous by descent for HLA-A26, B39, C4A3, C4B1, DR4 and isolated genomic DNA clones containing 21-OH A or 21-OH B. Partial nucleotide sequence analysis indicated that the 21-OH B from this patient was a pseudogene and identical to the 21-OH A gene. These data suggested that the gene conversion between these two genes would occur to cause the disease, and this mechanism might account in part for a predominant cause of CAH.

A48. Identification of a cDNA Clone for Human Prolidase. Fumio ENDO, Kunihiko MOTOHARA, Akira HATA, Yasuhiro INDO and Ichiro MATSUDA (Dept. Pediatr., Kumamoto Univ. Med. Sch., Kumamoto)

Prolidase is an ubiquitous peptidase which cleaves carboxy-terminal proline from di- or tripeptides. In humans, deficiency of prolidase results in an autosomal recessive disorder characterized by skin ulcer, mental retardation and massive imidodipeptiduria. We

have isolated prolidase from human liver and erythrocytes. The prolidase consists of two identical subunits of Mr=56,000. Using monoclonal and polyclonal antibodies directed against the enzyme, it is demonstrated that the subunit protein of prolidase is absent in a patient of prolidase deficiency. A cDNA clone for the subunit protein of prolidase has been isolated from a human liver cDNA expression library in λgt11 using antibody selection. By selective antibody elution from nitrocellulose filters containing the fusion protein, it is found that the IgG absorbed to the fusion protein reacts with the affinity purified prolidase. The relative molecular mass of the hybrid protein, which is expressed in *E. coli* Y1089, is estimated to be 160,000.

A49. Molecular Analysis of Red Cell Adenosine Deaminase Overproduction Associated with Hereditary Hemolytic Anemia. Hitoshi KANNO, Kenzaburo TANI, Hisaichi FUJII and Shiro MIWA (Dept. Pathol. Pharm., Inst. Med. Sci., Univ. Tokyo, Tokyo)

Hereditary hemolytic anemia with increased red cell adenosine deaminase (ADA) activity and decreased ATP concentration was first reported by Valentine *et al.* and we discovered the second family. In the second case, we found no abnormality in the biochemical, catalytic properties or immunological reactivity of purified enzyme of the patient. The rate of ADA synthesis in BFU-E colony cells cultured from the patient's bone marrow cells was 11-fold greater than normal. Recently, we discovered the fourth case. Western blotting of partially purified ADA from red cells revealed an increased amount of enzyme molecule in the patient's red cell. We investigated the molecular mechanism of the disease by using ADA cDNA (kindly provided from Dr. Orkin). No gene amplification or gene rearrangement was found by Southern blot analysis and no increase of ADA mRNA in the reticulocyte RNA was shown by dot blot analysis. These data suggest that the translational efficiency of ADA mRNA is elevated in the red cell precursors of the patient. At the next step, we constructed the genomic DNA library from the spleen cells of the patient and cloned the 5′-end DNA fragment of the ADA gene. To date, we have not been able to find any mutation from the putative cap site to the first intron of the gene compared with published data by Varelio *et al.*, except for the inverted sequences at −22 and −23 from the ATG as already pointed out by Bonthron *et al.* Because the disease is inherited as an autosomal dominant trait, we must sequence several clones to eliminate the possibility that the abnormal gene exists in the other homologous chromosome. It is also possible that the 3′ non-coding sequence contributes to the disorder. We, therefore, are preparing to clone the entire ADA gene of the patient.

A50. DNA probe (St14) を用いた血友病 A の保因者診断：予報. **鈴木信寛・長尾　大**（神奈川こども医療センター・血液），**中堀　豊・山田正夫・中込弥男**（国立小児医療研究センター・先天異常研究部）. **Carrier Detection in Hemophilia A with A DNA Prove (St14).** Nobuhiro SUZUKI, Takeshi NAGAO (Dept. Hematol., Kanagawa Child. Med. Cent., Yokohama), Yutaka NAKAHORI, Masao YAMADA and Yasuo NAKAGOME (Dept. Congen. Abnorm. Res., Natl. Child. Med. Res. Cent., Tokyo)

プローブ St14 は，白色人種において血友病 A の保因者診断にきわめて有用な extragenic なプローブとされている．そこでわれわれもプローブ St14 を用いて血友病 A の保因者診断を行うべく，まず正常日本人の RFLP について検討した．対象と方法：正常日本人 59 人（男性 24 人，女性 35 人）の白血球より DNA を抽出し *Taq*I で切断し，Southern-hybridize を行い RFLP を検討した．結果：1 本の X 染色体において constant band は 3.8, 2.2, 1.7 kb に 3 本認められたが，このほかに白色人種で constant band とされる 3.65 kb の band は検出されなかった．また白色人種で同様に constant band とされている 5.5 kb の band をもち，他に 1 本の variable band が見られる白色人種と同様の RFLP を示したものは 60% にしかすぎなかった．また 5.5 kb の band がなかったものでは，他に 2 本の variable band が検出された．これより日本人では 5.5 kb の band は constant band ではなく variable band と考えられ，つまり日本人では constant band 3 本のほかに，5.5 kb の band も含めた 2 本の variable band をもつものと考えられ，白色人種に比べより複雑な RFLP を示していた．また今回，女性において heterozygous な band pattern を示したものは約 63% に認められた．以上より，プローブ St14 は，日本人においても血友病 A の早期出生前診断や保因者診断にきわめて有用なプローブと考えられた．今後，凝固学的検査と併用して保因者診断を行っていく予定である．

A51. Characterization of the Y-Chromosome Specific Repeated DNA (DYZ1) Locus. **Yutaka NAKAHORI, Masao YAMADA and Yasuo NAKAGOME** (Dept. Congen. Abnorm. Res., Natl. Child. Med. Res. Cent., Tokyo)

We have determined the complete nucleotide sequence of a 3,564 bp *Eco*RI fragment which represents a major component of the human Y-chromosome specific repeated DNA family (DYZ1). Sequencing result showed a tandem array of pentanucleotides after five nucleotides were inserted or deleted at four positions. 229 out of the 713 pentanucleotides were TTCCA, and 297 were its single-base substituents. Southern hybridization analyses of male genomic DNAs showed that several endonuclease cleavage sites were located at intervals of 3.56 kb in the DYZ1 locus. This indicates that the DYZ1 repeated DNA family evolved and expanded by unequal crossovers which occurred at distances of 3.56 kb. As there is a uniformly distributed array of pentanucleotides on this locus, it is not a sequence homology that determines the distance of unequal crossovers. A higher order of chromatin structure may be involved in the determination of distance in unequal crossovers.

A52. A Novel Family of Variable Region Genes of the Human Immunoglobulin Heavy Chain. **Fumihiko MATSUDA,[1] Kwang Ho LEE,[1] Tatsuo KINASHI,[1] Mieko KODAIRA[2] and Tasuku HONJI[1]** ([1]Dept. Med. Chem., Kyoto Univ., Kyoto; [2]RERF, Hiroshima)

The human immunoglobulin heavy chain variable region (V_H) genes have been classified into three different families according to their nucleotide sequence homology. The $V_{71\text{-}2}$ gene, which is only 65% homologous to those of $V_{H\text{-}II}$ family, was considered to be a member of a subset of the $V_{H\text{-}II}$ family. Further characterization allowed us to find a new family ($V_{H\text{-}IV}$) of human V_H segments. *Methods:* The $V_{71\text{-}2}$ probe, which was tentatively classified into the $V_{H\text{-}II}$ family, detected 8–10 hybridization bands distinct from the $V_{H\text{-}II}$ family. Using this probe, we identified five V_H segments in cosmid clones from the human genomic libraries and one V_H segment in newly isolated phage clones, and then determined their nucleotide sequences. *Results:* 1) The patterns of the hybridized bands of these segments were identical to that obtained using the $V_{71\text{-}2}$ probe and distinct from that of the $V_{H\text{-}II}$ family. 2) Comparison of nucleotide sequence showed that the six new V_H sequences were more than 90% homologous with each other and less than 65% homologous to any other V_H family gene. 3) These were more than 78% homologous to the mouse $V_{h36\text{-}60}$ family genes. 4) All of these were functional genes. Therefore we designated the new V_H segments which were identified in this study as the $V_{H\text{-}IV}$ family.

A53. Studies on Factors Involved in Accurate Initiation of Human β-Globin Gene Transcription. **Yukio YASUKOCHI, Shigetaka KITAJIMA** (Dept. Hum. Genet., Tokyo Med. Dent. Univ., Tokyo) **and Sherman M. WEISSMAN** (Dept. Hum. Genet., Yale Univ., CT)

To isolate factors involved in accurate initiation of transcription of the human β-globin gene, HeLa cell nuclear extract was subject to two successive chromatographic steps. On an anion exchange high performance liquid chromatography (HPLC) column, three fractions were separated when linear gradient elution was employed. Each fraction was further subject to the HPLC gel filtration. From the flowthrough fraction and the fraction eluted at 0.3 M NaCl on DEAE-HPLC, two fractions were separated on the HPLC gel filtration, respectively. These five fractions were named Frs. A, B, C, D and E, and had activity in 52,000, 540,000, 285,000, 700,000 and 185,000 molecular weight regions, respectively, indicating that they were distinct. These fractions could reconstitute the activity toward the faithful transcription when assayed with partially purified calf thymus RNA polymerase II and stimulatory factor.

A54. Characteristics of β^A Chromosome Haplotypes in Japanese. **Koji SHIMIZU** (Inst. Develop. Res., Aichi Pref. Colony, Kasugai)

DNA polymorphism patterns linked to the β^A-globin gene were analyzed in healthy Japanese using four different restriction endonucleases. The chromosomes with the β^A-globin gene were mapped through an evaluation of the presence of seven different restriction sites (*Hin*cII 5′ to ε; *Hin*dIII in $^G\gamma$ and $^A\gamma$; *Hin*cII in, and 3′ to $\psi\beta_1$; *Ava*II in β; *Bam*HI 3′ to β). Among 36 chromosomes analyzed, 20 chromosomes had a haplotype of $+---$ $---+$. All Japanese with the $^A\gamma^T$-globin gene had a subhaplotype of $-+++-+$ 5′ to the δ-globin gene. It was expected that the presence of the $^A\gamma^T$-globin gene in Japanese may be deduced from subhaplotypes 5′ to the δ-globin gene. It may also be deduced that the framework 1, 2, and 3 of the β-globin gene in Japanese comprised 21, 17, and 62%, respectively. No characteristic haplotypes were found in β^A chromosomes from juvenile (JCML) and adult chronic myelogeneous leukemia (ACML) patients.

A55. βサラセミアをきたすエキソン内の4塩基欠失は，過去独立に数回生じたらしい． **服巻保幸[1]・松永栄治[2]**（九大・[1]遺伝情報，[2]小児），**多賀俊明**（岐阜大・小児），**瀧原義宏・中村崇規**（九大・生化）． **Multiple Origins of the β-Thalassemia Gene with a Four-Nucleotide Deletion in Its Second Exon.** Y. FUKUMAKI,[1] E. MATSUNAGA[2] ([1]Res. Lab. Genet. Inform., [2]Dept. Pediatr., Kyushu Univ., Fukuoka), T. TAGA (Dept. Pediatr., Gifu Univ., Gifu), Y. TAKIHARA and T. NAKAMURA (Dept. Biochem., Kyushu Univ., Fukuoka)

われわれはこの数年，日本をふくめアジアにおける遺伝性溶血性貧血症サラセミアの病因解析を行っている．先に台湾のβサラセミアにおいて，βグロビン遺伝子のコドン41, 42に生じた4塩基欠失によるフレームシフト変異を明らかにした．その後の解析で，同一の変異がタイ，マレーシアにおいても認められた．そこでこの変異の起源を探るため，βグロビン遺伝子群における7個所の制限酵素切断部位の多型（ハプロタイプ）およびβグロビン遺伝子内における5個所の塩基配列の多型（フレームワーク）を決定し，次の結果を得た．1) 台湾の患者では，ハプロタイプIとVIIがみられ，フレームワークはそれぞれ1と3_{Asian}であった．2) タイにおいてはVIIと3_{Asian}であった．3) マレーシアではIと1であった．最近，Kazazianらはインド人に同一の変異を認め，この変異がIIIとVaの2種のハプロタイプとフレームワーク2をともなっていることを報告している．VII, 3_{Asian}とI, 1が，さらにVa, 2およびIII, 2とVII, 3_{Asian}が互いに不等交叉で生じる確率は，いずれも245～247塩基，および205～207塩基内での二重交叉を必要とするためきわめて低いこと，さらに4塩基欠失の起こり方として，TTCT, TCTT, CTTTの三つの可能性があることなどから，この変異は過去少なくとも2回独立に生じたものと考えられた．

A56. High Implantation Rate of Transcervical Egg-Transfer Using Mice and a Proposal for Adopting This Technique in the Egg-Transfer of Transgenic Mice.
Yoshiyasu HOMBO (Kanazawa Natl. Hosp., Kanazawa), **Kazuko HAYASHI and Zenichi OGITA** (Oriental Med. Inst., Toyama Med. Pharmacol. Coll., Toyama)

In most experiments with egg-transfer in mice, operational approaches are adopted as the usual methods. So egg-transfer through the cervical canal is uncommon in this animal. If such a method like this can be established, we will be able to save time and effort because of its non-operational approach. In this experiment, the egg-transfer through the cervical canal is performed using mice. We get early blastocysts from the uterine cavity of BDFl mice by the flushing method. (It is 8-weeks old and injected with PMS and HCG as is done in the usual method, then killed by the cervical dislocation on the third day after mating with BDFl male.) In the next step, these blastocysts are picked up into a device made of lumbar puncture needles used in human beings (26 gage, Hakko-company, Japan). Then these blastocysts are transferred through the cervical canal into the uterine cavity of ICR mice using the device mentioned above. (This recipient mice has natural ovulational cycles and recieves egg-transfer on the fourth day after mating with vasectomized ICR male mice.) We obtained good results: Pregnancy rate, 11/11 (100%); implantation rate, 88/129 (68%). We are trying to utilize this technique in various kinds of egg-transfer in mice including transgenic mice egg-transfer. Further experiments will be needed.

A57. ヒト血清アミロイドP成分を産生するトランスジェニックマウスの作製.
前田秀一郎[1]・山村研一[2]・若杉正司[1]・大西修二[1]・井本岳秋[2]・島田和典[1]（熊本大・医・[1]生化一，[2]遺伝研）. **Production of Transgenic Mice Expressing the Human Serum Amyloid P Component Gene.**
Shuichiro MAEDA,[1] Ken-ichi YAMAMURA,[2] Shoji WAKASUGI,[1] Shuji OHNISHI,[1] Takeaki INOMOTO[2] and Kazunori SHIMADA[1] ([1]Dept. Biochem., [2]Inst. Med. Genet., Kumamoto Univ. Med. Sch., Kumamoto)

血清アミロイドP成分 (SAP) は，種々のアミロイドーシスで沈着する異なるアミロイド沈着物に共通に存在する血清糖タンパク質で，ヒトの代表的な急性期タンパク質であるC反応性タンパク質 (CRP) と一次構造上相同性を示す．われわれは，SAPがアミロイドの形成にどのように関与するかを明らかにすることを目的に研究をはじめ，まず完全長のヒトSAP cDNAクローンならびに全SAP遺伝子を運ぶクローンを単離し，それぞれの塩基配列構造を決定した．SAP遺伝子は約1 kb大で2個のエクソンと115 bp大の1個のイントロンから成り，ヒトCRP遺伝子構造と著明な相同性を示した．次に5′上流約0.7 kb，3′下流約1.2 kbを含むヒト全SAP遺伝子約200分子をマウス受精卵に導入し，仮親の卵管に移植したところ54匹が生まれた．このうち7匹がトランスジェニックマウスで，それぞれ1〜数十コピーのSAP遺伝子をタンデムに組み込んでいた．発現の程度を調べるために，血清中のヒトSAP量をオクタロニー法で調べたところ，7匹中5匹で沈降線が認められた．

このうち3匹では対照ヒト血清の形成する沈降線よりも著明な沈降線が生じた．また，血清中のヒトSAP量と組み込まれたSAP遺伝子数とには明らかな相関が見いだされた．これらトランスジェニックマウスは，SAPとアミロイド形成との関連を解明するために役立つものと考えられる．

A58. ヒト異型プレアルブミン遺伝子 (mPA) のトランスジェニックマウスにおける発現. **山村研一[1]・若杉正司[2]・岩永知久[3]・井本岳秋[1]・前田秀一郎[2]・島田和典[2]** (熊本大・医・[1]遺伝研，[2]生化一，[3]九大・医・生防研). **Expression of Human Atypical Prealbumin Gene in Transgenic Mice.** K. YAMAMURA,[1] S. WAKASUGI,[2] T. IWANAGA,[3] T. INOMOTO,[1] S. MAEDA[2] and K. SHIMADA[2] ([1]Inst. Med. Genet., [2]Dept. Biochem., Kumamoto Univ. Med. Sch., Kumamoto; [3]Res. Lab. Genet. Inform., Kyushu Univ., Fukuoka)

家族性アミロイドポリニューロパシー (FAP) は常染色体性優性遺伝病であり，その発症機序として各組織へのmPAの沈着が考えられている．mPA遺伝子は，すでに島田らによって単離され構造解析の結果，30番目のアミノ酸のコドンのGTGがATGへ変換しているのが明らかにされている．FAPの患者は100%このmPA遺伝子を有しているので，この遺伝子を導入したトランスジェニックマウスは，FAPの疾患モデルとなることが期待される．約200分子のmPA遺伝子をマウス受精卵に導入し，生き残った受精卵を仮親の卵管に移植したところ67匹が生まれた．このうち8匹がトランスジェニックマウスであり，それぞれ1～6コピーを組み込んでいた．発現の有無を解析するために血清中のヒトPA量をELISA法により測定したところ，8匹中7匹でヒトPAを検出した．またオクタロニー法でその抗原性を検討したところ，その沈降線は棘形成を示した．これはおそらく，ヒトPAとマウスPAとが雑種の四量体を構成しているためと考えられる．mPA遺伝子発現の組織特異性については解析中である．

A59. Preliminary Study on Transfection Efficiencies: Quantitative Difference of Uptake of DNA in Various Somatic Cells Cultured *In Vitro*. **Kiyomi YAMADA** (Div. Genet., Clin. Res. Inst., Natl. Med. Cent. Hosp., Tokyo)

Cell difference in the uptake of Ca-phosphate-coprecipitated DNA *in vitro* was analyzed. The purified ^{3}H-DNA (sp. activity, about 3×10^4 cpm) used in this experiment was obtained from EBV-stimulated human lymphocytes growing in medium containing [^{3}H]thymidine. As recipient cells on transfection, the following human cells were used after short term cultures: skin fibroblast cells of adult and fetal origin, T-cell lymphocytes growing in medium containing TCGF, B-cell lymphocytes stimulated by EBV, and bone marrow cells depleting phagocytic cells. The amount of DNA uptake of these human cells was compared with that of NIH 3T3 mouse cells which are widely used as recipient cells in transfection experiments. The amount of radioactivities of the cells growing 2–5 days after transfection was measured by a liquid scintillation counter, and the incorporation rate was calculated. In the dose range from 6 to 14 μg DNA per dish with 5×10^6 cells,

the following levels of incorporation rates ($\times 10^{-3}$) were obtained: 17.7–29.2 in NIH 3T3 cells, 3.6–4.5 in bone marrow cells, 0.8–1.9 in B-cell lymphocytes, 0.5–0.7 in PHA-stimulated lymphocytes, 0.4–0.5 in adult and fetal skin fibroblasts, and 0.1–0.4 in T-cell lymphocytes. Though a low level of DNA uptake was revealed in every example of human cells when compared with NIH 3T3 cells, bone marrow cells seemed to be a relatively good candidate as recipient cells for correcting a genetic defect by DNA transfection.

B1. Size Variation of the Y Chromosome in East and Southeast Asian Populations.
Momoki HIRAI and Keiichi OMOTO (Dept. Anthropol., Univ. Tokyo, Tokyo)

It is a well-established fact that the length of the human Y chromosome represents heteromorphic nature. There have been some works which confirm the findings of Cohen *et al.* (1966), in which the long Y of the Japanese was described for the first time. The question arises as to whether this is characteristic also for the other Asian populations. In the present study, a total of 434 blood samples were collected from 10 ethnic populations of east and southeast Asia: Ainu Japanese, non-Ainu Japanese, six Philippine populations (Tagalog, Manobo and four Negrito tribal groups) and two Chinese populations (Li and Miao living on Hainan island), As a control, Caucasian samples were also examined. Twenty cells per individual were photographed and the sizes of the Y chromosome and F group chromosomes were measured. According to the results of analyses, these 11 populations were categorized roughly into the following two groups in terms of Y/F index: a long Y group (Y/F=0.991–1.037) and a short Y group (Y/F=0.898–0.937). The long Y group includes three Negrito tribes (Atta, Aeta and Batak), Tagalog, Manobo, non-Ainu Japanese, Li and Miao. The short Y group includes Mamanwa (a Negrito tribe), Ainu Japanese and Caucasians. Therefore, the Negrito is to be divided into two groups in terms of Y chromosome size, as is the case with the Japanese. C-band study confirmed that, in all groups examined, the variation in size of the Y chromosome is mostly ascribed to the variation in size of the distal heterochromatin of the Y chromosome.

B2. Sister Chromatid Exchanges in Fibroblasts from Patients with Tuberous Sclerosis.
Tatsuya TAKESHITA, Sumio IIJIMA, Makoto HIGURASHI (Dept. Health Sci., Yamanashi Med. Coll., Yamanashi) **and Masataka ARIMA** (Div. Mental Retard. Birth Defect Res., Natl. Cent. Nerv. Mental Musc. Disord., Tokyo)

Fibroblast strains were studied for baseline and mitomycin C-induced sister chromatid exchange (SCE) frequencies. Strains included three from patients with tuberous sclerosis (TS), five from normal controls, and two from patients with Fanconi's anemia. Baseline SCE frequencies in TS cells were slightly higher (11.0 ± 0.4) than those in normal controls (9.3 ± 0.9), but not significantly. TS and normal cells were treated with mitomycin C for 1 hr just prior to the 72 hr incubation with BrdUrd. Either at 5×10^{-8} M (15.5 ± 0.4 and 13.1 ± 1.3) or at 1×10^{-7} M (21.2 ± 0.4 and 16.1 ± 1.4), TS cells exhibited slightly higher SCE responses compared to normal cells. However, there were no significant differences in the net SCE induction by mitomycin C between the two groups. Likewise, there were no significant differences in the cell cycle time between TS and normal cells. Two strains derived from patients with Fanconi's anemia did not show high sensitivity to mitomycin C.

B3. Proteinaceous Nuclear Factor Specifically Corrects Defects of DNA Repair in Group C of Xeroderma Pigmentosum Cells. Masaru YAMAIZUMI, Tatsuo SUGANO, Hiroshi ASAHINA and Tsuyoshi UCHIDA (Inst. Mol. Cell. Biol., Osaka Univ., Suita)

When crude cell extract prepared from HeLa cells is microinjected into XP cells of complementation groups A, B, C, D, F and G, normal level of UDS is recovered in these cells after UV-irradiation. We call these factors in wild type cell extract as XP factor A, B . . G (XPFA, XPFB . . .). Among those XP factors, we intensively study the nature of XPFC. XPFC is released from isolated nuclei only when these nuclei are treated with high salt solution (more than 0.4 M KCl). XPFC is easily precipitated under the condition of KCl concentration less than 0.2 M, sensitive to the trypsin treatment and partially purified by cation exchange chromatography suggesting that XPFC is a basic protein. Although XPFC is very stable in a crude cell extract, it becomes labile after partial purification. When XPFC is introduced into XP-C cells, it exerts maximal activity 3–4 hr after microinjection and is active in XP-C cells at least 24 hr without detectable loss of initial activity. The molecular weight of XPFC in a native form is 400 kDa by gel filtration of Sephacryl S 300. The relationship of XPFC to other XP factors located in nuclei will be discussed.

B4. Proliferating Characteristics and Proliferating Compentating Factors of Skin Fibroblasts from Patients with Down Syndrome. Atsushi IESHIMA and Kenzo TAKESHITA (Div. Child. Neurol., Inst. Neurol. Sci., Tottori Univ. Sch. Med., Yonago)

Proliferating characteristics and serum requirements have been studied in cultured fibroblasts derived from 3 Down syndrome (DS) infants, 3 DS school children and 5 DS adults. Fibroblasts from DS and age-matched controls were cultured in 1% FCS, 10% FCS, 20% FCS and 10% Nu serum. Growth curve, saturation density (SD) and population doubling time (PDT) were compared among each age group. Fibroblasts from DS, comparing with those from normal control, showed increasing tendency of PDT and decreasing tendency of SD. Infant DS strains demonstrated increase of PDT and decrease of SD in 1% FCS, 10% FCS and 10% Nu serum, whereas, in 20% FCS, those showed normal PDT and SD. DS strains of adult and school children, however, did not show proliferating compentation with 20% FCS as shown in infant cells. There were no differences of proliferating abilities between adult DS and control strains in 10% Nu serum. The reasons that proliferating capacities of DS infant and adult strains are compensated with different serum were unknown. These compensating factors may be some growth factors.

B5. Mapping Glutathione Reductase at 8p22. Yoshiharu AOKI, Ichiro MURANO, Tsuyako EGUCHI, Masato TSUKAHARA and Tadashi KAJII (Dept. Pediatr., Yamaguchi Univ. Sch. Med., Ube)

The glutathione reductase (GSR) gene has been mapped to 8p, but its localization on 8p is yet to be determined. We studied erythrocyte GSR levels in 4 patients with 8p chromosomal abnormalities. Their GSR levels, expressed as patient/control ratios, were: 0.97 in a patient with an 8p11.21p11.23 deletion, reduced at 0.58 in a patient with an 8p 11.12p22 deletion, 1.10 in one with an 8p11.23p22 inverted duplication, and 1.12 in one with a (8;X)(p21;q22.3) translocation. In the patient with the 8:X translocation, the normal X was preferentially inactivated. It was deduced from these findings that the GSR gene is at 8p22.

B6. Regional Assignment of the Gene for Diphtheria Toxin Sensitivity Using Subchromosomal Fragments in Microcell Hybrids. Yasufumi KANEDA, Helene HAYES, Tsuyoshi UCHIDA and Yoshio OKADA (Inst. Mol. Cell. Biol., Osaka Univ., Osaka)

Human × mouse microcell hybrids resistant to G418 were constructed between mouse hepatoma cells and human × mouse whole cell hybrids containing only intact human chromosome 5 and 22 having integrated the *neo*^{R} gene. Among these, one microcell hybrid BG15 produced four subclones BG15-4, BG15-6, BG15-7 nad BG15-9 which contained variously sized complements of human chromosome 5. BG15-6 contained an intact human chromosome 5, BG15-7 a deleted human chromosome 5 (5p*ter*-q22) and BG15-4 and BG15-9 a translocation between parts of human chromosome 5 (p*ter*-q*ter*? and p*ter*-q23, respectively) and mouse chromosome. Southern blot analysis showed that human DHFR gene was present in all four subclones, whereas human homolog of v-*fms* gene was present in BG15-4 and 15-6, but absent in BG15-7 and 15-9. BG15-4, 15-6 and 15-9 were sensitive to diphtheria toxin, and only BG15-7 was resistant to the toxin. We used these microcell hybrids to further restrict the regional location of the gene for diphtheria toxin sensitivity to the q23 region of human chromosome 5.

B7. Interleukin-1 Gene Locus was Assigned to Human Chromosome 2q13-2q21 by *In Situ* Hybridization. Hiroshi NAKAI, Keiya TADA (Dept. Pediatr., Tohoku Univ., Sendai), **M. G. BYERS, R. EDDY, T. B. SHOWS** (Dept. Hum. Genet., Roswell Park Memorial Inst., Buffalo, NY) **and A. C. WEBBS** (Dept. Biol. Sci., Wellesley Coll., Wellesley, MA)

A complementary DNA (cDNA) probe of an interleukin-1 (IL-1) was used to map its gene locus on a human chromosome. Interleukin-1 is one of intercellular mediators

at acute phase infectious responce of a host. The cDNA was cloned with mRNA of *E. coli* endotoxin-stimulated monocytes, using an Okayama-Berg's expression vector system. The cloned IL-1 gene, 1,496 base pair DNA, codes for 269 amino acid residues for human IL-1 precurcer protein, which become 17–18 kDa and pI 7 form of IL-1 after processing. The vector (pcDhIL1) also expressed biologically active IL-1 protein in cultured simian kidney cells (COB). The gene locus was assigned to chromosome 2 by Southern blot analysis between the radio-labeled IL-1 probe and *Bgl*II restriction endonuclease-digested genomic DNAs of 30 human-mouse hybrid cells. Separately, leaving this result unknown, *in situ* hybridization-group of our member mapped the prove, following to a technique of Zabel *et al.* (1983). Normal lymphocytes were stimulated by PHA and synchronized by addition of BrdU and thymidine. Prometaphase G-bands were obtained, staining with Hoechst 33258, UV exposure and Giemsa solution. Three hundreds and ninety-five cells were analyzed for total 1,024 silver grains on or attached to chromosomes by autoradiography. Seventy-one grains (33.8%) located in the specific region 2q13-2q21 among 210 grains (20% of the total 1,024 grains) which were observed on or by chromosome 2. This 2q13-2q21 region are close to 2 fragile sites. No reported tumors had break points on this region. If such proliferative disorders, however, were found, this mapping IL-1 will contribute to reveal a fine mechanism of the tumorigenesis.

B8. Porphobilinogen Deaminase (PBGD) の遺伝子量効果に関する研究. **難波弘志・楢原幸二・木村俊介・木本 浩**（岡山大・医・小児），**笠井良造・村上政江**（旭川児童院），**小谷信行**（三菱水島病院・小児）. **Gene Dosage Study of Porphobilinogen Deaminase (PBGD).** Hiroshi NAMBA, Kouji NARAHARA, Shunsuke KIMURA, Hiroshi KIMOTO (Dept. Pediatr., Okayama Univ., Okayama), Ryozo KASAI, Masae MURAKAMI (Asahigawa Jidoin Child. Hosp., Okayama) and Nobuyuki KOTANI (Dept. Pediatr., Mitsubishi Mizushima Hosp., Kurashiki)

PBGD はウロポルフィリンの合成に関与する酵素で，その欠損は急性間歇性ポルフィリン症を惹起する．体細胞雑種形成法により，PBGD 座位は 11q23→qter に決定されている．11q 遠位部異常の 2 症例で，PBGS の遺伝子量効果を研究した．症例 1 は 3 歳の女児で，精神遅滞，両眼離開および耳介奇形が認められた．核型は 46,XX,del (11) (pter→ q24.2::) *de novo* であった．症例 2 は生後 1 カ月の男児．臨床症状は 11q トリソミー症候群に類似していた．核型は 46,XY,−14,+der(14), t(11; 14)(q22.2; p11) *de novo* であった．赤血球 PBGD 活性を，Sassa ら (1974) の方法を改変して測定した．赤血球 PBGD 活性は，臍帯血では成人の 2 倍の値を示し，出生後より急激に下降し 1 歳で成人と同様の値を示した．赤血球 PBGD 活性の正常値は，生後 1 カ月，4 カ月および成人でそれぞれ 155.9±26.2, 141.7±21.9 および 101.5±19.8 nmol/hr/gHb であった．症例 1 の活性値は 108.1 nmol/hr/gHb と正常で，一方，症例 2 の活性値は生後 1 カ月および 4 カ月でそれぞれ 193.0 および 196.6 nmol/hr/gHb と対照に比し高値であり，PBGS に 1.5 倍の遺伝子量効果が推測された．以上の結果から，PBGD の遺伝子座位は 11q23.1→q24.2 の間に存在すると考えられた．発達により活性値が著

明に変動する酵素の遺伝子量効果の研究では，対照との慎重な比較が必要であろう．

B9. Selection of Human Cells Having Two Different Types of Mutations in Single Cells (Genetic/Artificial Mutants). Naoyuki KAMATANI, Shoko KUROSHIMA, Kusuki NISHIOKA and Kiyonobu MIKANAGI (Inst. Rheum., Tokyo Women's Med. Coll., Tokyo)

We have established and characterized B cell lines from patients and family members of various types of adenine phosphoribosyltransferase (APRT) deficiencies. These patients and family members have three different APRT alleles (*APRT*1*, *APRT*QO* and *APRT*J*) in various combinations. From 5 heterozygous cell lines (genotype *APRT*1/APRT*QO* and *APRT*1/APRT*J*), we selected 48 clones that are resistant to 2,6-diaminopurine in order to select double mutational clones. APRT activities of the clones from a complete type heterozygote were very low (mean=0.04 nmol/min/mg protein), while those of the clones from 4 Japanese type heterozygous cell lines were approximately two magnitude as high as the former cell lines. Kinetic studies on 2 of the mutants from 2 Japanese type heterozygous cell lines have shown that affinity to a substrate 5-phosphosphoribosyl-1-pyrophosphate was reduced, indicating that APRT in those clones reflected the characteristics of the Japanese type enzyme. The data presented here indicate that clones we obtained are genetic/artificial mutants each having a genetic mutation in a single allele (*APRT*J* or *APRT*QO*) and an artificially produced mutation in the other previously functional allele (*APRT*1*). The present procedure provided the only diagnostic method for Japanese type APRT heterozygotes.

B10. N-*Myc* Oncogene Was Amplified in a Rhabdomyosarcoma. Hidemitsu KUROSAWA,[1] Kounosuke MITANI,[1] Yasuhide HAYASHI,[2] Akio KOMATSU,[2] Keiko YAMAMOTO,[2] Masao YAMADA[1] and Yasuo NAKAGOME[1] ([1]Natl. Child. Med. Cent., Tokyo; [2]Saitama Child. Med. Cent., Saitama)

Detection of possible amplification of oncogenes in various tumors in children were attempted. DNA was obtained from surgically removed tumors in children, 109 cases of more than 20 different kinds. Each tumor was analyzed by the Southern blot hybridization using up to 15 different oncogene probes. Amplification of N-*myc* oncogene was detected in one (MM227) out of 6 cases of rhabdomyosarcoma in addition to 4 cases of neuroblastoma in advanced stages. N-*myc* has been accepted to be specific to neurogenic tumors such as neuroblastoma and retinoblastoma. The present result indicates that N-*myc* amplification is not limited to neurogenic tumors. Further analysis of MM-227 DNA reveals that a portion of amplified DNA was rearranged in N-*myc* promoter region.

B11. Genetic Analysis of Familial Polyposis Coli (II): Amplification of c-*Myc* Oncogene in Adenocarcinoma from the Patient with FPC. **Kenji SUGIO and Takehiko SASAZUKI** (Dept. Genet., Med. Inst. Bioregul., Kyushu Univ., Fukuoka)

Familial polyposis coli (FPC) inherited as an autosomal dominant trait is characterized by numerous colorectal adenomas, and carcinoma induced from these adenomas at high frequency. In this study, DNA analysis was performed in 13 normal colonic mucosas, 14 polyps, 19 primary adenocarcinomas, 1 metastatic lung cancer, and 2 metastatic liver cancers of the 15 patients with FPC. Southern blot analysis showed that 1 primary adenocarcinoma (KU-PL14C) had about 16-fold amplification of c-*myc* gene compared with normal colonic mucosa, but no rearrangement was detected. The expression of c-*myc* gene of both its adenocarcinoma and tumor transplanted to nude mouse from its adenocarcinoma, using Northern blot analysis of total RNA, was markedly elevated compared with normal colonic mucosa. Other 3 cases also had elevated expression of c-*myc* gene in polyp and adenocarcinoma. Elevated expression of c-*myc* gene was demonstrated in the premalignant and malignant state of patients with FPC, and amplification of c-*myc* gene may be one of the factors involved in carcinogenesis in the patient with FPC.

B12. Spontaneous Chromosome Aberrations Clustering to Band 3q21 in Cultured Leukemic Bone Marrow Cells: A New Fragile Site on Human Chromosome? **Syuiti ABE and Motomichi SASAKI** (Chromosome Res. Unit., Fac. Sci., Hokkaido Univ., Sapporo)

A 54-year-old man with acute myelomonocytic leukemia was found to have spontaneous chromosome aberrations including chromatid gaps and breaks in leukemic bone marrow cells with trisomy 8, prior to any treatment for the disease. Chromosome aberrations were observed in 22% of leukemic cells (43/200) cultured for 24 hr. Q-banding analysis unequivocally revealed a cluster of such aberrations to the long arm of chromosome No. 3, *i.e.* band 2q21 in 14% of cells analyzed (28/200) or 65% of cells with aberrations (28/43). The frequency of cells with aberrations including those occurred at 3q21 decreased with time and dropped to 1% in bone marrow cultured for 96 hr. The negligible frequency of concurrent karyotypically normal cells seen at each sampling occasion had no chromosome aberrations. Analysis of chromosome aberrations in PHA-stimulated lymphocytes and fibroblasts of the patient after exposure to various culture conditions is now ongoing. The chromosome fragility at band 3q21 has not yet been reported. The present findings are discussed in relation to the known chromosome fragile sites and breakpoints of specific chromosome rearrangements occurring in human cancer and leukemia.

B13. Induction of Differentiation of Ph¹-Positive and Ph¹-Negative B Lymphoblastoid Cell Lines Established from a Patient with Chronic Myelogenous Leukemia (CML) by Treatment with a Tumor Promoter, 12-*O*-Tetradecanoyl-Phorbol-13-Acetate (TPA). **Toshiyuki YAMADA and Motomichi SASAKI** (Chromosome Res. Unit., Fac. Sci., Hokkaido Univ., Sapporo)

It is well documented that CML is a clonal disorder arising from Ph¹-positive pluripotent hematopoietic stem cells capable of differentiation into granulocytes, erythrocytes, platelets, monocytes/macrophages and lymphocytes. It seems worthy to examine whether Ph¹-positive cells perform their proper functions in each of the cell lineages mentioned above. We have previously established Ph¹-positive (PB-1049) and Ph¹-negative (LN-1049) B lymphoblastoid cell lines from a patient with CML, and a Ph¹-positive cell line (PB-1049-T) from a tumor nodule formed by inoculation of PB-1049 cells in nude mice (Yamada *et al.*, 1985. *Jpn. J. Cancer Res. (Gann)*, **76**: 365–373). In this report, by adding TPA (1.6, 16, 160 nM) in the culture medium, an attempt was made to induce differentiation in these cell lines. The major changes thus far observed were consistent with differentiation towards plasma cells, showing enhanced clustering of floating cells, reduced DNA synthesis, increase of the cytoplasm/nucleus ratio, appearance of numerous rough endoplasmic reticulum in cytoplasm, and increase of immunoglobulin concentration estimated by ELISA in the supernatant of PB-1049 and PB-1049-T, but not LN-1049, cultures. These data indicate that the lymphoblastoid cells originated from the Ph¹-positive stem cell of CML have an ability to differentiate into functional plasma cells.

B14. Changes of α(1→3)-L-Fucosyltransferase Activities in Human Saliva Induced by Malignancy. **Shin YAZAWA, Ken FURUKAWA** (Dept. Legal Med., Sch. Med. Gunma Univ., Maebashi) **and Hideaki IZAWA** (Gunma Cancer Cent., Ohta)

GDP-Fucose:*N*-acetylglucosaminide and glucoside α(1→3)-L-fucosyltransferase has received much attention recently because of the presence and accumulation of Galβ(1→4)-[Fucα(1→3)]GlcNAc linkage in tumor associated antigens. This enzyme was found to be present in human saliva (Yazawa and Furukawa, 1980) and two different α(1→3)-L-fucosyltransferases have also been reported in saliva corresponding to the Lewis blood group, *i.e.*, *Le* gene dependent and independent α(1→3)-L-fucosyltransferase (Johnson *et al.*, 1981). The level of the enzyme was significantly higher in saliva of patients with epithelial ovarian cancer (Yazawa *et al.*, 1986). GDP-Fuc:GlcNac α(1→3)-L-fucosyltransferase was found elevated in salivas from patients known to have ovary, kidney, rectum, breast and lingua cancer, respectively, irrespective of their ABH and Lewis blood group phenotypes. GDP-Fuc:Glc α(1→3)-L-fucosyltransferase was also elevated in

salivas from both Lewis positive and negative patients, although the enzyme activity was very low or absent in salivas from Lewis negative healthy controls. Chromatofocusing profile of saliva from Lewis negative patient (pH 7–10.5) showed the presence of α(1→3)-L-fucosyltransferase eluted at pH 8.7 which was unable to be detected in saliva from Lewis negative healthy controls. The presence of the *Le* gene dependent α(1→3)-L-fucosyltransferase in saliva of Lewis negative patients with various cancers may suggest an unusual fucosyltransferase being derepressed during oncogenic process.

B15. Cytogenetic Effects of an Alkylating Agent, MMS, on Human Sperm Chromosomes. **Yujiro KAMIGUCHI and Kazuya MIKAMO** (Dept. Biol. Sci., Asahikawa Med. Coll., Asahikawa)

Using our interspecific *in vitro* fertilization system between human spermatozoa and zona-free hamster ova (Kamiguchi and Mikamo, *Am. J. Hum. Genet.*, 1986), we studied cytogenetic effects of an alkylating agent, methyl methanesulfonate (MMS), on human sperm chromosomes. Semen samples from 3 donors were treated with BWW medium containing various concentrations of MMS (0, 5, 10, 25, 50 μg/ml) for 4 hr. Total numbers of 1,552 and 1,543 spermatozoa were karyotyped in the control and the MMS-treated groups, respectively. Our results were as follows: 1) Incidences of spermatozoa with structural chromosome aberrations were 14.6% (controls), 22.8% (5 μg/ml), 29.5% (10 μg/ml), 53.5% (25 μg/ml) and 81.7% (50 μg/ml), showing a linear increase of affected spermatozoa with increase of MMS dosage. On the other hand, chromosome aberrations per sperm increased exponentially. 2) The most predominant type of structural chromosome aberrations was chromosome-type break (1.12/sperm in the highest dose group) which was followed by the chromatid-type exchange (0.58/sperm), the chromatid-type break (0.21/sperm) and the chromosome-type exchange (0.06/sperm). 3) Dose-dependent increase was linear regarding the breakage type of aberrations, whereas it was quadratic regarding the exchange type of aberrations. 4) More than 90% of the exchange type of aberrations were of chromatid type, suggesting that some of MMS-induced DNA damages in spermatozoa were repaired after fertilization mainly by postreplication repair system of the ovum. These results were discussed in relation to the previous cytogenetic studies on X-irradiated human spermatozoa and MMS-treated mouse spermatozoa.

B16. Chromosome Aberrations of Human Lymphocytes after γ-Irradiation Combined with MMC and Sister Chromatid Exchanges (SCEs) of Human Lymphocytes after MMC Treatments Combined with γ-Rays. **Kumiko IIJIMA[1] and Kanehisa MORIMOTO[2]** ([1]Dept. Maternal Child Health, [2]Dept. Public Health, Univ. Tokyo Tokyo)

Peripheral blood lymphocytes from healthy adults were studied for detecting the combined effects with γ-rays and mitomycin C (MMC). In the first experiment, cells in the G_0 stage were irradiated with different doses of γ-rays in combination with MMC (1×10^{-6} M). Chromosome aberrations (dicentrics and centric rings: D+R) were scored at the first mitosis after stimulation with phytohemagglutinin (PHA). The frequencies of D+R after γ-irradiation alone were 0.080 ± 0.019 (0.5Gy), 0.150 ± 0.034 (1Gy), 0.385 ± 0.047 (2Gy) and 1.740 ± 0.091 (4Gy). After the combined treatments with MMC the D+R frequencies were 0.050 ± 0.017 (0.5Gy), 0.155 ± 0.031 (1Gy), 0.480 ± 0.050 (2Gy) and 1.431 ± 0.114 (4Gy). In the second experiment, effects of combined treatments with increasing concentrations of MMC on the D+R frequency in cells exposed to γ-rays (4Gy) were examined. The yields of D+R were almost the same up to 3×10^{-6} M of MMC. In the third experiment, cells in the G_0 stage were treated with different doses of MMC in combination with γ-rays (2Gy) to determine whether MMC-induced SCEs were affected by the radiation. Cells were cultured for 72 hr in medium containing 40 μM BUdR. The average frequencies of SCEs in the cells treated with MMC alone were as follows: 8.8 ± 0.7 (no MMC); 11.7 ± 1.0 (MMC: 1×10^{-7}); 15.6 ± 0.9 (3×10^{-7} M); 33.7 ± 1.3 (1×10^{-6} M); 64.6 ± 2.6 (3×10^{-6} M). The SCE frequencies after the combined treatment with γ-rays were: 8.6 ± 0.6 (no MMC); 10.9 ± 0.6 (MMC: 1×10^{-7} M); 15.6 ± 0.9 (3×10^{-7} M); 32.6 ± 1.6 (1×10^{-6} M); 54.0 ± 3.0 (3×10^{-6} M). The yieled of SCEs were almost the same up to the concentration of 1×10^{-6} M. The difference in the frequency at the concentration of 3×10^{-6} M MMC might be caused by cell cycle delay.

B17. Sister Chromatid Exchanges (SCEs) and Cell Cycle Kinetics in Human Lymphocyte Cultures Exposed to Methylxanthines. **Kumiko IIJIMA, Hiroaki NOBUHARA and Munehiro HIRAYAMA** (Dept. Maternal Child Health, Univ. Tokyo, Tokyo)

Cytogenetic assay systems based on the detection of sister chromatid exchanges (SCEs) are widely advocated as a sensitive screening method for assessing genotoxic potential. While many agents have been examined for their own ability to induce SCEs, information of their combined effects and dose-response has been limited. We have examined the ability of methylxantines (caffeine, theobromine, theophylline) to induce SCEs, as well as these combined effects with mitomycin C (MMC). Heparinized human peripheral blood was cultured in the medium containing 40 μM BUdR. Two experimental sets of cultures were incubated continuously in the presence of various concentrations (0–300 μg/ml) of methylxanthines. One set of cultures was exposed initially to MMC (3×10^{-6} M) for 1 hr immediately before adding PHA. Harlequine chromosomes were obtained by the FPG technique. Treatment with caffeine or theobromine induced SCEs in a dose-

dependent manner, and caffeine or theobromine treatment combined with MMC also induced SCEs in the same manner: calculated linear regression lines were $Y=9.4+0.04X$ ($r=0.9897$; caffeine), $Y=8.6+0.03X$ ($r=0.9844$; theophylline), $Y=23.8+0.1X$ ($r=0.9216$; caffeine+MMC) and $Y=32.9+0.1X$ ($r=0.8333$; theophylline+MMC) (Y: SCEs per cell; X: dose of chemical). SCE frequencies induced by theobromine did not change with increasing dose, clearly. Effects observed in this *in vitro* system decreased in the order of caffeine > theophylline > theobromine. Proliferative inhibition occurred during the exposure to methylxanthines as shown by a decline in the proportion of the third or subsequent generation metaphase cells concomitant with an increase in the proportion of the first generation metaphase cells.

B18. Mutational Properties of Fanconi's Anemia Lymphoblastoid Cells. **Kouichi TATSUMI, Mariko TOYODA, Akira TACHIBANA, Hiraku TAKEBE** (Dept. Mol. Oncol., Fac. Med., Kyoto Univ., Kyoto) **and Ryouji ISHIDA** (Dept. Biochem., Aichi Cancer Cent. Res. Inst., Nagoya)

Fanconi's anemia (FA) is an autosomal recessive disease characterized by progressive pancytopenia, hyperpigmentation, variable congenital anomaly, low birth weight, growth retardation, and predisposition to malignancy. Surviving fractions based on grow-back extrapolations of growth curves and mutations for 6-thioguanine resistance (TG^r) or ouabain resistance (oua^r) measured by the limiting dilution technique using microtiter plates were compared between two FA lymphoblastoid cell lines (LCLs) and a normal control LCL after treatment with DNA cross-linking agents; diepoxybutane (DBM) and mitomycin-C (MMC). Both DBM and MMC induced a dose dependent increase of TG^r and oua^r mutations in the normal LCL. Although the FA LCLs were 8 times as sensitive as the normal LCL to the cytotoxic effect of DEB, no mutation was induced in the FA LCLs by DEB above 1 μM at which concentration surviving fraction was approximately 50%. However, the treatment of the FA LCLs with essentially non-cytotoxic concentrations of DEB (0.01–0.3 μM) resulted in an increase of TG^r frequency up to 3×10^{-5} with the background spontaneous frequency of 4×10^{-6}. Similar results were obtained for the treatment of the FA LCLs with MMC. These FA LCLs could be regarded as hypersensitive to the mutagenic activity of extremely low concentrations of DNA cross-linking agents, whereas the FA LCLs were immutable to cytotoxic concentrations of the agents. (Supported in part by Grants-in-Aid from the Ministry of Education, Science and Culture and a grant from Nissan Science Foundation.)

B19. Nonrandom Distribution of Chromosome and Chromatid Breaks (or Gaps) in Cultured Lymphocytes from a Patient with Habitual Abortion. **Yohko YAMANE,[2] Hikari NISHIGAKI,[1] Shohei YOKOTA,[1] Shoichiroh TSUDA,[1] Masafumi TANIWAKI,[1] Shinichi MISAWA,[1] Tatsuo ABE[1] and Tatsuro TAKINO[1]** ([1]Dept. Med., Kyoto Pref. Univ. Med., [2]Dept. Lab. Med., Kyoto)

Spontaneous breaks and gaps of chromosome and chromatid were observed in cultured lymphocytes from a patient with habitual abortion. The karyotypes of the patient and her husband were normal. We investigated the frequency of breaks and gaps at the various culture conditions. The lymphocytes of peripheral blood were cultured in medium RPMI 1640, TC 199, MEM-folate (−), and RPMI 1640+MTX, harvested after 72 hr of cultivation, and stained with G banding method. At the condition of RPMI 1640+MTX, methotrexate (final conc. 10^{-7} M) were added to the culture 48 hr before harvesting. The frequencies of the cell bearing chromosome aberrations in the above conditions were 14/50, 14/50, 18/50, and 30/50, respectively. Breaks (or gaps) per cell were 0.48(0.02), 0.24(0.04), 0.30(0.08), and 1.46(0.30), respectively. Breakpoint distribution was also studied. The hot spots were located at regions 1q21, 3p13, 3p21, 6q21, 16q22, and 16q23. It was known that distamycin A-induced fragile sites, fra(16)(q22) and fra (17)(p12), were associated with some forms of congenital anomaly and habitual abortion. Therefore, it is likely that chromosome fragility including fra(16)(q22) found in our patient is correlated with habitual abortion.

B20. Mechanism of the Expression of Heritable Fragile Sites on Human Chromosomes. **Tada-aki HORI, Ei-ichi TAKAHASHI, Satsuki TSUJI** (Div. Genet., Natl. Inst. Radiol. Sci., Chiba) **and Motoi MURATA** (Div. Epidemiol., Chiba Cancer Cent., Chiba)

Heritable fragile sites are specific points on human chromosomes which appear as nonstaining gaps or breaks under certain physiological conditions and are inherited in a Mendelian codominant fashion. The majority (15) of 18 known heritable fragile sites, including fragile X, are classified in the folate-sensitive group and are expressed under conditions of thymidylate stress. In thymidine-auxotrophic somatic cell hybrids constructed by cell fusion between human skin fibroblasts derived from a male patient with fragile X syndrome and thymidylate synthase-negative mouse mutant cells, we have shown that thymidine deprivation alone can induce the expression of fragile X site. Furthermore, in the other human-mouse hybrid clones which contain fragile X chromosome as the only human chromosome, thymidylate stress achieved by FUdR treatment did induce the fragile X expression. These results strongly suggest that a mutation in fragile X site itself is responsible for its expression. A fragile site on human chromosome 17, fra(17)(p12) is

the distamycin A-inducible fragile site and are found in association with spontaneous abortions, malformations, aneuploidy and leukemia. In somatic cell hybrids constructed by human lymphocytes derived from a fra(17)(p12) carrier and mouse L cells (tk^- and $aprt^-$), distamycin A induced the expression of fra(17)(p12). Since TK gene is located on human chromosome 17, it is possible to isolate a hybrid clone which contains only a human fra(17)(p12) chromosome. These hybrid cellular systems would be useful for studying molecular basis of fragile X syndrome and possible roles of fragile sites as predisposing factors for chromosome rearrangements.

B21. Rare Fragile Sites in a Healthy Japanese Population. Ei-ichi TAKAHASHI, Tada-aki HORI (Div. Genet., Natl. Inst. Radiol. Sci., Chiba) **and Motoi MURATA** (Div. Epidemiol., Chiba Cancer Cent., Chiba)

Heritable (rare) fragile sites (FS or fra) on human chromosomes are of great interest, because they may play a potential role in inducing genomic instability. We have made a population survey of FS, using peripheral lymphocytes from healthy Japanese subjects. Three types of culture conditions were used for detecting the following FS. For folate-sensitive FS, we used folic acid and thymidine-free Ham's F10 medium containing 5% fetal calf serum and 2% PHA. For distamycin A-inducible FS and BrdU-requiring FS, the cultures were treated with distamycin A (50 μg/ml) and BrdU (7 μg/ml), respectively, during the final 24 hr of culture in RPMI1640 medium supplemented with 10% fetal calf serum and 2% PHA. After 72 hr culture, chromosome preparations were made by a standard method. The chromosome aberrations, such as isochromatid gaps and breaks and triradials, were scored in at least 50 metaphases. Trypsin G-banding was applied for detailed analysis on the breakpoints. We have examined 1,022 subjects for folate-sensitive (1) and BrdU-requiring FS (3), and 845 for distamycin A-inducible FS (2). We detected the following FS; (1) one carrier of fra(2)(q11), 2 of fra(11)(q13) and one of fra (17)(p12), (2) 6 of fra(8)(q24), 12 of fra(16)(q22) and 26 of fra(17)(p12), and (3) 3 of fra (10)(q25), respectively. Fra(8)(q24) is a new FS which was induced by distamycin A and Hoechst 33258. Genetic heterogeneity was found in fra(17)(p12). The incidence (%) of each FS was: (1) 0.10, 0.20 and 0.10, (2) 0.71, 1.42 and 3.08, and (3) 0.29, respectively. Compared with other FS in the present study, the incidences of fra(16)(q22) and fra(17) (p12) are remarkably higher in Japan.

B22. The Fragile X Syndrome in a Japanese Population of Institutionalized Mentally Retarded Females. Tadao ARINAMI, Susumu NAKAJIMA (Ibaraki Pref. Colony Hosp., Ibaraki) **and Ikuko KONDO** (Dept. Hum. Genet., Univ. Tsukuba, Ibaraki)

The fragile X chromosome was screened on 190 institutionalized females with moderate to profound mental retardation, without Down syndrome. Two patients were detected to have the fragile X chromosome in 26 and 15% of the cells examined, respectively. Both had brothers with the fragile X syndrome, and accounted for 10% of 20 women who had a family history of mental retardation in this population. Though the fragile X syndrome was much less frequently found in the severely retarded females than in the males surveyed previously in the same institution, the present finding indicates that the fragile X syndrome should not be ignored as a cause of retardation even in females with severe level of retardation. Comparison between the result of this study and those of studies in Caucasian female populations suggests that the frequency of the fragile X in Japanese females is similar to those in Caucasians as is male populations. In addition, the replication study of X chromosome of these probands, in which early replicating fragile X chromosome was observed in 82 and 73% of informative cells, supported the proposal that the replication status of the fragile X chromosome is related to the intellectual handicap in heterozygotes.

B23. 施設入所中の精神遅滞者集団における fra(X) の頻度. 笠井良造[1]・楢原幸二[2]・村上政江[1,2]・吉川清志[2]・木村俊介[2]・平本　啓[2]・木本　浩[2] ([1]旭川児童院, [2]岡山大・医・小児). **Prevalence of the Fragile (X) Syndrome in Institutionalized Mentally Retarded Individuals.** R. KASAI,[1] K. NARAHARA,[2] M. MURAKAMI,[1,2] K. KIKKAWA,[2] S. KIMURA,[2] K. HIRAMOTO[2] and H. KIMOTO[2] ([1]Asahigawa Jidoin Hosp.; [2]Dept. Pediatr., Okayama Univ., Okayama)

施設入所中の精神遅滞者集団で，Fragile (X) 症候群の頻度およびその臨床症状を検討した．対象は社会福祉法人旭川荘に入所中の精神遅滞者 196 例（男子 134 例，女子 62 例）で，その年齢分布は 2～46 歳（平均年齢 18.1 歳），知能障害の程度は軽度 29 例，中等度 50 例，重度 64 例，最重度 53 例であった．なお，他の染色体異常を有する者は調査対象から除外した．5% ウシ胎児血清を含む MEM-FA 培地 5 ml に対象者の全血 0.3 ml を加え，72 時間培養の後，通常の方法で標本を作製し，ギムザ染色で 1 症例あたり 50 個の核板を分析した．その結果，男子 6 例（4.5%，うち 2 例は兄弟例），女子 2 例（3.2%）に fra(X)(q27 or q28) が認められた．各症例の fra(X) の出現率は 5 例（男子 3 例，女子 2 例）で 1～3%，男子 3 例で 40～54% であった．精神遅滞の程度は，男女各 1 例で中等度，男子 5 例と女子 1 例で重度～最重度であり，男子 3 例には自閉傾向が認められた．また，男子 6 例中 5 例には巨大睾丸が，男子 1 例を除く全例にはてんかん，あるいは脳波異常がみられた．以上の結果，精神遅滞者男子における fra(X) の頻度は，有波ら (1986) の報告した茨城コロニーの頻度と近似し，欧米での頻度（2～9%）と比較して大差なく，本邦においても fragile(X) 症候群が，精神遅滞の主要な原因の一つであると考えられる．

B24. Two Cases of 8p Trisomy. Hiromi SAKAMOTO,[1] Osamu MIKAMI,[1] Noriko MATSUMOTO,[1] Yoshie SUGAHARA,[2] Satoko YOKOTA,[2] Hiroko FUJITA,[3] Masanori NISHIGAKI[4] and Jun-ichi FURUYAMA[1] ([1]Dept. Genet., [2]Dept. Clin. Lab., Hyogo Coll. Med., Nishinomiya; [3]Dept. Child Health, Osaka City Univ., Osaka; [4]Dept. Pediatr., Osaka Kaisei Hosp., Osaka)

Case 1: A pregnant woman who had 3 previous pregnancies visited for amniocenthesis because of her 2-year-old son's chromosomal abnormality (3p+). After checking his parents' chromosomes, the son's karyotype was decided as 46,XY,der(3),t(3;8)(p26;p12)pat. The son had been delivered after an uncomplicated 40-week gestation and weighed 3,056 g at birth. The father was 35 years old and the mother was 28 years old at that time. He had a large mouth and an everted lower lip. His mental development was severely retarded. Chromosomal analysis from amniotic fluid cells revealed a 46,XX karyotype and after 40-week gestation a healthy baby was delivered.

Case 2: A girl was referred to us for her delayed development and multiple anomalies. She was delivered after an uncomplicated 37-week and 5-day gestation. The father was 36 years old and the mother was 35 years old. Her birth weight was 2,283 g. On the 3rd day she showed symptoms of depressed respiration with groaning. She had small and receding chin. Her mouth was large and the lower lip was everted. Her forehead was high with temporal retraction. Her palpebral fissures were large and almond shaped. Her philtrum was long with undefined pillars. Her limbs were normal. Her DQ was about 40. Her parents had a normal karyotype. Her karyotype was decided as 46,XX,dup(8)(p21.1p21.3).

B25. A Partial 10p Trisomy due to Maternal Translocation t(10;18)(p12.2:q21.3). Masahiko MAEDA, Yoshiaki ABE, Junichi EDAGAWA (Kohoku Gen. Hosp., Shiga), **Keiko OKUMURA, Morimi SHIMADA** (Dept. Pediatr., Shiga Univ. Med. Sci., Otsu), **Shigeo HORIIKE and Tatsuo ABE** (3rd Dept. Med., Kyoto Pref. Univ. Med., Kyoto)

Some cases of 10p trisomy were reported in Japan since the first description by Insley. We report a partial 10p trisomy due to maternal translocation t(10;18)(p12.2;q21.3). She was born by C-Section after 41-week gestational period. Birth weight was 2,720 g. She had the peculiar appearance of face and physical abnormalities; hypertelorism, bulky forehead, high-arched palate, widely spaced nipple, heart murmur, umbilical herniation, clinodactyly, and hypotonia. At the age of 4 months, her weight was 5,525 g (−2SD) and her head circumference was 39 cm (−2SD). Atonic seizure and apnea attack appeared. Visual and auditory inacuity were also noticed. EEG and blood examination were normal. CT-scan showed mild atrophy of the anterior lobe. Her DQ was 62.8.

Pulmonary stenosis was confirmed by cathetelization at the age of 6 months. Repeated apnea attack with myoclonus like movement lasted. At the age of 9 months, EEG showed hypsarythmia. We followed her by anticonvulsant drugs. That seizure decreased but continued. At the age of 1 year, she died by respiratory failure due to pneumonia. Chromosomal analysis revealed a structural abnormality in the patient and her mother. The karyotype of her mother showed 46,XX,t(10;18)(p12.2;q21.3), and thus the patient's karyotype was designated as 46,XX,−18,+der(18)(18pter→18q21.3::10p12.2→10pter).

B26. Siblings with Suspected Tetrasomy 18p Syndrome. **Kaoru TAKEDA, Toshihiro OKAMURA** (Dept. Pediatr., Yuri-Kumiai Gen. Hosp., Honjo, Akita), **Isamu SUZUKI** (Dept. Lab., Yuri-Kumiai Gen. Hosp., Honjo), **Tomoko HASEGAWA[1] and Tsunehiro YOKOCHI[2]** ([1]Dept. Genet., [2]Dept. Clin. Pathol., Shizuoka Child. Hosp., Shizuoka)

In 1984 Rivera *et al.* concluded the tetrasomy 18p has actually constituted a distinct syndrome by the comparative analysis with 17 similar cases from the literature and their cases. The principal symptoms and signs consist of mental retardation, microcephaly, low-set ears, high-arched palate, asthenic bodily habitus, increased deep tendon reflexes *etc.* A family is presented here in which 2 daughters have been suspected to have this syndrome clinically and by chromosomal studies, including the G, Q, and C banding technics. The daughters were born to the phenotypically normal and healthy mother, 2-para (both: abortion), with *de novo* trisomy 18 [47,XX,del(18)(pter→p11.21),+i(18p)]. The older sister has, in addition to the above symptoms, growth retardation, pintched-up nose, small triangular mouth, micrognatia, facial asymmetry, and 0.5 cm shortening of the left lower extremety. The low level of serum IgA, and scoliosis with the defect of a pair of ribs were also found. The younger sister was the stillborn with birth weight 1,010 g and gestational age 29 weeks, and had the extensive defects of the skull, congenital hydrocephalus, lumbosacral meningocele, and severely anomalous facies including rudimentary eyes and nose *etc.* These two daughters are suggested to have inherited one normal 18 chromosome and i(18p) from their mother and one normal 18 from their father by the clinical, chromosomal, and familial evidences. In the literature, it is only Taylor *et al.* (1975) who reported a family in which the mother is trisomic for 18p, one daughter tetrasomic and the other daughter monosomic for this chromosomal region.

B27. A Case of Deletion of the Long Arm of No. 20 Chromosome. Yukihisa MATSUDA, Takako UEMURA, Shusuke OTSUBO, Tetsuo TAKESUE, Hiroyuki HATANAKA (Natl. Minami Kyushu Hosp., Kagoshima) **and Koji SAMESHIMA** (Dept. Pediatr., Kagoshima Univ., Kagoshima)

Anomalies of the long arm of No. 20 chromosome are extremely rare. A female patient with a deletion of 20q11.2-20q12 or 20q12-20q13.1 was reported. The proband, the second child of healthy non-consanguineous parents, was born at 38 weeks after uneventful pregnancy. There was no family history of congenital anomaly or developmental delay. Her birth weight was 3,072 g. When she was 5 days old, she was cured in incubator for 3 days because of heavy neonatal jaundice. Physical examinations revealed microcephalus, brushy eye brows, epicanthus, bulbous nose, flat nasal bridge, long philtrum, micrognathia, short neck, abnormalities of fingers *etc.* These clinical features were similar to those of reported cases of partial monosomy 20q and ring chromosome 20. Chromosomal study using high resolution banding technique revealed a balanced reciprocal translocation, t(6;10)(p23;p15) and a deletion, del(20)(q11.2q12) or (q12q13.1). Karyotypes of the parents and the first child were normal.

B28. A Family Study of Complex Glycerol Kinase Deficiency Syndrome. Fumiko SAITO, Akira TONOMURA (Dept. Cytogenet., Tokyo Med. Dent. Univ., Tokyo), **Jun GOTO,[1] Imaharu NAKANO,[1] Hiroaki KAKINUMA[2]** ([1]Dept. Neurol., [2]Dept. Pediatr., Shimoshizu Natl. Hosp., Chiba) **and Shigeo MURAKAMI** (Dept. Neurol., Univ. Tokyo, Tokyo)

The patient was a ten-year-old boy with complex glycerol kinase deficiency syndrome suffering from glycerol kinase deficiency (GKD), progressive muscular dystrophy similar to the Duchenne type, congenital adrenal hypoplasia (CAH) and mental retardation. Detailed cytogenetic banding analysis revealed that he had a small deletion in the band of Xp21. We interpret these results to suggest that X-linked GKD and CAH genes are mapped to Xp21 region together with Duchenne muscular dystrophy (DMD) gene. Furthermore, his mother was found to be a carrier of the deleted X chromosome showing random inactivation pattern in her lymphocytes. Her Gk activity showed a half of normal level in lymphocytes and this is reasonably thought to be the result of the random X inactivation. She also had slight abnormalities in her muscle. It is very interesting for us to consider it to be the result of the random X inactivation in her muscle cells. We are now searching the deleted region of X chromosome by molecular study.

B29. A Case of Ring Chromosome 22[46,XX,r(22)(p11.2→q13.3)] Presenting with Leukemoid Reaction. Hiroshi WATANABE and Tatsuhiro YAMANAKA (Dept. Pediatr., Yaizu Municipal Hosp., Yaizu)

We had a case who presented marked hypotonia, mental retardation, growth and developmental delay, epicanthal folds, low nasal bridge and large ear lobes. Hematologic study on admission revealed leukemoid reaction, but it returned to be normal within a week. Her karyotype was shown to be 46,XX,r(22)(p11.2→q13.3) by high-resolution chromosome analysis. There has been no report about the relation between the ring chromosome 22 and leukemoid reaction. This is the second case with a ring chromosome 22 in which the breakpoints are determined by high-resolution chromosome analysis in Japan. Accumulation of cases with the breakpoints determined by high-resolution technique would help to explain the phenotypic variation of this syndrome.

B30. The Philadelphia Chromosome: Considerations from the Study of Variant Ph^1 Translocations. Takaaki ISHIHARA and Masako MINAMIHISAMATSU (Div. Radiat. Hazards, Natl. Inst. Radiol. Sci., Chiba)

Since the discovery of the Philadelphia (Ph^1) chromosome as a specific chromosome abnormality in chronic myelocytic leukemia (CML) by Nowell and Hungerford in 1960, much information on this specific chromosome has been accumulated with the developments of banding methods and molecular biology. On the other hand, the definition of the Ph^1 chromosome itself has not yet been distinctively framed, and it is still in much confusion. In order to clarify this point at the chromosomal level as much as possible, we have investigated the problem mainly by the analysis of variant Ph^1 translocations. Among 210 cases of Ph^1-positive CML analyzed in our laboratory, 17 cases of variant Ph^1 translocations were detected. All of these variant Ph^1 translocations were revealed to be complex type involving the specific portions of both #9 and #22 chromosomes. Based on the results of the analysis, we have reached the conclusion that the Ph^1 translocation can be defined as follows: 1) An indispensable condition of the Ph^1 translocation is the involvement of the specific portions of both #9 and #22 chromosomes, q34 and q11, respectively. 2) Variant Ph^1 translocations are always complex type, which are formed from the standard Ph^1 translocation as its secondary changes.

B31. Cytogenetic Study of Adult T-Cell Leukemia. Tamiko SHINOHARA (Dept. Hum. Cytogenet., Japan Red Cross Med. Cent., Tokyo), **Shiro MIWA** (Inst. Med. Sci., Univ. Tokyo, Tokyo), **Yuichi FUKUIYA** (Dept. Hematol., Second Tokyo Natl. Hosp., Tokyo), **Kazunori MIYAKE** (Dept. Clin. Pathol., Juntendo Univ., Tokyo), **Kenji SUZUKI** (Dept. Intern. Med., Japan Red Cross Med. Cent., Tokyo), **Setsuo HASEGAWA** (Dept. Intern. Med., Kanto Teishin Hosp., Tokyo) **and Kohtaro YAMAMOTO** (Dept. Cytogenet., Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo)

Adult T-cell leukemia (ATL) was advocated by Takatsuki *et al.* in Japan, as a clinical entity characterized by the following findings: subacute or chronic leukemia with a rapidly progressive terminal course, leukemic cells with T-cell markers, appearance of pleomorphic leukemic cells with markedly deformed unclei, frequent skin involvement and positive findings of anti ATL antigen and HTLV-1 viruses. In this report, a cytogenetic study on 6 patients with ATL was presented. All the patients were positive for anti ATL antigen, whose ages ranged from 35 to 59 years. Chromosome analyses with the trypsin-Giemsa banding technique were performed on peripheral blood lymphocytes after 18 hr, 3 or 5 days of incubation, and on the bone marrow and lymph node after 18 hr of incubation. Five of the 6 cases showed abnormal clones with multiple numerical and structural abnormalities, with modal chromosome numbers ranging from 45 to 50. The karyotype of the first case was 45,X(−X),−1,−1,+i(1p),+i(1q),3p+,5q−,6q−,−9,10p+,−11,+t(5;11)(q13;q23),del(11)(p11),−14,+15,−18,+i(18q),+m. The second showed a normal karyotype. The third was 50,Xp+,Y,+3,4q+,6q−,14p+,t(15q+;17q−),+18,+2m. The fourth case had two abnormal clones: One was 47,X(−),+(1q;3q),+3q−,−14,+m, and the other was 47,X(−X),+3p−,−14,+2m. The fifth case had 46,XX/48,XXX,+11 or +18. In the fifth case, all the cells after 5 months of incubation with TCGF showed 46,X,−X,+der(X)t(X;1)(q28;q21). The sixth case had 47,XX,4q+,6q−,8p+,9p+,−18,+i(18q),+m. There were no abnormalities common to the 6 cases, and we found neither trisomy 7, as indicated by Ueshima *et al.*, nor a distinct inversion of chromosome 14 as pointed out by Sadamori. However, the abnormalities of Nos. 1, 3, 14, and 18 chromosomes and 6q− were observed in the 5 patients with ATL.

B32. Tandem Triplication of 1q(q21→32), Three Cases of Myelodysplastic Syndrome. Tamiko SHINOHARA (Dept. Hum. Cytogenet., Japan Red Cross Med. Cent., Tokyo), **Kazunori WAKASUGI** (Hachioji Med. Cent., Tokyo Med. Coll. Hosp., Tokyo), **Takayuki MORISAKI, Shigetaka ASANO, Shiro MIWA** (Inst. Med. Sci., Univ. Tokyo, Toyko), **Kazuo DAN gnd Takeo NOMURA** (Nihon Med. Coll. Hosp., Tokyo)

Three cases of myelodysplastic syndrome (MDS) with a tandem triplication of

1q(q21→32) are reported. Case 1: S.O., a 49-year-old male, was diagnosed as an aplastic anemia on March 1982. On July 1984, he was admitted to the Hachioji Medical Center because of abscess on the both legs and continuous suffering from severe pneumonia. During the episode of pneumonia, monocytoid blast cells appeared in peripheral blood and increased gradually. The bone marrow aspirates showed increased cellularity. He was diagnosed as MDS because of the presence of 10% blasts. Case 2: M.I., a 52-year-old male, was pointed out neutropenia and thrombocytopenia by medical examinations and followed up at the Institute of Medical Science, University of Tokyo. On October 1985, blood examination showed WBC 2,500/mm^3 with 2.5% immature cells. Bone marrow aspirates showed slightly dyserythropoietic changes and he was diagnosed as MDS. Case 3: M.K., a 47-year-old male, was admitted to the Nihon Medical College Hospital because of fever and pancytopenia on September 1985. On admission, white blood counts were 800/mm^3 with a differential count of 1% blasts, 4% bands and 95% lymphocytes. He was diagnosed as a refractory anemia with excess of blasts (RAEM) in transformation. Cytogenetic studies were carried out on bone marrow cells according to the trypsin-Giemsa banding technique. A tandem triplication of a part of chromosome No. 1 (q21→32) was found in all the three patients. The karyotypes were designated in each as 46,XY,tan tri(1)(pter→q32::q21→q32::q21→qter). Rowley (1977) has reported the cases with trisomy 1q in various hematologic disorders, and suggested that the occurrence of duplication of 1q21→32 is a nonrandom event in various malignant states. The tandem triplication of 1q21→32, resulting in a partial tetrasomy of 1q21→32, was a very rare abnormality. In literatures only two cases have been reported: one was an essential thrombocythemia (Knuutila *et al.*, 1983) and the other was MDS (Pappenhausen *et al.*, 1984). The presence of nonrandom numerical chromosome change of 1q21→32 might be highly significant in the genesis and/or the progression of MDS.

B33. Anbormal Short Arm of Chromosome 11 in Childhood Malignant Solid Tumor.

Yasuhide HAYASHI, Toshiya INABA, Masahiro NAKASHIMA, Ryoji HANADA, Keiko YAMAMOTO (Div. Mematol. Oncol., Saitama Child. Med. Cent., Saitama), **Toshiro NISHIDA** (Div. Lab., SCMC, Saitama), **Takashi ABE** (Dept. Pediatr., Keio Univ. Med., Tokyo), **Hiromu MUCHI** (Dept. Pediatr., Jichi Med. Sch., Tochigi) **and Yasunori TOYODA** (Div. Hematol. Oncol., Shizuoka Children's Hosp., Shizuoka)

Loss of heterozygosity in three embryonal tumors (Wilms' tumor, WT; Rhabdomyosarcoma, RM; hepatoblastoma, HB) has been reported using restriction fragment length polymorphism (RFLP). We performed chromosome analysis on 40 neuroblastomas, 5 RMs, 5 WTs, 1 malignant mesenchymoma, and 4 miscellaneous tumors. Among

them abnormalities of a short arm of chromosome 11 (11p) were observed in 3 tumors. One was found in a 2-year-old girl with WT (favorable histology, stage III). The karyotype of her tumor cells showed 46,XX,t(11;11)(p13;p15). The other was found in a 3-year-old boy with retroperitoneal RM (embryonal type, stage II). The karyotype of his tumor cells was 72,XXYY,+1,+2,+2,+2,+3,+3,+3,+6,+7,+7,+8,+8,+10,+der(11)-t(11;?)(p13:?),+der(11),+12,+12,−13,+16,+16,+18,+19,+20,+20,+21,+21. The remaining one was found in a 9-month-old girl with abdominal MM (stage II). The karyotype of her tumor cells showed 53,XX,+der(2)t(2;?)(q37;?),+3,+7,+8,+9,−11,+der (11)t(11;?)(p13;?),+der(11),−17,+der(17)t(17;1)(p11;q12),+18. Each three tumor had different histology, but had similar undifferentiated one, embryonal type. It is possible that the present cases with 11p abnormality may have a common pathogeneic mechanism.

B34. A Case of Shwachman Syndrome with a High Incidence of Spontaneous Chromosome Breakage. **Hanako TADA, Tugio RI, Kaoru OBINATA, Nobutaka KIYOKAWA, Hisakuni YOSHIDA, Koichi ISHIMOTO, Masahumi KANEKO, Yuichiro YAMASHIRO** (Dept. Pediatr., Juntendo Univ., Tokyo) **and Tamiko SHINOHARA** (Dept. Hum. Cytogenet., Japan Red Cross Med. Cent., Tokyo)

Shwachman Syndrome is a rare autosomal recessive disease associated with exocrine pancreatic insufficiency and bone marrow hypoplasia, but the etiology remains obscure. We have examined chromosome breakages in a patient with Shwachman syndrome. The patient, a female infant, was admitted to this hospital at 1 month of age for evaluation of failure to thrive and an anaemia. Her brother with a diagnosis of Shwachman syndrome had died of myocarditis at the age of 3 years. The patient was found to have an anaemia and hypocellular bone marrow. Pancreatic function tests revealed her exocrine pancreatic dysfunction. Chromosome studies were done three times at the ages of 1 month, 3 months and 10 months. The first analysis revealed normal karyotype with a high incidence of gaps and breaks. Chromatid damages per cell reached 0.27. In the second and third studies peripheral blood lymphocytes were cultured for 48 and 72 hr, respectively, and control cultures were simultaneously set up. The averages of chromatid damages per cell from each sample were 0.15 for this patient and 0.02 for controls. And this patient did not show increased chromosome breakages with MMC. Therefore these results suggested that this case with Shwachman syndrome has a defect in the different type of DNA repair mechanism from Fanconi anaemia. Although no patients with Shwachman syndrome with chromosomal instability have been reported so far, some patients have been reported with leukemia, immunodeficiencies and skin disorders as would be expected in the chromosome breakage syndromes. Our results suggest that Shwachman syndrome may be a candidate for inclusion in the chromosome breakage syndromes.

B35. Inheritance of Reciprocal Translocation Chromosomes in Man (2). **Hidetsune OISHI[1] and Tsutomu YAMANAKA[2]** ([1]Dept. Genet., Inst. Develop. Res., [2]Cent. Hosp., Aichi Pref. Colony, Kasugai)

The frequencies of balanced autosome rearrangements with reciprocal translocation were estimated from our records and published reports. The study was carried out on 383 families with abnormal probands for pedigree analyses. All abnormal chromosomes of probands were derived from one of the parents. Numbers of male and female probands were 198 and 185 respectively, while balanced carriers were found in 116 of their fathers and 267 of their mothers. By the pedigree analyses balanced carriers with the same reciprocal translocation for two or more generations were ascertained in 226 families. In these families balanced carriers were found in 216 of fathers and 377 of mothers. On the other hand, male and female children of these balanced carriers in normal, balanced and unbalanced conditions of chromosomes were 184 and 198, 327 and 390, and 231 and 222, respectively, and it is apparent that the proportion of female children was larger than that of male ones in these balanced carriers. In addition, 153 fathers with balanced translocations have had 118 sons and 124 daughters with the same conditions of chromosomes whereas 163 sons and 217 daughters of 251 mothers were under the same situation. For inheritance of balanced chromosomes through generations the estimated number of the daughters was higher than that of the sons from mothers, but not from fathers. Average number of spontaneous abortions in balanced carriers of female was also higher than that in these of male.

B36. Chromosomal Abnormalities in Pediatric Clinic. **Junji KAMEYAMA, Eizo NAKADA, Hajime YOSHIMITSU, Takahiro HAYAKAWA, Mikio MORI, Kazuo KIDANI, Toshihiro MITOMORI, Kazuyo MITSUDO, Nobuaki TAKEDA, Kiyoshi BABA, Mutsuo TANAKA** (Dept. Pediatr., Kurashiki Cent. Hosp., Kurashiki) **and Ken HAYASHI** (Dept. Obstet. Gynec., Kyoto Univ., Kyoto)

Fifty cases of chromosomal abnormalities were diagnosed in the Pediatric Clinic of Kurashiki Central Hospital in a 6-year period from 1980 to 1986. All karyotypic analyses were carried out on peripheral blood cultures. Chromosomes were stained with diffeernt banding techniques (G, Q, N, C and high-resolution bandings). Autosomal chromosome abnormalities comprised numerical and structural aberrations. Twenty-two cases of trisomy 21, 3 of trisomy 18 and 1 of trisomy 13 were detected. Structural chromosome abnormalities were observed in fifteen cases. They were 2p partial trisomy, 3q partial trisomy, 4p trisomy, 4q partial trisomy, 5p partial monosomy, 11q22q partial trisomy, 13q partial trisomy, 13q partial monosomy and ring 13. Sex chromosomal abnormalities included three cases of mosaics with Turner's syndrome and one of XXX. Their karyotypes and clinical manifestations were discussed.

B37. Chromosome Segregation from Quadrivalents in Male Chinese Hamsters Heterozygous for Reciprocal Trgnslocations. **Shin-ichi SONTA and Kazuyo KITAYAMA**
(Dept. Genet., Inst. Develop. Res., Aichi Pref. Colony, Kasugai)

It is difficult to estimate the real segregation ratio from quadrivalents in man heterozygous for reciprocal translocations. We studied here the relationship between characteristics of the translocations ans chromosome segregation ratios from the quadrivalents in experimental animals (Chinese hamsters) heterozygous for different reciprocal translocations. Males of eight different strains heterozygous for reciprocal translocations were used in the present study. Chromosome analyses of metaphase II cells in these heterozygotes indicated that the frequencies of cells with a balanced chromosome constitution, which resulted from alternate disjunction of quadrivalents, ranged from 38.3 to 48.0%. The frequencies of cells resulted from adjacent-1, adjacent-2 and 3:1 disjunctions were 27.3–36.0%, 6.0–19.4%, and 4.1–22.0%, respectively. These results showed that the length of chromosomes involved in the translocation was related to the frequency of 3:1 disjunction. The present findings demonstrated no possible factors predisposing to adjacent-2 disjunction, such as the shortness of the interstitial segments between the centromeres and the breakpoints of translocation chromosomes, which has previously been suggested by the study of human reciprocal translocations (Jalbert and Sele, 1979).

B38. Feminity Control at the Universiade 1985, Kobe, Japgn. **Hiromi SAKAMOTO,[1] Norimitsu OHTSUKA,[2] Hitoshi KOMATSU,[3] Kunihiko NAKANOIN[3] and Jun-ichi FURUYAMA[1]** ([1]Dept. Genet., [2]Dept. Clin. Lab., Hyogo Coll. Med., Nishinomiya; [3]Dept. Pathol., Public Health Res. Inst. Kobe City, Kobe)

We experienced the feminity control at the Universiade 1985, Kobe. Following the CMI (International Medical Committee of The Federation Internationale du Sport Universitaire) regulations, the feminity is certified on the basis of X chromatin determination conducted on a smear of buccal mucous membrane or by keryotyping. In this opportunity, we chose for the screening test checking both X chromatin from buccal smears and Y chromatin from hair roots. The number of female competitors that attended the Universiade except tennis, gymnastics, and fencing was 631. Among them, 108 had already had the certificate of feminity, and thus we examined 523 female competitors. All of them except 3 had an X chromatin and no Y chromatin. Of these exceptional 3 cases 2 had a Y chromatin but no X chromatin, and the chromosomal analyses revealed a 46,XX karyotype in both of them. The remaining one case had both X and Y chromatins, but we could find a Y chromatin on only one slide. Since this person refused a chromosomal analysis, we can only suppose her karyotype to be 46,XX/46,XY or 46,XX/47,XXY. We reported these results to the CMI. For the purpose of the feminity control, it is safer to

screen Y chromatin rather than X chromatin, since Kleinefelter syndrome with 47,XXY cannot be screened only by checking the X chromatin, for instance. For the above reasons we strongly advise the use of both X and Y chromatin tests for the feminity control.

B39. Distribution of Serum Protein Types among Two Chinese Populations (Beijing and Guangzhou). Keiichi OMOTO, Zhimin ZENG and Katsushi TOKUNAGA (Dept. Anthropol., Univ. Tokyo, Tokyo)

As an attempt to investigate the genetic and geographical variation among Chinese (Han), blood samples from northern (Beijing, N=155) and southern (Guangzhou, N=255) Chinese were examined for the following serum protein polymorphic systems: Hp, Tf, Gc, C6, and C7. Starch gel electrophoresis was used for typing of Hp and Tf, while polyacrylamide gel isoelectric focusing was used for Gc, C6 and C7. The main results obtained were as follows: 1) Hp*1 gene frequency was higher in south than in north, but the difference was statistically not significant. 2) Frequency of Tf*D·CHI was 0.017–0.022. 3) Besides 3 common Gc alleles, 6 rare variants were detected, among which two were considered to be new: Gc*1C50 (Beijing) and Gc*2A19 (Guangzhou). Gc J (1A2) was not found. The frequency of Gc*1S was significantly higher in Guangzhou than in Beijing. 4) In C6, 4 rare variants were detected besides 3 common alleles, and one of the variant was considered to be new and named C6 B21. Geographical difference in gene frequency was not significant. 5) Besides 4 common alleles of C7, a new variant C7*6 was detected. The geographical difference was noted for the frequency of C7*4, suggesting a focus of this allele in northern Chinese.

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B40. Distribution of Gm Genes, in China, Southeast Asia, and India (Assam). T. MIYAZAKI, H. MATSUMOTO, K. YAMAZAKI, K. SUZUKI, N. KAWAI (Osaka Med. Sch., Takatsuki), **T. M. ZHAO** (China), **H. WALTER** (Bremen Univ., FRG) **and N. SAHA** (Singapore Univ., Malaysia)

Since the discovery of Gm st gene in 1966, the distribution of Gm genes has been investigated for various ethnic groups from Southeast Asia to South America, centering around East Asia. Including the Gm data on China, Southeast Asia, and India (Assam) recently investigated, we conclude as follows: 1) Mongoloid populations are divided into two groups on the basis of analysis of the genetic distances based on the Gm gene frequencies: one is a southern group characterized by a remarkably high frequency of Gm afb^1b^3 and a low frequency of Gm ag and the other is a northern group characterized by a high frequency of Gm ag and an extremely low frequency of Gm afb^1b^3. 2) Populations

in China, mainly Han race including minority nationalities, show remarkable heterogeneities from north to south, in sharp contrast to Korean and Japanese populations which show homogeneities. The Gm afb^1b^3 gene which characterized South Mongoloids must exist in Gangxi and Yunnan area in the southwest of China. 3) The Gm ab^3st gene found in the highest incidence in north Baikal Briats flows in all directions. The gene, however, shows precipitous drops which occur from Mainland China to South East Asia and from North to South America, although the gene is still found in high incidences among Eskimos, Yakuts, Tibetans, Oloqen, Korean, Japanese and Ainu. On the other hand, this gene is introduced into Hui, Uygur, Indian, Iranians and far into Saldinians in Italy through Silk Road. On the bases of these results, it should be concluded that Japanese race belongs to northern Mongoloids and that the origin of Japanese must exist in Siberia, most likely in the Baikal area.

B41. Population Genetic Study in Isolated Communities: IV. Trends on Mean Inbreeding Coefficients in Miyamacho, Fukui Pref. **Masao NAKANAGA, Masanori DOHCHIN, Motozumi NOMURA, Norio FUJIKI** (Dept. Intern. Med., Fukui Med. Sch., Fukui), **Yoshiyuki OHNISHI** (Sabae Health Cent., Fukui) **and Kazuo MANO** (Nagoya Natl. Hosp., Nagoya)

For over 30 years we have already investigated the effect of inbreeding and genetic polymorphisms in 9 isolated communities in Japan. This time genetic and medical survey was performed in 2 isolared areas (A.K.) in Miyamacho, Fukui. Koseki study was done in 409 couples with 373 sibs. Endogamy and consanguinity rates were calculated as high as 26.6% (21.7% in A, 28.7% in K) and 15.7% (6.8% in A, 19.3% in K), respectively. Mean inbreeding coefficients per couple and per sib were 0.0066 (0.0037 in A, 0.0068 in K) and 0.0059 (0.0034 in A, 0.0094 in K), which corresponds to slightly remote consanguinity of the second cousin marriage on an average. Inbreeding rate was significantly different in some hamlets in the same area; possibly not only the geographical but socioeconomical factors were working. The socioeconomical effects were also supported by the chronological analysis showing still high repetitive inbreeding instead of isolate-breaking. The medical survey done in 516 of 876 inhabitants (58.9%) did not reveal any specific genetic diseases. Genetic risk factors to common adult diseases are now under study, clarifying the genetic susceptibility of such diseases.

B42. Studies on Complement Component Deficiencies in Osaka Blood Donors (IV). **Yasuo FUKUMORI, Keiji YOSHIMURA, Shiro OHNOKI, Yasuto OKUBO, Hideo YAMAGUCHI** (Osaka Red Cross Blood Cent., Osaka), **Takeshi MORIYAMA, Youji AKAGAKI and Shinya INAI** (Dept. Clin. Pathol., Osaka Med. Coll., Takatsuki)

In order to examine the incidence of the deficiencies of the complement components in Japan, mass examinations were carried out in Osaka blood donors by microtiter methods of hemolytic complement activities using sensitized sheep red blood cells in sucrose gelatin veronal buffer. We have already reported two individuals with C5 deficiency (C5D), two with C6D, five with C7D, two with C8D and 100 with C9D in 100,802 donors. This report deals with the results of further screening test done on another 54,136 blood donors. Newly, two of them were identified as C6D, one as C7D, two as C8D and 42 as C9D. The two donors with C6D, C.C. (33-year-old male) and T.N. (24-year-old male), were both healthy and had no infection history. The donor with C7D, S.I. (23-year-old male), and two donors with C8D, Y.H. (33-year-old male) and K.T. (38-year-old female), looked healthy. A study on the K.T. family showed that one sister and one brother of the proposita had half the normal amount of C8. The 42 donors with C9D were healthy as the previously reported cases. The results hitherto obtained indicated that the incidences of complement component deficiencies were 1/73,240 for C5D, 1/36,620 for C6D, 1/24,410 for C7D, 1/36,620 for C8D and 1/1,061 for C9D. We could not find C1D, C4D, C2D and C3D at all. It should be noted that the incidence of C9D was remarkably higher than those of any other complement deficiencies in Japan and that of C9D in Europe and America, whereas C2D, which is the most popular complement deficiencies in Europe and America, has not been detected in Japan.

B43. Analysis of High Myopia by Quantification Method: Relation to Status of Fundus of the Eye. **Keiko FUJIKI, Atsushi KANAI, Akira NAKAJIMA** (Dept. Ophthal., Juntendo Univ. Sch. Med., Tokyo), **Akira SATO, Takashi TOKORO** (Dept. Ophthal., Tokyo Med. Dent. Univ., Tokyo), **and Kazuyuki KABASAWA** (Computer Cent., Juntendo Univ., Tokyo)

High myopia is one of the most important causes of visual impairment. We already showed that the refractive errors and status of fundus of the eye are the important factors for visual impairment in high myopia by multiple regression analysis. In this report, in order to see the relation between high myopia and the status of fundus of the eye, 848 patients, 1,358 eyes with more than −8.25D myopic eye, which were obtained from 83 University Hospitals in Japan during the two months since June of 1982, were analyzed by quantification method in which status of fundus was separated into 13 clinical features.

Posterior staphyloma, myopic macular hemorrhage, localized chorio-retinal atrophy and lacquer crack lesion were selected as important factors. Analysis of pattern divided the status of fundus into four groups. The first is conus and tigroid which are usually recognized in high myopic eye. The second is white without pressure, lattice degeneration and silent hole which are seen in peripheral fundus. The third is macular hemorrhage, Fucks's spot, posterior staphyloma and lacquer crack lesion and chorio-retinal atrophy which are phenomena seen in posterior pole of the pathological myopic eye. The fourth is retinal detachment and hole.

B44. Genetic Analysis of Psoriasis Vulgaris. Masahiko MUTO, Hideto KIMURA and Yoshio NAKAMIZO (Dept. Derm., Med. Inst. Bioregul., Kyushu Univ., Oita)

We investigated, by segregation analysis, the mode of inheritance of psoriasis vulgaris (PV) by using 93 psoriatic families. Out of the 93, 7 families of normal × affected mating and 83 families of normal × normal mating were collected by single selection, and 3 families of normal × affected mating were ascertained through parents (complete selection). Eighty-one normal × normal families (2 noninformative families out of the 83 families were excluded) were used. Out of the 81, 9 have two or more affected children. The hypothesis of a single dominant trait for the susceptibility to PV could be ruled out from the observation that many affected children were segregated from matings of normal parents. The family data were then analyzed under the null hypothesis that the susceptibility to PV was a single recessive or double recessive trait. In both cases of 81 whole intercross families and 9 multiplex intercross families, chi square values in the double recessive model were smaller than those in the single recessive model (109.57 *vs.* 127.39 in 81 families, and 2.10 *vs.* 3.22 in 9 multiplex families, respectively). When the single locus model was accepted, penetrance of the recessive gene ranged from 16% to 40%. These results suggest that the double recessive model than the single recessive model for PV is more tenable. Furthermore we suggested that there is a genetic heterogeneity for PV.

B45. Immunogenetic Analysis of Cryptomeria Pollinosis: V. Analysis of the Immune Suppression Using Monoclonal Antibodies. Sho MATSUSHITA,[1] Nobuo SOH,[2] Yozo SAITO[3] and Takehiko SASAZUKI[1] ([1]Dept. Genet., Med. Inst. Bioregul., [2]Dept. Otorhinolaryngol., Kyushu Univ., Fukuoka; [3]Dept. Otorhinolaryngol., Tokyo Med. Dent. Univ., Tokyo)

We have already demonstrated that the resistance to cryptomeria pollinosis (CP) is controlled by an HLA-linked gene through cryptomeria pollen antigen (CPAg)-specific suppressor T cells as a single dominant trait (Is-CPAg). To investigate the mechanism

of suppression in the molecular level, we tested the effects of monoclonal antibodies (MAbs) to T cell surface antigens on the immune suppression. Among 48 MAbs associated with T cell activation, MAb 4B4 blocked the $CD8^+$ T cell-mediated suppression of IgE response to CPAg, without direct stimulation of the immune response. The cross-linking of cell surface proteins with DSP, and immunoprecipitation with MAb 4B4 followed by SDS-PAGE showed that the 4B4 molecule was a heterodimer and was not cross-linked with any other surface molecules. Furthermore, the 4B4 molecule on PPD-specific $CD4^+$T cell line revealed a different pattern from that on PBL. The molecule was not polymorphic in terms of molecular weight and fluorescence staining. From these observations, it was conceivable that the 4B4 molecule plays an important role in the cell-cell interaction, in the suppression of immune response to CPAg.

B46. Segregation and Linkage Analysis of *In Vivo* IgE Response to Cryptomeria Japonica Pollen Antigen (CPAg). Kazuyuki HONDA, Sho MATSUSHITA, Takehiko SASAZUKI (Dept. Genet., Kyushu Univ., Fukuoka), **Norikazu YASUDA** (Div. Genet., Natl. Inst. Radiol. Sci., Chiba) **and Takeo JUJI** (Blood Transfus. Ser., Tokyo Univ., Tokyo)

We have already demonstrated that the resistance to Cryptomeria pollinosis (CP) was controlled by the HLA-linked immune suppresion gene (Is-CPAg) through antigen-specific suppressor T cells. In this study, genetic control of the *in vivo* IgE response to CPAg in human was analyzed using plasma of 525 members in 98 families. The 525 members were classed into the non and low responder group and the high responder group in terms of IgE response to CPAg. Segregation analysis by Morton's maximum likelihood scoring method revealed that the IgE non and low responsiveness to CPAg was a single dominant trait. The gene was designated as Is-CPAg. Is-CPAg was shown to be linked to HLA by using Morton's sequential linkage test, because a maximum lod score 3.40 was obtained at $\theta=0.18$. Gene frequency of Is-CPAg was calculated at 0.60. From these observations we concluded that the resistance to CP was mediated by an HLA-linked Is-CPAg not only using clinical manifestation, but also using anti CPAg antibody titer *in vivo*.

B47. 近親婚の家族集積性について. 今泉洋子 (厚生省人口問題研). **Familial Accumulation of Consanguineous Marriages in Japan. Y.** IMAIZUMI (Inst. Population Problems, Minist. Health Welfare, Tokyo)

最近調べた近親婚調査資料を用いて，近親婚の家族集積性が見られるか否か，さらに，近親婚の家族集積性に影響を及ぼす要因について検討を行った．その結果，旭川市を除いた5地域で近親婚の家族集積性は得られた．次に，年次別に見ると，夫側では1年次群を除いたすべての年次群において，

近親婚の家族集積性が得られた．一方，妻側では年次が新しくなるほど，家族集積性は見られなくなった．次に近親婚の家族集積性はなぜ生じるのかを検討した．まず，配偶者との出会いが，幼なじみ，他人の紹介，学校・職場・社会的な場に分けて近親婚の家族集積性が見られるか否かを見た．その結果，学校・職場・社会的な場での出会いのときには，近親婚の家族集積性は見られないが，幼なじみや他人の紹介の場合には家族集積性が見られた．次に，夫婦の出生地組み合わせ別に，近親婚の家族集積性を見ると，どの出生地組み合わせ別でも，近親婚の家族集積性が見られた．同じく，夫妻の学歴別に近親婚の家族集積性を検討した．その結果，夫妻の学歴が大学以上の場合と妻が短大・専門学校卒では，近親婚の家族集積性は見られなかったが，新制中学，新制高校卒では，まだ家族集積性が見られた．

B48. 寿命の基本的遺伝様式. 米村 勇[1]・中城巳佐男[1]・太田正穂[1]・福島弘文[1]・支倉逸人[1]・本山十三生[2]（信州大・[1]法医，[2]心脈管病研・生理）. **The Fundamentals of Inheritance of Longevity.** Isamu YONEMURA,[1] Misao NAKAJOH,[1] Masao OTA,[1] Hirohumi FUKUSHIMA,[1] Hayato HASEKURA[1] and Tomio MOTOYAMA[2] ([1]Dept. Legal Med., [2]Dept. Physiol., Inst. Cardiovasc. Dis., Shinshu Univ., Matsumoto)

高度純系のキイロショウジョウバエで短命系（S系，寿命遺伝子型は雄で SSX_1Y_1，雌で SSX_1X_1 と推定）および長命系（L系，雄は LLX_2Y_2，雌は LLX_2X_2 と推定）を用い，交配実験により寿命の遺伝様式を検討した．飼育条件は 27°C, 8% ドライイースト，新しく考案したプラスチック飼育瓶に雌雄別々に 30 匹ずつ飼育，餌は毎日交換，死亡観察は 24 時間ごと．その結果，正交配（S♂×L♀），逆交配（S♀×L♂）で F1♂ 寿命のみに相違が見られた．2 種類の F1 をそれぞれ S♂，S♀，L♂，L♀ に戻し交配したところ，交配の組み合わせにより寿命の分離は，きわめて複雑なものから比較的単純なものまでさまざまであったが，強い法則性が見られた．この実験系では，寿命遺伝子 (Jm) の S, L は常染色体上の対立遺伝子で S は劣性であった．交配の仕方により寿命の分離比，性差，死亡の開始日，最長寿命等に著しい変異が見られるが，すべて常染色体性および性染色体性 Jm の遺伝子型に基づいて細部にわたり説明しえた．新分野が開拓された．

B49. ヒト寿命の遺伝性. 大橋正明[1]・米村 勇[1]・中城巳佐男[1]・杉山ひろみ[1]・由井寿美江[1]・山崎百合子[1]・太田正穂[1]・福島弘文[1]・支倉逸人[1]・本山十三生[2]・釘本 完[3]・那須 裕[3]（信州大・[1]法医，[2]心脈管病研・生理，[3]公衛）. **Inheritance of Longevity Suggested in Man.** Masaaki OHASHI,[1] Isamu YONEMURA,[1] Misao NAKAJOH,[1] Hiromi SUGIYAMA,[1] Sumie YUI,[1] Yuriko YAMAZAKI,[1] Masao OTA,[1] Hirohumi FUKUSHIMA,[1] Hayato HASEKURA,[1] Tomio MOTOYAMA,[2] Mamoru KUGIMOTO[3] and Yutaka NASU[3] ([1]Dept. Legal Med., [2]Dept. Physiol., Inst. Cardiovasc. Dis., [3]Dept. Public Health, Shinshu Univ., Matsumoto)

共同研究者の米村，本山，支倉らにより解明されつつあるショウジョウバエにおける寿命の遺伝様式が，どの程度ヒトに適合するか検討を試みた．約 10 年前に長野県松本市近郊の人口 5,000 人ほどの A 村において高齢者を対象に聞き取った家系調査資料から，死亡年齢および死因の記載されているものについて親子間の寿命の関係を調べた．若年の死因には結核や出産時の死亡等が過半数を占め

ていたので，44歳以上の自然死のみを抽出した．この目的に合った資料は非常に少なかったが，同性の親子間に有意の正の相関が見られた．これは純系ショウジョウバエの結果に類似している．また，子の癌による死亡年齢は親子間に逆相関の傾向があり，とくに父と息子では有意であった．

B50. Yatabe-Guilford Personality Inventory in Twins. A. ASAKA, T. SAITO and M. OHNUMA (Dept. Mental Health, Univ. Tokyo Sch. Med., Tokyo)

Subjects were 50 twins, consisting of 40 MZ and 10 DZ pairs aged from 20 to 46. Among 12 subscales 8 intraclass correlation coefficients were highly significant in MZ, but none in DZ. These were A: leadership (0.68), G: activity (0.63), I: insufficiency (0.62), S: sociability (0.51), R: impulsiveness (0.43), T: superficiality (0.42), O: subjectivity (0.40), N: nervousness (0.33). As for the percent deviation, two subscales (S and I) were significantly smaller in living together than in living apart MZ. No association was observed between the percent deviation of each subscale and the present ages.

B51. The Frequencies of the Chromosomal Aberration and the Sister Chromatid Exchange in Lymphocytes from Twins. Kunihiko MIURA,[1] Kanehisa MORIMOTO,[1] Akira KOIZUMI, Kazuaki YAMADA[2] and Akio ASAKA[2] ([1]Dept. Public Health, [2]Dept. Mental Health, Univ. Tokyo, Tokyo)

Whole blood was drawn from monozygotic (pairs; 24) or dizygotic (pairs; 6) twins (aged 11.87 ± 0.34; mean $\pm$ SD) and their mothers (aged 40.16 ± 4.26) and fathers (aged 43.65 ± 5.24). Macro cultures have been done for each sample for 52 hr for the chromosomal aberration (CA) analysis, and for 72 hr with bromodeoxyuridine (40 μM) for the sister chromatid exchange (SCE) analysis. The cells for CA analysis were also exposed to γ-rays (2 Gy; dose rate, 0.5 Gy/hr) only or γ-rays and cytosine arabinoside (ara-C; 5×10^{-5} M) simultaneously at G_0 phase. The cells for SCE analysis were also treated with mitomycin-C (MMC; 3×10^{8} M) or 4-nitroquinoline 1-oxide (4NQO; 40 ng/ml) for the entire culture. The frequencies of the dicentric and ring (D+R) chromosomes and the SCEs were investigated on the air-dried samples. The D+R frequencies in cells exposed to γ-rays only or γ-rays plus ara-C showed no significant difference regarding to the zygosity. The SCE frequencies in non-treated, or MMC- or 4NQO-treated cultures also showed no difference regarding to the zygosity. Snedecor and Cochran's intra-class correlation coefficients between twin childrens showed no consistent tendency. SCE frequencies between twin children and their mothers showed no difference in zygosity.

B52. Analysis of Blood Lipids in Twins. A. ASAKA, K. YAMADA, T. MOTONAGA, K. TAKAHASHI, T. KADOWAKI and F. TAKAKU (Dept. Mental Health, Dept. 3rd Intern. Med., Univ. Tokyo Sch. Med., Tokyo)

Subjects were 45 twin pairs, consisting of 38 MZ and 7 DZ aged from 20 to 46. Intraclass correlation coefficients of MZ and DZ concerning blood lipids were as follows in the order of MZ and DZ: Triglyceride (0.64* (MZ), 0.37 (DZ)); total cholesterol (0.71*, 0.22); HDL cholesterol (0.55*, 0.76); LDL chilesterol (0.67*, 0.16); phospholipids (0.53*, 0.42); free cholesterol (0.75*, −0.12). The asterisk indicates significance at the level of 0.1%. If MZ and DZ were combined, these values were all significantly high also. The values of random pairs (N=45) (unrelated pairs) were ranged from −0.05 to 0.20, which were all not significant.

B53. Genetic Counseling: III. Comparative Study of Followup in Different Areas. Yoshiyuki OHNISHI (Sabae Health Cent., Fukui), **Kazuo MANO** (Nagoya Natl. Hosp., Nagoya), **Norio FUJIKI, Mikio HIRAYAMA, Tazuro MUTOH, Fumiko SATO, Akira TOKUDA and Shigeaki NAKAZAKI** (Dept. Intern. Med., Fukui Med. Sch., Fukui)

Our 2,205 cases of genetic counseling in Kyoto (1961–'70), Nagoya ('70–'81), and Fukui ('81–'86) were analyzed. The followup study was carried out three times in '69–'72, '77–'80 and '81–'86 successfully so that 231 of 698 counselees (33.1%) responded. Precise estimation of recurrence risk and treatment following early diagnosis were valuable for the client to understand the situation correctly and to influence their reproductive performance. It is evident that genetic problems exist troublesomely but correct common sense is spreading gradually in general public. The evaluation of clients in Fukui coincided with counselor slightly less, compared with that in Nagoya, and they inclined to react in a pessimistic or optimistic way. Misunderstanding and prejudice in Japanese general public is still so common. Since tremendous development of biotechnology has been caused the changes on the quality of life, we should discuss very carefully the moral norm and make our decision on the common understanding through both newly developed and old traditional evaluations. Therefore more time should be devoted to the knowledge of human genetics and bioethics in medical and postgraduate curriculum, in order to educate health personnels and general public. We emphasize significance of heredity clinic as a useful service for preventative measures of genetic medicine in the public health areas.

B54. 岐阜市中央保健所における遺伝相談：10年間の相談内容のまとめ. **安田寛二・服部　悟・松島昭廣・折居忠夫**（岐阜大・医・小児），**関谷貞子・中島恵子**（岐阜市中央保健所）. **Genetic Counseling in Gifu City Central Medical Health Center.** K. YASUDA, S. HATTORI, A. MATSUSHIMA, T. ORII (Dept. Pediatr., Gifu Univ. Sch. Med., Gifu), S. SEKIYA and K. NAKASHIMA (Gifu City Central Med. Health Cent., Gifu)

岐阜市中央保健所では，昭和52年9月から月1回の定期的な遺伝相談事業を開始し，本年で10年目を迎えたので，10年間の相談内容をまとめた．本年7月までの全相談件数は309件で，クライアントは20代，30代の女性が60%を占め，50代が次いで多かった．相談内容としては，1) 妊娠中の服薬，ウイルス感染などの胎児への影響を問うもの，2) 遺伝性疾患をもつ児の養育およびその再発危険率を問うもの，3) クライアント自身または子供の結婚に際し，近親婚の影響，クライアント側および相手側の家族のもつ疾患—精神疾患，口唇口蓋裂，色覚異常など—の再発危険率を問うもの，が大半を占めた．10年間の相談内容の変化は乏しかったが，この数年間に反復流死産や新生児，乳児早期死亡に関するものが数件あり注目された．医療機関からの紹介が少なく，市の広報活動や保健婦の日常活動に依存しており，保健所の特徴と思われた．今後，追跡調査を試みるとともに，高度化する診断技術に対応できる地域遺伝相談システムをすすめたい．

B55. 染色体異常が認められない両側性網膜芽細胞腫 (Rtb) の遺伝相談における Esterase D (EsD) の応用. **高橋幸雄・楢原幸二・吉川清志・脇田宜治・小田　慈・木村俊介・木本　浩**（岡山大・医・小児）. **Use of Esterase D (EsD) Polymorphism in Genetic Counseling of Bilateral Retinoblastoma (Rtb) without Chromosomal Abnormalities.** Y. TAKAHASHI, K. NARAHARA, K. KIKKAWA, Y. WAKITA, K. ODA, S. KIMURA and H. KIMOTO (Dept. Pediatr., Okayama Univ., Okayama)

両側性 Rtb は優性遺伝性疾患で，その浸透率は100%に近い．Rtb の発症には，Rtb 座位のホモ接合あるいはヘミ接合が重要であると考えられている．Rtb と EsD の遺伝子座位とは密接に連関していることが知られている．したがって，家族例で Rtb の親が EsD ヘテロ，あるいは散発例で体細胞が EsD ヘテロ腫瘍細胞がホモであれば，配偶者が EsD ホモの場合，同胞あるいは子孫の発症予知は全例可能である．一方，配偶者が EsD ヘテロの場合，それぞれ25%および50%の確率で予知可能である．症例および父親が Rtb である家族例2例（家系1, 2）および両側性 Rtb 散発例2例（症例3, 4）を対象として，同胞あるいは子孫の発症予知に EsD の多型性が応用されるかどうかを検討した．家系1における EsD 表現型は症例および母親で2型，父親および同胞で2-1型であり，家系2においては症例で1型，両親および同胞で2-1型であった．家系1では同胞の発症予知が可能であったが，家系2では不可能であった．症例3では，体細胞の EsD 表現型は2-1型，腫瘍細胞は1型であったことより，Rtb 座位は EsD 1遺伝子と連関していると考えられた．症例4では，体細胞・腫瘍細胞とも EsD 表現型は1型で有意義な情報が得られなかった．ヘテロの頻度が高い（約50%）日本人では EsD は有用な遺伝標識であり，その応用により約30%の家系で両側性 Rtb の発症予知が可能である．

B56. The Investigation of Psychological Reaction of Down Syndrome Parents. Mitsushiro KIDA (Dept. Pediatr., Teikyo Univ. Sch. Med., Tokyo)

The investigation was carried out by the questionnaire to parents of Down syndrome. The number of questionnaires answered and returned were 134. The range of patients age extends from 4 months to 36-year-old and the average age is 8-year-old 11 months. As for the distinction of sex, male patients take up 34.3% of the whole (46 persons) and female patients 65.7% (88). The number of patient's brothers and sisters were 104 and made up as follows: elder brothers 52, elder sisters 56, younger brothers 20 and younger sisters 22. Parents who had the feeling of heavy shock when their children were born were predominant and occupied 47.0% of the whole (63). The number of parents that had the feeling of confusion and anxiety were 21 (15.7%). The number of parents who calmly received handicap of their children were 18 (13.4%). The number of parents who have discussed the problems of handicap of their children were 32 (about 50%). The number of parents who were perplexed were 15 (23.5%). The number of parents who rejected their children passively were 9 (14.1%). The number of parents who rejected actively were 8 (12.5%). Twenty-two (27.8%) parents had impression that their children seemed to be very weak. Twenty (25.3%) parents thought that there were characteristics in their children's face and 18 (22.8%) parents felt that their children were pretty. Fifty-five (74.3%) parents answered that there were no troubles among their family including the patient's grandfathers, grandmothers, brothers and sisters who received warmly the patient. Seventeen (23%) parents answered that there were many troubles. Consultating with other Down syndrome parents, 29 (41.4%) parents were strongly supported mentally. On the other hand, only 8 (11.3%) parents were supported mentally by doctors and consultants. The result of this investigation indicates that it is very important for the doctor who consults Down syndrome patients to grasp the state of their parent's minds sufficiently.

B57. 臨床遺伝学における倫理的問題に関する調査. 大倉興司（東医歯大・難研・人類遺伝）. **A Survey as to Bioethics in Clinical Genetics.** K. OHKURA (Dept. Hum. Genet., Tokyo Med. Dent. Univ., Tokyo)

臨床遺伝学における倫理問題に関する異文化間の比較を行う目的で，Fletcher, J. C. (NIH) を中心に，世界19か国で行った調査のうち，17か国の資料を用い，わが国における倫理問題への対応の状況をアンケート調査に基づいて分析，比較した結果の一部を報告した．調査の対象は臨床遺伝学，とくに遺伝相談にかかわる医師，Ph.D.，その他で，回答数643，わが国はすべて医師で51である．アンケートには25の質問に対し，それぞれ5～8の対応を準備し，そのどれかを選択し，それを選んだ倫理的理由を記すものである．対応はごく日常に行われるものであるが，それぞれ，倫理的保証，すなわち，個人の自律性の尊重，第三者の（健康上の）利益，個人および家族に及ぼす害の排除去，平等などに関する判断が配慮されているかがわかるようになっている．

今回は，多数の分析結果のうち，情報提供，第三者への秘密保持と義務，カウンセリングが指示的か非指示的か，胎児診断の適用に関し，さまざまな条件に意見の一致の様相について分析したが，わが国では意見の一致をみるものもあったが，概して一致しない場合が多かった．また，今後 10～15 年以内に臨床遺伝学上重要となる問題について 10 の設問に対する順位づけでは，世界全体での対応とかなり大きく異なり，世界的に大きな問題となった有限の資源の配分に対して関心が示されなかった．

B58. Some Problems in Education of Human Genetics in the Medical Course of Japan. Hideaki CHIYO (Dept. Clin. Genet., Inst. Hum. Genet., Kanazawa Med. Univ., Ishikawa)

General professional educations in medical schools in our country have been reported to be too much biased for a specialized doctor and not suitable for a primary care doctor. Recently, the national examination for license of medical practice has changed very much by the opinions that the goal of general educations should be aimed in acquiring of the minimum knowledges and techniques which should be essential for primary care. So, when we plan to make a curriculum of human genetics, special cares such as 1) What are the minimum essential knowledges and techniques in human genetics? 2) How to teach and evaluate? would be desirable. To improve the education in human genetics in our country, 1) workshop on teaching methodology in human genetics, 2) publishment of a guide book in human genetics for primary care doctors, and 3) improvement of the national examination for license of medical practice, were proposed.

C1. Human Gamma-Globin Gene Arrangement and Expression. **Teruo HARANO, Keiko HARANO** (Kawasaki Med. Sch., Kurashiki), **Masahiko UKITA** (Kurashiki Cent. Hosp., Kurashiki), **Yoshinao WADA, Akira HAYASHI** (Osaka Med. Cent. Res. Inst., M.C.H., Osaka), **Yuzo OHBA, Takaoki MIYAJI** (Yamaguchi Univ., Ube) and **Titus H. J. HUISMAN** (Med. Coll. Georgia, USA)

Cord blood samples of 889 Japanese newborn babies from hospital in Osaka, Okayama and Yamaguchi Prefectures were analyzed for variations in the quantities of the γ chains ($^{A}\gamma^{T}$, $^{G}\gamma$ and $^{A}\gamma^{I}$) in Hb F. The DNAs prepared from these samples were digested with restriction endonucleases (*Xmn*I, *Bgl*II, *etc.*) and hybridized with a γ IVS II probe to detect presence of modifications in the γ-globin gene arrangement. Of the 889 newborns, 266 had the $^{A}\gamma^{T}$ chain in Hb F, and 15 were homozygotes. This corresponds to a frequency of 0.158, which is equal to that (f=0.156) in newborns from the Tokyo area previously reported. A modified γ-gene arrangement existed in 73 babies. Of these, 52, including one homozygote, had a γ-globin gene triplication ($^{G}\gamma$-$^{G}\gamma$-$^{A}\gamma^{I}$ and $^{G}\gamma$-$^{G}\gamma$-$^{A}\gamma^{T}$ types). Two had a γ-globin gene quadruplication ($^{G}\gamma$-$^{G}\gamma$-$^{G}\gamma$-$^{A}\gamma^{I}$ type). Eighteen, including one homozygote, had a different type of γ-globin gene arrangement, $^{A}\gamma$-$^{A}\gamma$. None, however, had a $^{G}\gamma$-$^{G}\gamma$ type arrangement. All of the babies with tri- or quadruplication γ-globin gene arrangement had a negative polymorphism for the *Xmn*I 5′ site to the first γ-globin gene ($^{G}\gamma$) in the arrangement, revealing a 13 kb or 18 kb fragment in addition to the normal 7 kb or 8 kb fragment when the *Xmn*I-digest was hybridized with the γ IVS II probe. The $^{G}\gamma$ value in the Hb F of these babies with tri- or quadruplication of the γ-globin gene was 77.5–84.8%, and that of the baby homozygous for the triplication γ-globin gene arrangement was 91.6%. From these γ chain analyses of babies possessing an $^{A}\gamma^{T}$ mutant in trans, it was expected that the production level of the $^{A}\gamma$ chain from the $^{A}\gamma$-globin gene in the 3′ position in the tri- and quadruplication arrangement would be lower than that from the $^{A}\gamma$-globin gene in the normal arrangement. The $^{G}\gamma$ value of the babies with the gene deletion was 35.0–51.6%, and that of the homozygote was 0% ($^{A}\gamma$ value: 100%), which suggests that the transcription of the single globin gene might be higher or equal to that of the 5′ γ-globin gene in the normal (or duplication) gene arrangement. In addition, four babies, who possessed normal γ chain proportions in Hb F, were observed to have two new fragment bands, 3 kb and 10 kb, in addition to the normal 13 kb fragment band when the *Bgl*II-digest was hybridized with the γ IVS II probe. This may become a new polymorphism for *Bgl*II around the γ-globin gene.

C2. Not Presented

C3. **Genetic Analysis of Familial Polyposis Coli (FPC): Linkage Analysis between FPC and HLA. Masayuki SASAKI, Jun-ichi SOEJIMA, Kenji SUGIO and Takehiko SASAZUKI** (Dept. Genet., Med. Inst. Bioregul., Kyushu Univ., Fukuoka)

FPC is transmitted as an autosomal dominant trait and is characterized by multiple adenomatous polyps localized in the large intestine and by high incidence of malignancy. Although the polyposis gene(s) is not identified, possible linkage between FPC and HLA has been suspected. We analyzed the linkage between them in this study. One hundred and eighty-two individuals from 66 pedigrees of FPC and the 108 individuals from normal population were assigned their HLA-A, B, C antigens. First, frequency of HLA class I antigens were compared between 66 unrelated patients of FPC and 108 normal controls, and no association of FPC with HLA was observed. Secondly, for linkage analysis, HLA haplotypes of 17 affected sib pairs were investigated by affected sib pair method. Number of pairs which shared 2, 1 and 0 haplotypes were 4, 9 and 4, respectively. The distribution was not significantly different from the random expected (4.25 : 8.5 : 4.25), indicating that there is no major gene for FPC that linked to HLA. Lastly, 7 families were analyzed by Morton's sequencial linkage test. A maximum lod score of -0.056 at a recombination fraction of 0.4, and a lod score of -3.089 at a recombination fraction of 0.05 was obtained. In conclusion, no linkage between FPC and HLA was confirmed by this study.

C4. **Mitochondrial DNA Polymorphisms among Five Asian Populations. Shinji HARIHARA, Momoki HIRAI, Naruya SAITOU** (Dept. Anthropol., Univ. Tokyo, Tokyo), **Takashi GOJOBORI** (Natl. Inst. Genet., Mishima), **Kyung Sook PARK** (Dept. Biol., Sung-Shing Women's Univ., Seoul), **Shogo MISAWA** (Dept. Legal Med., Univ. Tsukuba, Ibaraki), **Srinama Bandara ELLEPOLA** (Dept. Med., Univ. Peradeniya, Peradeniya), **Takafumi ISHIDA** (Primate Res. Inst., Univ. Kyoto, Inuyama) **and Keiichi OMOTO** (Dept. Anthropol., Univ. Tokyo, Tokyo)

Restriction enzyme fragment patterns of mitochondrial DNA (mtDNA) were analyzed using blood samples from five populations of east and south Asia: Ainu of northern Japan, non-Ainu Japanese, Korean, Negrito (Aeta) of the Philippines and Vedda of Sri-Lanka. Of 13 restriction enzymes used, eight exhibited polymorphism in mtDNA cleavage patterns. Among the mtDNA morphs observed, ten morphs have not been reported previously. Three aboriginal populations (Ainu, Aeta and Vedda) tend to bear poorer variation, though each showed one or two unique morphs with relatively high frequency. This particular distribution of mtDNA morphs may partly be attributed to random genetic drift in these relatively isolated populations. By combining the restriction enzyme morphs for each

individual, a total of 243 samples from five populations were classified into 20 mtDNA types. By comparing morph frequencies among the five populations and with those published for other racial groups, it is noted that the Ainu showed close affinity to the other Mongoloid populations. The Negrito, whose racial affinity has been of controversy, appears to be far separated genetically from the African populations including Pygmies. Putting the present results of mtDNA detected by four enzymes (*Ava*II, *Bam*HI, *Hpa*I and *Msp*I) and those reported by Johnson *et al.* (1983) together, the phylogeny among mtDNA types was analyzed. In the phylogenetic tree constructed by the method of Nei and Li (1979), it appears to exist two main clusters of mtDNA types, namely, an Asian and an African clusters. Whereas in the phylogenetic network made by the maximum parsimony method, there appears to be three main groups of types. One group is composed of the types detected only in the African populations. The other group is consisted of types related to one or two African mtDNA types. The last group contains the most frequent type (type 1) and its derivative types.

C5. Genetic Polymorphism of Human Factor H (β1H Globulin). Shigeki NAKAMURA, Osamu OHUE and Kazue ABE (Dept. Legal Med., Tokyo Women's Med. Coll., Tokyo)

Polyacrylamide gel isoelectric focusing (PAGIEF) of EDTA plasma samples at pH 3.5–9.5 with 8.0 M urea followed by an electroblotting with enzyme immunoassay was done for the detection of factor H(HF) phenotypes in 536 unrelated Japanese blood donors living in Tokyo and 63 matings with 76 offspring. Phenotypes of HF detected in the Japanese population were classified into three common and five rare patterns, and these were considered to be controlled by two common and two rare alleles. Recently, genetic polymorphism of HF was demonstrated by Rodriguez de Cordoba and Rubinstein (1984), by using high resolution isoelectric focusing of immunoprecipitated proteins under denaturing conditions. The results of the reference typing of HF by us and by Dr. Rodriguez de Cordoba failed to show coincidence, so these alleles were tentatively named *HF*A*, *HF*B*, *HF*A1*, and *HF*M*, respectively. The *HF*QO* allele was also detected in the Japanese population. The results of typing family material suggested the hypothesis that the genetic model of HF polymorphism was controlled by autosomal codominant Mendelian inheritance at a single locus. The gene frequencies were estimated as $HF^*A=0.4261$, $HF^*B=0.4895$, $HF^*A1=0.0103$, $HF^{**}M=0.0009$, and $HF^*QO=0.0732$, respectively. The difference of the gene frequencies of two common alleles, *HF*A* and *HF*B*, was very little. The distribution of phenotypes fitted the Hardy-Weinberg equilibrium.

C6. Gene Frequencies of *S*-Formylglutathione Hydrolase Isozyme in Japanese Population. Katsunori AKIYAMA and Kazue ABE (Dept. Legal Med., Tokyo Women's Med. Coll., Tokyo)

Genetic polymorphism of *S*-formylglutathione hydrolase (FGH) was investigated in a total of 581 red blood cell samples unrelated Japanese using the starch gel electrophoresis and enzyme activity staining procedure. Three common phenotypes were observed which corresponded to FGH 1, FGH 2-1 and FGH 2 controlled by two alleles, *FGH*1* and *FGH*2*. The estimated gene frequencies of *FGH*1* and *FGH*2* in Japanese were 0.67 and 0.33, respectively. This result was different from the result of the Japanese samples reported by Board and Coggan (1986). However, *S*-formylglutathione hydrolase phenotypes and esterase D phenotypes of these red blood cell samples were identical. It seemed that esterase D hydrolyzed *S*-formylglutathione in glutathione thiol ester group. Therefore, *S*-glutathione hydrolase reported by Uotila (1984) and Board and Coggan (1986) is possible to be esterase D.

C7. Two Families with a C7 Silent Gene (*C7*Q0*). Hiroaki NISHIMUKAI and Yoshihiro TAMAKI (Dept. Forensic Med., Med. Coll. Oita, Oita)

The existence of *C7*Q0* was found in six members of two Japanese families. C7 phenotyping was done by the method of agarose gel isoelectric focusing (AGIEF; pH 5–8) followed by immunoblotting (IB). Serum samples were treated with neuraminidase prior to isoelectric focusing. C7 protein concentration and C7 hemolytic activity in serum were measured by SRID and by a microtiter method using EAC1423 cell, purified C5, C6, C8 and C9, respectively. C6 phenotype was also determined by AGIEF and IB. [Family 1] C7 types were as follows: I-1 (father)=5-1, I-2 (mother)=2, II-1=5-2, II-2=5-2, and II-3=3-1. Both C7 protein concentration and hemolytic activity in sera from I-2 and II-3 were approximately half of NHS (normal control serum); the presence of *C7*Q0* was indicated. C7 genotypes in I-2 and II-3 were considered to be *C7*2/C7*Q0* and *C7*1/C7*Q0*, respectively. [Family 2] This is one of the cases of disputed paternity examined in our laboratory. C7 phenotypes were: child (III-1)=1, mother (II-1)=2, and the accused man (AM)=1. The C7 protein concentration and hemolytic activity in III-1 and II-2 samples were approximately half of NHS, indicating the existence of *C7*Q0*. Samples from the mother's family members (parents I-1 and I-2, brothers II-2 and II-3) were also analyzed; I-2 and II-3 were considered to be heterozygous for C7 deficiency. *C7*Q0* was transmitted from I-2 to II-1, and from II-1 to III-1. C7 genotypes were considered to be: I-1=*C7*2/C7*1*, I-2=*C7*1/C7*Q0*, AM=*C7*1/C7*1*, II-1=*C7*2/C7*Q0*, II-2=*C7*2/C7*1*, II-3=*C7*1/C7*Q0*, and III-1=*C7*1/C7*Q0*. (In this case, AM was shown to be the biological father with a high probability, from the results of 29 blood group typings excluding C7.)

In the two families, *C7*Q0* was transmitted as a haplotype *C7*Q0-C6*B*, suggesting an existence of the association between the two genes.

C8. Amino Acid Substitutions Responsible for Subtypes (2, 1F, 1S) of Human Gc Protein. **Shigenori ITO, Kouichi SUZUKI, Kiyoshi MATSUI and Hideo MATSUMOTO** (Dept. Legal Med., Osaka Med. Sch., Osaka)

We confirmed the two of four substitutions, which were suggested by Cooke (*J. Clin. Invest.* **76**: 2420–2424, 1985), by sequence analysis of subtype-specific peptides. Gc protein (subtype 2, 1F, or 1S) was purified from normal human serum with an individual homozygote by the method according to Hara (*Jpn. J. Legal Med.* **38**: 273–279, 1983). BrCN peptides of reduced and carboxymethylated Gc proteins were purified by gel filtration (Sephadex G-50) and ion-exchanger column chromatography (FPLC-mono Q), and then the tryptic digests responsible for a subtype were chromatographed on HPLC-RPC (Cosmosil 5C18). The results, from sequence analysis of the subtype-specific tryptic peptides, revealed that Gc2 protein had an aspartic acid at position 416 and other proteins had glutamic acids. On the other hand, Gc2 and 1S had the same residue (lysine) at position 420 and Gc1F had a threonine.

C9. 骨髄移植における患者の血液および唾液系遺伝標識の挙動. **池本卯典[1]・梶井英次[1]・土田修一[1], 中木陽子[2]・橋本好一[2]・高木省治郎[2]・雨宮洋一[2]・三浦恭定[2]** (自治医大・[1]人間生物, [2]輸血). **Genetic Markers in Blood and Saliva of Bone Marrow Transplantation.** Shigenori IKEMOTO,[1] Eiji KAJII,[1] Syuichi TSUCHIDA,[1] Yoko NAKAKI,[2] Koichi HASHIMOTO,[2] Shojiro TAKAGI,[2] Yoichi AMEMIYA[2] and Yasusada MIURA[2] ([1]Dept. Hum. Biol., [2]Dept. Hemat., Jichi Med. Sch., Tochigi)

ある骨髄移植における患者の血液および唾液系遺伝標識41座位，すなわち赤血球系12，白血球系5，血清(補体)系12，血球酵素系5，唾液系7について，移植後約7カ月後の遺伝標識の挙動を観察した．その結果，Donor 型に転換した標識は ABO(O→B), P(P_1(+)→P_1(−)), Duffy($Fy^{a,b}$→Fy^a), EsD(2-1→1-1) であった．その際，ABO システムは O と B のモザイク状態を経て B 型に転換した．血清中の抗 A と抗 B は抗 A のみになった．注目していた Gm, Km システムは当事者はともに同じタイプであった．なお，毛髪の ABO システムは転換しなかった．転換しなかった遺伝標識は Lewis, Se, Hp, F13-B などの血液系遺伝標識と，Pa, Pr, PmF, Db などの唾液系遺伝標識であった．これらは，骨髄以外で産生されるものと思われる．Donor と Recipient の間で適合していた遺伝標識は，MNSs, Rh (CcDEe 因子), Kidd, Lutheran, Kell-Cellano, Diego, Xg, HLA(A, B, C, DR, D 座位), GLO, AcP, 6PGD, PGM, Gc, Tf, Gm, Km, Bf, PLG, C2, C6, C7, C8-1, Pb, PIF, Amylase (Amy_1) システムなどであった．これらの成績から，取りあえず骨髄から産生される抗原系およびそれ以外の組織（たとえば唾液腺など）から産生される抗原系を区別することが可能と思われる．また，抗原の挙動から移植細胞の生着程度を推定できるかもしれないと考えている．

C10. Analysis of 6-Phosphogluconate Dehydrogenase Isozyme by Polyacrylamide Gel Isoelectric Focusing Electrophoresis. Katsunori AKIYAMA and Kazue ABE
(Dept. Legal Med., Tokyo Women's Med. Coll., Tokyo)

Using polyacrylamide gel isoelectric focusing electrophoresis, genetic polymorphism of 6-phosphogluconate dehydrogenase (6PGD) was investigated in total of 429 red blood cell samples from unrelated Japanese. The samples were a 1 : 10 dilution of 0.05 M (DTT), and applied to the gel surface at a distance of 1 cm from the anodal end. Polyacrylamide gel consisted of 3.45 ml acrylamide (29.1%), 5.25 ml bisacrylamide (0.9%), 0.2 ml riboflavin (20 mg/%), 0.68 g MOPS, 2.5 g sucrose, 1.5 ml carrier Ampholytes LKB (pH 5–7, pH 7–9; 1 : 2), and adjusted to 40 ml. IEF was carried out at 1,200 V, 50 mA and 25 W for 3 hr with cooling at 4°C. The enzyme activity staining procedures were carried out according to the method by Harris and Hopkinson (1976). The three common 6-PGD phenotypes were detected by different isoelectric points and the enzyme activity of isoelectric focusing patterns. These 6PGD isozymes were not detected by polyacrylamide gel using *N,N,N′,N′*-tetramethylethylenediamine (TEMED) and ammonium peroxodisulfate. Gene frequencies calculated from 429 individuals were 0.915 and 0.085 for 6PGD A and 6PGD C, respectively. These frequencies were similar to the gene frequencies of Japanese samples reported by several authors in Japan.

C11. Control of Lewis, H and Secretor Genes in Primates. Tamiko NAKAJIMA, Shin YAZAWA, Seiko MIYAZAKI, Tadahisa KOGURE and Ken FURUKAWA
(Dept. Legal Med., Sch. Med., Gunma Univ., Maebashi)

The glycoprotein and glycolipid fractions of primate tissues were extracted by saline and chloroform-methanol (CM). ABH and Lewis activities of the extracts were examined by agglutination inhibition test. Although the red cell ABH antigens were recognized only by the elution test, the saline extract of tissues from prosimians, new and old world monkeys tested in this series showed ABH activities correspond to the human secretors. Le^a antigen was developed in tissues of new world monkeys as well as on red cells. Japanese monkeys and baboon which belong to the old world monkeys had Le^a and Le^b antigens in their tissues. Like in humans ABH and Lewis antigens were detected strongly in upper part of digestion system, especially stomach in ABH and small intestine in Lewis. In humans the ABH and Lewis antigens on soluble glycoproteins result from the action of genes at three independent loci, the *ABO*, *Hh* and *Lele* loci. The presence of the ABH antigens, but not on red cells is also affected by the action of the independent secretor genes *Se* and *se*. The most of these genes act by controlling the enzymic addition of single sugar residue to the glycoprotein. The red cell Lewis phenotypes was not always correlate with ABH secretor status of monkey tissues. Human Le(a−b−) cells transformed to Le(a+) or Le(b+) after

incubation with CM extracts of the Japanese monkeys. The Lewis antigens on red cells of monkeys were not integral parts of the red cell membrane like the ABH antigens, but were acquired from the plasma glycolipid as in humans.

C12. Effects of 5-Azacytidine on the Stalks of Human Acrocentrics Reveal the Presence of at Least Two Stalk-Sub-Regions and Suppression of Satellite Association.
Y. HIRAISHI, M. KATO and K. IINUMA (Natl. Child. Med. Res. Cent., Tokyo)

5-Azacytidine (AZ) was used in the last 7 hr of peripheral leukocyte culture, at a final concentration of 3×10^{-7} mole. It's effects were monitored on the short arms, stalks, and satellite regions of human acrocentrics (chromosomes 13–15, 21 and 22) obtained from 11 males and 9 females, whose phenotypes and karyotypes were normal. Q- and Ag-double staining technique revealed prominent elongation of stalks after AZ treatment. Furthermore, localization of silver grains, interpreted to be identical to nucleolus-organizing-regions (MOR), was limited to the distal area of the elongated stalks. There was apparently no change in the NOR size after AZ treatment. These results suggest that effects of AZ are expressed exclusively upon the proximal area of stalks. The frequencies of satellite association (SA) in three persons were also analyzed to see if there was any correlation with AZ treatment. The total frequency of SA in the AZ-treated cultures was 160/780, compared with the control value of 132/820 ($p < .025$). It still remains to be determined whether such a suppression effect by AZ is variable with individual chromosomes.

C13. Investigation of High Resolution G-Band Patterns of Human Chromosomes.
Shizuhiro NIIHIRA and Hiroko FUJITA (Dept. Child Health, Osaka City Univ., Osaka)

1) Shading patterns of 550-band idiogram: Standard idiograms of the International System for Human Cytogenetic Nomenclature (ISCN) are used to analyze high resolution G-bands of human chromosomes. The idiograms are expressed in black and white, but it is not enough to analyze them accurately. We studied 550-band idiograms using their shading pattern. We classified the 225 dark bands into three degrees of darkness. There were 68 very dark bands, 83 moderately dark bands, and 74 lightly dark bands. Some bands showed individual differences. The pattern of shading corresponded fairly well to that of ISCN idiograms (154 of 225 bands). This method would increase the efficiency of analysis of high resolution G-bands of human chromosomes. 2) Analysis of subdivided bands: Each of the 550- or 850-band idiograms of ISCN shows one stage of the mitotic chromosomes between prophase and metaphase, and there was not an intermediate standard banding pattern. We studied the patterns of subdivided bands in 550- to 850-banded

chromosomes. They varied from cell to cell, and homologous chromosomes did not always show the same pattern of subdivisions. These results are essentially important when small constitutional chromosome abnormalities are analyzed.

C14. Studies on Characterizations and Staining Affinities of Quinoline Derivatives to Human Chromosomes. Kouichi MAMBA (Dept. Vet. Anat., Yamaguchi Univ., Yamaguchi), **Misako GOMI, Mutsuo KITAHAMA** (Dept. Legal Med., St. Marianna Univ. Sch. Med., Kawasaki) **and Akira UCHIUMI** (Natl. Chem. Lab. Indust., Tsukuba, Ibaraki)

The present study was carried out to examine the characters and staining affinities of four quinoline derivatives as new fluorescent dyes to human chromosome samples. These four quinoline derivatives synthesized were 9,10-anthracene-dialdehyde-bis(4-methyl-quinoline-2-yl) hydrazone, 9,10-anthracene-dialdehyde-bis(4,6-dimethyl-quinoline-2-yl) hydrazone, 9,10-anthracene-dialdehyde-bis(4-methyl-6-methoxy-quinoline-2-yl) hydrazone and 9,10-anthracene-dialdehyde-bis(benzothiazolyl) hydrazone. The following results were obtained. 1) The colors of fluorescences of four quinoline derivatives showed yellowish-green. 2) The absorption maximum values of these derivatives were between 348 and 440 nm, and the dissociation constants (pK_a) were between 5 and 6. 3) 9,10-Anthracene-dialdehyde-bis(benzothiazolyl) hydrazone showed less staining affinity among these derivatives to the samples. 4) The dye pair 9,10-anthracene-dialdehyde-bis(4-methyl-quinoline-2-yl) hydrazone/methyl green, 9,10-anthracene-dialdehyde-bis(4,6-dimethyl-quinoline-2-yl) hydrazone/methyl green, 9,10-anthracene-dialdehyde-bis(4-methyl-6-methoxy-quinoline-2-yl) hydrazone/methyl green produce a strong banding pattern in the centromeric area of a pair of chromosomes 1 and 9.

C15. A Fluorescence Spectroscopic Study in Counterstain of Distamycin A(DA) and 4′,6-Bis(2′-Imidazolinyl-4′,5′-H)2-Phenylindole (DAPI). Norio MIYOSHI,[1] Sakon NORIKI,[1] Mamoru OZAKI,[2] Mashio KITATANI,[2] Yoshiaki CHIYO[2] and Masaru FUKUDA[1] ([1]Dept. Pathol., Fukui Med. Sch., Fukui; [2]Dept. Clin. Genet., Inst. Hum. Genet., Kanazawa Med. Univ., Ishikawa)

Recently, it has been studied by Schweizer that the chromosome banding patterns produced by certain fluorescent dyes could be enhanced or modified by counterstaining. The dye combination of the type A-T/A-T produces a specific pattern of brightly fluorescent heterochromatic regions (DA-DAPI bands). In man, this method highlights the C bands of chromosomes 1, 9, 15, 16 and Y. In this study, we measured the fluorescence spectra and intensity of DAPI in various polynucleotide solutions. In double-strand (A-T) and

double-strand (C-G) polymer solutions, the enhancement efficiency of the DAPI fluorescence by polynucleotides and the quenching constant of the DAPI fluorescence by DA were obtained by using a fluorescence spectrophotometer (Hitachi Co., Ltd., Model 850). As a result of the measurements, the DAPI fluorescence was enhanced remarkably in double-strand (A-T) polymer solutions, and was markedly quenched by DA molecule in double-strand (C-G) polymer solutions. From these results, it was considered that the DA-DAPI band brightly fluoresced at the homogeneous A-T rich regions of heterochromatin. In contrast, it was assumed that there was the quenching of the DAPI fluorescence by DA at the heterochromatic regions which contained C-G paris, because of the absorption spectral overlap of DAPI and DA.

C16. 染色体検査における画像解析装置の導入. 後藤俊博・藤沢美朗・松田正利・大久保三郎 (塩野義製薬・臨床検), **北谷真潮・千代豪昭** (金沢医大・人類遺伝研).
Introduction of Automatic Image Analyzer in Chromosome Analysis. Toshihiro GOTO, Yoshio FUJISAWA, Masatoshi MATSUDA and Saburo OKUBO (Clin. Lab., Shionogi Co., Ltd.), Mashio KITATANI and Hideaki CHIYO (Dept. Hum. Genet., Kanazawa Med. Univ., Ishikawa)

近年，染色体分析に画像解析装置と専用のプログラムが導入されるようになってきた．ルーチン染色体検査にこのシステムを導入する場合，種々の問題点が考えられる．今回，当検査室に導入した画像解析装置 MAGISCAN 2 (Joyce Loeble 社) の検体処理能力，分析の信頼性および本システムを活用するための条件について検討した．その結果，全自動でのスキャニングが可能 (8 slides/day) なため検鏡時間が従来よりも短縮できた．また，メタフェーズ検出能力は検査員と比べて遜色がなく，順次明瞭なメタフェーズを呼び出せるうえ，各操作段階が簡便で筆記による記録が不要のため分析時間も短縮できる．1メタフェーズ当たりの染色体数のカウントと核型分析の所要時間はそれぞれ約37秒，4分30秒であるが，標本の作製状態により分析の速度と信頼性は大きく左右された．分析の信頼性については，染色体数をカウントする場合，標本の状態にかかわらず約30～33本となり10本以上少なく認識し，カリオグラムの作製の場合は良好な標本ほど適中率が高くはなるが 60～70% までであり，さらに構造異常の同定能力を有していないため，いずれの場合も検査員の関与が必須であった．なお，付属のハードコピー装置を用いることで従来の写真撮影以降の手間が省けるが，解像力にやや難点がある．［まとめ］本装置により染色体検査の大幅な効率化が図れるが，分析（カウント，カリオグラムの作製および異常の検出）には熟練した検査員の関与が必須である．

C17. Localization of Multidrug Resistance-Associated DNA Sequences to Human Chromosome 7. N. SHIMIZU,[1] A. FOJO,[2] R. LEBO,[3] J.E. CHIN,[4] I.B. RONINSON,[4] G.T. MERLINO,[2] M.M. GOTTESMAN[2] and I. PASTAN[2] ([1]Dept. Mol. Biol., Keio Univ. Sch. Med., Tokyo; [2]Lab. Mol. Biol., NCI, USA; [3]Univ. California, USA; [4]Univ. Illinois Coll. Med., USA)

Multidrug resistance in several human cell lines correlates with amplification or in-

creased expression of two related DNA sequences, designated *mdr*1 and *mdr*2. *mdr*1 encodes a 4.5 kb mRNA, and it is amplified or overexpressed in all multidrug-resistant human cell lines analyzed. No mRNA corresponding to *mdr*2 has so far been detected. *mdr*2 DNA sequences are coamplified with *mdr*1 in some but not all multidrug-resistant cell lines, and it was unknown whether *mdr*1 and *mdr*2 DNA sequences are linked in the genome. To further characterize the human *mdr* genes, we have attempted to determine their chromosomal localization. For this, DNA sequences *mdr*1 and *mdr*2 were used as probes for blot hybridization with DNA from a panel of human-mouse somatic cell hybrids and from individual human chromosomes separated by fluorescence-activated chromosome sorting. These analyses indicated that both *mdr*1 and *mdr*2 sequences were localized to human chromosome 7.

C18. Mapping of Human Insulin Receptor-Related Genes Using Human-Mouse Somatic Cell Hybrid Clone Panel. **Jun KUDOH,[1] Axel ULLRICH[2] and Nobuyoshi SHIMIZU** ([1]Dept. Mol. Biol., Keio Univ. Sch. Med., Tokyo; [2]Dept. Devel. Biol., Genentech. Inc., South San Francisco)

Southern blot analysis of DNAs from a panel of human-mouse somatic cell hybrid clones revealed that human insulin receptor (INSR) gene is localized to chromosome 19. For this, ^{32}P-labeled 1 kb-*Eco*RI fragment of p12.2 probe which covers amino-terminal coding region of the human INSR cDNA was hybridized to the *Eco*RI digests of DNAs from 7 human-mouse cell hybrid clones. A major 2.7 kb-*Eco*RI fragment was detected only in hybrids containing human chromosome 19. This chromosome assignment agrees well with the previous reports[1,2]. Interestingly, we found three weakly hybridizable fragments of 5.0, 5.4 and 11 kb in the *Eco*RI digests of human placenta DNA, suggesting the existence of the INSR-related genes. To clone these fragments, we have constructed a human placenta DNA library containing *Eco*RI fragments using λgt11 phage vector. About 100,000 independent clones were screened with the INSR cDNA probe and 4 positive clones were obtained. Structural analysis and chromosome mapping of these INSR-related genes are currently under investigation.

1) Ebina, Y. *et al.* 1985. *Cell* **40**: 747–758.
2) Yang-Feng, T.L. *et al.* 1985. *Science* **228**: 728–731.

C19. 染色体異常児の胎内発育について. 笹本喜代・高林俊文・佐々木裕之・小沢信義・新宅裕子・曽 宗仁・斉藤純也・矢嶋 聰(東北大・医・産婦人). **Intrauterine Growth of Fetus with Chromosome Abnormalities.** K. SASAMOTO, T. TAKABAYASHI, H. SASAKI, N. OZAWA, Y. SHINTAKU, S. SOU, J. SAITO and A. YAJIMA (Dept. Obstet. Gynec., Tohoku Univ., Sendai)

高年齢の妊婦より染色体異常児出生率が高くなることは知られている. しかし35歳未満の母親よりの出生数は全出生数の約95%を占め, 出生率は低いといえども染色体異常児の出生実数は多い. 妊婦全例に対しての染色体検査は不可能であり, その発生率から考えても不必要とするのが妥当である. そこで, 染色体異常児を生む危険率が35歳以上のものと同じぐらいの群を選び出すなんらかのスクリーニングが必要となる. 昭和56年10月より昭和61年7月までに当科で出生または出生後他施設より搬送され染色体異常と診断された21 trisomy 8例, 18 trisomy 2例, 13 trisomy 1例につきretrospectiveに BPD (biparietal diameter), FFL (fetal femur length) を検討した. 当科で作製したBPD, FFL曲線にプロットしたところ, 21 trisomyでは10パーセンタイル値付近, 18 trisomyでは10パーセンタイル以下の値を示していた. これらは, 胎児のIUGRの予測とともに染色体異常児の胎内診断のスクリーニングの一助となると考えられた.

C20. Hereditary Spherocytosis in the *de novo* Interstitial Deletion of the Short Arm of Chromosome 8. Mashio KITATANI,[1] Hide-aki CHIYO,[1] Mamoru OZAKI,[1] Hiroko KAWASHIMA,[1] Norimasa SERA[2] and Shoichiro SHIKE[2] ([1]Inst. Hum. Genet., [2]Dept. Pediatr., Kanazawa Med. Univ., Ishikawa)

The hereditary spherocytosis (HS) gene has been mapped to the short arm of chromosome 8. Kimberling *et al.* (1975) reported the close linkage between HS and familial translocation t(8;12) (p11;p13). Bass *et al.* (1983) reported a similar case with HS and familial translocation t(3;8)(p21;p11). Thus, the HS gene locus was suggested to be on the short arm of chromosome 8. We investigated a 17-months-old boy with HS and an interstitial deletion of the short arm of chromosome 8. His karyotype was 46,XY,del(8)(p11.22p21.1). He had pre- and postnatal growth retardation, psychomoter retardation, microcephaly, frontal bossing, epicanthal folds, high arched palate, Cupid's bow mouth, micrognathia, micropenis, cryptorchidism, hypoplastic nail of second finger and sacral dimple. The gene for glutathione reductase has been mapped to chromosome 8p21.1, but his glutathione reductase activity was within a normal range. There was no spherocytosis on the blood films of his parents who had normal karyotypes. In our case, the HS gene was not transmitted from his parents, but due to *de novo* mutation. The fortuitous concurrence of HS and interstitial deletion in one person is very unlikely. The common breakpoint of 8p11 in the reported and our patients seems to have a significance. The chromosome aberration might cause the disfunction of HS structural gene or disturb the regulating system. Beighle *et al.* (1977) also reported a case with deletion of the short arm of chromosome 8, but there was no description of spherocytosis.

C21. A Case of Chromosome 11 Short Arm Deletion. **Kazumi IKAWA, Emiko NAKAYAMA** (Ishikawa Health Service, Kanazawa), **Hideo NAKAMURA** (Kanazawa Red Cross Hosp., Kanazawa), **Shigeru MARUYAMA** (Holly Spirit Hosp., Kanazawa), **Seizo MASUTANI and Naoyuki TANIGUCHI** (Dept. Biochem., Osaka Univ., Osaka)

A three-months-old female was diagnosed as having chromosome 11p− because of bilateral aniridia, nystagmus, enlarged fontanel, prominent nasal bridge, and CHD (ASD+ peripheral PS). Wilms tumor was not found by ultrasonography. High resolution G-banding revealed normal chromosomes in the parents, and 46,XX,del(11)(p12p14) or 46,XX,del(11)(p13p15) in the patient. Low catalase (gene locus at 11p13) activity and normal LDH isozyme (gene locus at 11p12) pattern revealed the break point at 11p1300. Thus, the deleted segment was determined to be 11p1300→p1500. Although the high resolution G-banding technique can detect very small chromosomal abnormalities, it is necessary to use gene dosage or DNA studies to determine the exact chromosomal defect.

C22. A Case of 13q Proximal Partial Trisomy. **K. WAKUI,[1] N. HASHIMOTO,[1] A. YAMAGISHI,[1] T. NISHIDA,[1] Y. HAYASHI[2]** ([1]Dept. Clin. Lab., [2]Div. Hematol. Oncol., SCMC, Saitama), **I. KONDO** (Dept. Hum. Genet., Inst. Basic Med. Genet., Univ. Tsukuba, Ibaraki) **and Y. FUKUSHIMA** (Dept. Hum. Genet., Roswell Park Memorial Inst., USA)

The patient, a 4-month-old male infant, was born to unrelated healthy parents after a 41-week pregnancy. At birth the father was 31 years old, and the mother was 26. The birth weight was 2,706 g, length 48 cm, and head circumference 33 cm. He had many unusual features including growth failure, developmental delay, peculiar facies characterized by microcephaly, short palpebral fissures with upward slant, strabismus internus, low nasal root, large nose, high nasal bridge, micrognatia, small mouth, hypoplastic herix and malformed ears, cleft palate, small penis, cryptorchidism, contracture of fingerjoints, tapering fingers, overlapping fingers, single flexion crease, hydronephrosis of the left kidney, and Morgagni hernia. Hematological studies showed an elevated number of nuclear projections in neutrophils, and high level of fetal hemoglobin. Chromosome analysis of the patient showed an extra small abnormal acrocentric chromosome. The patient's mother had a balanced translocation: 46,XX,t(10;13)(p13;q14.3). The patient's karyotype was interpreted as 47,XY,+der(13),t(10;13)(p13;q14.3)mat. A gene for esterase D (ESD) is assigned to human chromosome 13q14.11 (Ward *et al. J. Med. Genet.* **21**: 92–95, 1984), and a gene for lymphocyte cytosol polypeptide with molecular weight of 64,000 (LCP1) is located in the region q14.1-14.3 of chromosome 13 (Kondo *et al. Cytogenet. Cell Genet.* **40**: 673, 1985). We have studied phenotypes and enzyme activities of ESD or protein amounts of

LCPl in the patient with dup(13)(pter-q14.3) and his parents. The patient had a type 1 of ESD and the enzyme activity was 1.5 times greater than that of individuals with normal karyotype. He had a type 1 of LCPl, and the protein amount was 1.09 to the mean protein amounts of the parents. The data indicates that the gene order for ESD and LCPl is: cen---ESD---LCPl---qter.

C23. Pseudodicentric 18 Associated with Hypoglycemia and Cholestasis Due to ACTH Deficiency and Hyperammoniemia. Mitsuo MASUNO,[1] Yoshitsugu SUGIO,[1] Yoshikazu KUROKI[1] and Yasunobu NAKANO[2] ([1]Div. Med. Genet., [2]Div. Neonatol., Kanagawa Child. Med. Cent., Yokohama)

A five-month-old boy with 45,X,−18,−Y,+psu dic(18)t(18;Y)(p11.2;p11.2) is described. This is the third case with unbalanced translocation between 18 and Y chromosome, but the first with pseudodicentric. The proband was the second product of 29-year-old mother who had the history of two artificial abortions and 30-year-old father, who were unrelated. An elder brother is normal. He was born at 38 weeks of gestation. Birth weight was 2,495 g. The early neonatal period was complicated with convulsion due to hypoglycemia and hypocalcemia. For prolonged jaundice and craniotabes, we diagnosed neonatal hepatitis and rickets. On 86th day after birth, he became lethargy. He had hypoglycemia (7 mg/dl) and hyperammoniemia (740 μg/dl). The cause of hypoglycemia and cholestasis was attributable to cortisol deficiency due to ACTH deficiency. Two months later from the beginning of supplementary therapy of hydrocortisone, jaundice disappeared. But the cause of hyperammoniemia was unclear. Thyroid function and immunoglobulin were within normal range. CT scan of the brain was normal. Skeletal survey was normal except for rt-lumbar rib. He had mental retardation, severe growth retardation, hypotonia, frontal bossing, epicanthus, rt-blepharoptosis, depressed nasal bridge, short nose, high arched palate, preauricular dimples, mild micrognathia, short neck, redundant skin at nape, short limbs, diastasis recti, coccygeal sinus, small penis, hypoplastic scrotum, bilateral cryptorchidism. These clinical features were compatible with 18p− syndrome. Finger patterns were all whorls and TFRC was 161.

C24. Ring Chromosome 21 in a Mother and Daughter. Tatsuro IKEUCHI, Fu QIAO, Kohtaro YAMAMOTO (Dept. Cytogenet., Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo), **Yoshishige NISHIKAWA and Takuo MIGITA** (Dept. Pediatr., Tokyo Metropol. Hosp., Tokyo)

Familial transmission of unbalanced chromosome structural abnormalities is quite rare. We report here a case of ring chromosome 21 which was transmitted from the mother. The

proband was a 1.5-year-old female infant born to a 25-year-old mother and a 32-year-old father. The birth weight was 2,303 g. At the age of 4 months, it became apparent that she had a high-pitched cry and hypertelorism. No other characteristic clinical features were noted. DQ at 1 year of age was 102. At the age of 1 year and 5 months, her weight was 8.5 kg, and height 72 cm. There was no mental or growth retardation, except for a slightly poor weight increase. The mother showed no remarkable clinical signs, although her facial features were somewhat similar to those of the daughter. Chromosome analyses using peripheral leucocyte cultures from the patient and her mother demonstrated that both had a ring chromosome 21, r(21). Prometaphase analyses at the 550-band level revealed the break points in the formation of r(21) to be at the distal ends of both arms. The r(21) was never involved in satellite association, and had no NORs as revealed by Ag-staining. There was no evidence of mosaicism with karyotypically normal cells or cells lacking the r(21) in either the daughter or her mother. A lymphoblastic cell line (8328L) was established from peripheral blood of the patient by EBV-mediated transformation, and the ring was found in most of the cells examined even after prolonged culture for 4 months. The mild or little phenotypic abnormality in the present two cases might have been attributable to the very small amount of deletion in the r(21) and/or the intrinsic morphological stability of the ring chromosome, which might also have facilitated transmission of the ring chromosome through the maternal meiotic process to the daughter.

C25. Two Cases of Down Syndrome with Hallucinatory-Delusional States. **Touru ISHIDA, Hiroshi YONEDA and Toshiaki SAKAI** (Dept. Neuropsychiat., Osaka Med. Coll., Osaka)

Two cases of Down syndrome with hallucinatory-delusional states are reported. Case 1: The patient is a 28-year-old male. In Oct. 1983, he began having auditory and visual hallucinations, and delusional perception, and was admitted to our hospital. After the admission his florid pathological experiences disappeared with the treatment of neuroleptics. However, he remained in an apathetic state. His karyotype was 47,XY,+21. His pre-psychotic IQ was 42. His maternal cousin has also a history of admission to a mental hospital because of psychotic symptoms. Case 2: The patient is a 30-year-old female. Since Aug. 1984, she gradually became hyperkinetic and experienced auditory hallucinations. These psychotic symptoms disappeared with the treatment of neuroleptics. Her karyotype was 47,XX,+21. Before the psychotic episodes, she was cheerful and had many friends. Her mother was hypervigilant and paranoic. It has been reported that the psychotic symptoms associated with Down syndrome are mainly cataleptic or hyperkinetic. It is rare that patients with Down syndrome show hallucinatory-delusional states. Some researchers suggest that, because of the low intellectual level, psychotic patients of Down

syndrome may display bizarre behavioral symptoms rather than recognizable hallucinatory-delusional states. However, the IQs of our cases were 35 and 42, *i.e.* within the expected range of Down syndrome patients. From our two cases, we suspect that the other factors than the low intelligence level, *i.e.* the prepsychotic level of social adaptation and a family history of psychiatric disorders may play an important role in manifesting hallucinatory-delusional symptoms.

C26. Late Replication Pattern of a Familial Balanced X/4 Translocation. Kenji NARITOMI, Kiyotake HIRAYAMA and Chuken MIYAGI (Dept. Pediatr., Univ. Ryukyus, Okinawa)

Late replication pattern of the X chromosome was analyzed by means of BrdU-Hoechst 33258-Giemsa method in a family with a balanced X/4 translocation. BrdU was added to the medium 4 to 5 hr prior to the harvest of lymphocytes. The propositus was a 7-year-old girl. She visited to our clinic because of short stature, mental retardation and minimal Turner phenotype. The karyotype was verified as 46,X,t(X;4)(p21.2;q12) by high resolution banding technique (GTG, RHG). Family study revealed that the same translocation was found in her mother and two sisters. All of them had mental retardation and minimal Turner phenotype. One sister, one brother and their father had a normal karyotype. DNA replication pattern of lymphocytes was the same in all of four translocation carriers. Namely, the normal X chromosome showed selective late replication in all the cells observed (50 to 100 cell counts). Correlation between phenotype and karyotype in balanced X/autosome translocations was reviewed in 49 previously reported cases with replication study and four cases in this presentation. Mental retardation is associated with breakpoints in Xp, *i.e.* p11 to p12. Primary amenorrhea is associated with breakpoints in Xq, *i.e.* q13 to q26.

C27. 羊水染色体検査における性染色体異常. 木下芳広（慶応健康相談センター），**畑中 諭・田村昭蔵**（慶大・医・産婦人）. **Sex Chromosome Abnormalities from Prenatal Cytogenetic Diagnosis.** Yoshihiro KINOSHITA (Keio Health Counsel. Cent., Tokyo), Satoshi HATANAKA and Shozo TAMURA (Dept. Obstet. Gynec., Keio Univ., Tokyo)

1972年から始めた羊水染色体検査は，関連病院等からの検体受付を含めて1986年9月に1,215例に達した．そしてこのうち30例に不均衡型染色体異常（*de novo* 均衡転座1例を含む）を認めた．このうち性染色体異常は12例で，全異常例の40.0%と大きな部分を占めている．性染色体異常の内訳は，45,X 2例，47,XYY 3例，47,XXY 2例，47,XXX 3例，45,X/46,XX 1例，および45,X/47,XXX 1例であった．またこれらの適応別内訳は，40歳以上の高年齢妊娠3，35～39歳の高年齢妊娠3例，

染色体異常児出産既往 1 例，その他の適応 4 例および産科適応（羊水過多等，妊娠 25 週以降）1 例であった．その後，これらの性染色体異常例のうち 1 例は自然流産，1 例は妊娠中期胎児死亡，8 例が両親の希望による妊娠中絶，1 例が妊娠継続中そして 1 例が未報告である．胎児死亡あるいは妊娠中絶後に胎児に外表奇形あるいは臓器奇形が認められたのは，2 例であった．羊水染色体検査ではもし異常が認められた場合に，性染色体異常の占める割合が大きいこと，またそれぞれの性染色体異常の phenotype についても事前に client に十分説明しておくことが必要だと思われる．

C28. Skeletal Anomalies in a Patient with the Pallister/Teschler-Nicola/Killian Syndrome. Hiroko KAWASHIMA (Inst. Hum. Genet., Kanazawa Med. Univ., Ishikawa)

We report a 3 8/12-year-old boy with the Pallister/Teschler-Nicola/Killian syndrome and previously unreported bilateral skeletal anomalies consisting of small feet and short but otherwise normal humeri, ulnae, femora and fibulae. His peripheral blood chromosomes were normal; however, an abnormal karyotype of 47,XY,+i(12p) was found in 100% of his fibroblasts.

C29. Two Cases of Beckwith-Wiedeman Syndrome. Masafumi HANDA,[1] Shizuhiro NIIHIRA,[2] Tomoko HASHIMOTO,[1] Noriko MATSUMOTO,[1] Sawako TACHIBANA,[3] Ikuko AMEMIYA,[4] Chieko KOIKE,[5] Nobuhiko OKAMOTO,[6] Masaru NISHIDA[7] and Jun-ichi FURUYAMA[1] ([1]Dept. Genet., Hyogo Coll. Med., Nishinomiya; [2]Dept. Child. Health, Osaka City Univ., Osaka; [3]Dept. Plastic Surg., Kyoto Univ., Kyoto; [4]Dept. Pediatr., Kansaidenryoku Hosp., Osaka; [5]Dept. Pediatr., Izumi-Ootsu City Hosp., Izumi-Ootsu; [6]Osaka Med. Cent. Res. Inst., Maternal Child Health, Osaka; [7]Dept. Pediatr., Osaka Pref. Hosp., Osaka)

Beckwith-Wiedeman syndrome (B.W.S.) is an autosomal dominant disease characterized by three principal features: exomphalos, macroglossia and giantism. Recently much attention is being given to B.W.S. because it has been related to the high frequency of chromosome 11 abnormalities and neoplasms. Here we report two cases of B.W.S. Case 1: This patient (Y.F.) is a 4-year-old male infant. The birth weight was 4,400 g. He had macroglossia, diastasis recti, dysmorphic face, ear lobe anomalies and cardiac deformity (small VSD). There was no hemihypertrophy, mental retardation or abdominal malignant tumor. Chromosome analyses from peripheral blood lymphocytes and skin fibroblasts revealed a karyotype of 46,XY,t(4;11)(q28;p15). His mother had the same balanced translocation. His father was normal. Case 2: This patient (N.F.) is a 1-year-old male infant. His birth weight was 4,600 g. He had macroglossia, exomphalos, right hemihypertrophy, cryptorchism and hepatomegaly. There was no cardiac deformity, mental retardation or

abdominal malignant tumor. His karyotype was normal. Our two patients showed typical clinical features of B.W.S. compared with the those of 11p trisomy syndrome.

C30. **多数の切断点を有する不均衡型複合転座 t(2;3;11;12) の双生児例.** **脇田宣治・楢原幸二・吉川清志・木村俊介・木本 浩** (岡山大・医・小児), **依田忠雄** (岡山赤十字・小児) **Monozygotic Twin Cases with an Unbalanced Complex Translocation Involving Chromosomes 2.3.11. and 12.** Y. WAKITA, K. NARAHARA, K. KIKKAWA, S. KIMURA, H. KIMOTO (Dept. Pediatr., Okayama Univ., Okayama) and T. YODA (Dept. Pediatr., Okayama Red Cross Hosp., Okayama)

複雑な染色体構造異常の解析には，高精度分染法のみならず遺伝子量効果研究の応用が不可欠である．2,3,11 および 12 番染色体間にみられた複合転座の双生児例を経験した．症例は生後 1 カ月の女子双生児．父親 26 歳，母親 20 歳の時に出生．在胎 38 週，出生体重はそれぞれ 1,840 g および 2,034 g．2 症例いずれにも，前頭部突出，眼裂狭小，鞍鼻，小顎症，高口蓋，低位で後方へ回転した耳介，ブロンドの頭髪，両側第 5 指内彎，両側第 2 および低位鎖肛がみられ，また，仔猫様の泣き声が認められた．染色体分析で，2 症例いずれにも 2, 3, 11, 12 番染色体に 8 個の切断点を有する複雑な不均衡型相互転座が認められた．核型は，46,XX,t(2; 3; 11; 12) (11qter→11q13.1::2p23→2p16.2::2p15→2q21::2p16.2→2p15; 2qter→2q21::3p23→3qter; 11pter→11q13.1::3p23→3pter; 12pter→12q24.1::2p23→2p25.1::12q24.1→12qter) と考えられ，2p25.1→2pter の欠失が推測された．2p23 および 2p25.1 に存在する malate dehydrogenase (MDH_1) および acid phosphatase (ACP_1) の遺伝子量効果は正常で，核型分析の結果と一致していた．両親の染色体は正常であった．なお，14 種類の血液型を用いて検討した結果，症例の卵性は一卵性であった．

C31. **Hoechst 33258 Inducible Chromosomal Fragile Sites.** **Motoi MURATA** (Div. Epidemiol., Chiba Cancer Cent., Chiba), **Ei-ichi TAKAHASHI and Tada-aki HORI** (Div. Genet., Natl. Inst. Radiol. Sci., Chiba)

A number of heritable fragile sites (FS) have been identified on human chromosomes. They are classified into three groups, *i.e.* folate sensitive, BrdU requiring, and distamycin A inducible ones. Although Hoechst 33258 treatment has been regarded as having a comparable effect with distamycin A, we sometimes experience a qualitative or quantitative disagreement for the induction of FS by the two chemicals. Thus, a survey of FS on a healthy population was conducted by using Hoechst 33258 treatment. Peripheral whole blood samples were cultured for 72 hr in a folic acid and thymidine deprived Ham's F10 medium including 5% fetal calf serum and 2% PHA for testing folate sensitive FS, and in an RPMI 1640 medium including 10% fetal calf serum and 2% PHA for testing the other kinds of FS. Treatments of BrdU (7 μg/ml), distamycin A (50 μg/ml) and Hoechst 33258 (25 μg/ml) were done for the last 24 hr. Among 300 blood donors, 20 carriers of Hoechst 33258 inducible FS at the following chromosome sites were detected; 8q24 (4 cases), 16q22

(2 cases), 17p12 (8 cases), 6p2 (1 case), 16p11 (1 case), 16q13 (4 cases). While the former 3 FSs can also be induced by distamycin A, the latter FSs are not. A family study in one case of FS at 16q13 revealed that both parents of two carrier sibs were not a carrier. We have not yet done a family study for FSs at 6p2 and 16p11. Thus, at present the exact characteristics of these FSs, including their heritability, are not clear.

C32. Three Cases of *de novo* Multibreak Chromosome Rearrangements: Negative Relationship to Folic Acid-Sensitive Fragile Sites in the Parents. Tsutomu KAMEI, Sei OKIMOTO, Norio NIIKAWA, Yasusi YAMADA (Dept. Hum. Genet. Dept. Psychiat., Nagasaki Univ., Nagasaki) **and Masato TSUKAHARA** (Dept. Pediatr., Yamaguchi Univ., Ube)

Three patients with *de novo* complex chromosome rearrangements are reported. These patients all had multiple anomalies and mental retardation. The karyotype of Patient 1 showing 7 breakpoints was as follows: 46,XX,t(1;2)(1pter→1q32::2q37→2qter), t(6;10)(6pter→6q25::10p13→10pter;6qter→6q25::10p13→10qter), dir ins(3;5)(3pter→3q26.2::5q11.2→5q15::3q26.2→3qter;5pter→5q11.2::5q15→5qter). The karyotype of Patient 2 with 4 breakpoints was: 46,XX,t(8;11)(11p13→11p15::8p11→8pter;8pter→8p11::11p15 11qter), inv(5)(pter→q13::q35→q13::q35→qter). The karyotype of Patient 3 with 7 breakpoints was: 46,XY,t(6;10;10)(6pter→6q15::10q22→10q25::10p13→10pter;10qter →10q24::10p13→10q22::6q21→6q15::6q21→6qter), del(4)(pter→q21::q25→qter). The chromosome rearrangements of Patients 1 and 2 seem to be balanced, while those of Patient 3 included a partial monosomy for 4q22-24 which was ascertained to the paternal origin by the analysis on QFQ-heteromorphism. All of the parents had a normal karyotype. The folic acid-sensitive fragile sites of the parents of Patients 1 and 2 did not correspond with the breakpoints of the patients.

C33. Chromatid Interchanges and Mitotic Chiasmata Induced by Ethanol and Aphidicolin. Akira KUWANO and Tadashi KAJII (Dept. Pediatr., Yamaguchi Univ. Sch. Med., Ube)

This report deals with the location of 2,732 breaks induced in 600 lymphocytes from 2 healthy women, cultured with 0.2 μM aphidicolin plus 0.02% or 1% ethanol. A total of 35 common fragile sites, representing 77% to 89% of total breaks, were identified. Most frequent among them were those at 3p14, 16q23, 7q32, 14q24, 2q32, Xp22 and 1p31. Chromatid interchanges in 2,300 lymphocytes, most of them quadriradials, were observed among 78 chromosomes with their exchange points proportional in frequency to the fragile sites observed. Mitotic chiasmata were encountered 5 times, involving 1p31, 2q37, 3p14,

16q23 and Xp22, and triradials were observed at 2p13, 2p11.2, 3p14, 5q22, 6q21, 9q21 and 13q13.

C34. The Effect of Arabinosylcytosine or Uridine on the Expression of Fragile Sites in Human Cultured Lymphocytes: fra(3p14) in Congenital Anomaly and Cancer. **Mariko UEHARA and Mitsushiro KIDA** (Dept. Pediatr., Teikyo Univ., Tokyo)

We studied the effects of arabinosylcyltosine (ara-C, AC) or uridine (Urd) on the expression of fragile sites in human cultured lymphocytes from patients with different diagnoses. Seven patients with a normal karyotype included one each case of growth retardation, leukemia, primary amenorrhea, growth retardation, mental retardation, Wilms' tumor, Werner's syndrome. Three subjects with an abnormal karyotype were: one case of Prader-Willi syndrome (PW) [46,XX,del(15)(q11q13)], the mother of the PW patient [46, XX,del(15)(q11q13)/47,XX,del(15)(q11q13), +minute], and a case of Down's syndrome (DS) (47,XX,+21). Peripheral blood lymphocytes were cultured for three or four days in medium RPMI 1640 (−folic acid), supplemented with 5% fetal calf serum and 2% phytohemagglutinin. Urd (8 mM) or AC (1, 2.5 and 5 μg/ml) was added to the medium for the last 24 or 48 hr of cultures. Non-banded or G-banded chromosomes were analyzed in 50 cells in each preparation. In the subjects with spontaneously high expression of fra(3p14) the expression was suppressed with Urd-treatment. Conversely, spontaneously low expression was enhanced with Urd. AC-treatments slightly enhanced ($p < 0.01$ in mean frequencies) the spontaneous expression of fra(3p14). In the Prader-Willi patient and the mother the yields of breaks, gaps and fragile sites were similar in both the Urd-treated and untreated preparations. In Wilms' tumor 75 total breaks, 12 fra(1p31) and 32 fra(3p14) were observed in 50 untreated cells, showing the highest frequencies in the ten subjects studied. In Werner's syndrome, although AC enhanced expression of fra(3p14), Urd reduced it. Dose response of fra(3p14) or total breaks was not observed with 1–5 μg/ml AC.

C35. A Fragile X Female with Down Syndrome—A Case Report. **Tadao ARINAMI** (Ibaraki Pref. Colony Hosp., Ibaraki), **Kazuki TAMURA** (Ibaraki Child. Hosp., Ibaraki) **and Ikuko KONDO** (Dept. Hum. Genet., Univ. Tsukuba, Ibaraki)

The propositus was born at 38 weeks' gestation as an eighth child of a 40-year-old mother and a 50-year-old father. Birth weight was 2,468 g. Most of the craniofacial features at the age of 2 months were similar to those of Down syndrome, but the following clinical features, which might be attributed to the fragile X syndrome, would lead to the "atypical" appearance of Down syndrome: a long head without flat occiput, a relatively long face, relatively large earlobes, and relatively prominent jaw. In family history, the

mother, one brother, one sister, and three male cousins (sons of a sister of the mother) were mentally retarded. Chromosome analysis of the proband's lymphocytes cultured in TC199 medium and treated with 10^{-6} M of FUdR for the last 24 hr showed that 21% of the cells examined had the fragile X chromosome and every cell had the extra 21 chromosome, which was identified to be of maternal first meiotic origin with QFQ banding. On the other family members, the fra(X) was seen in 13, 15, 10 and 27% of cells examined in the mother, one brother and two sisters, respectively. Her development was extremely retarded at the age of five months and is expected to be so serious as to need constant care in the future, as was another case with trisomy 21 and fra(X) reported by Dunn *et al.* (1962) and Jacobs *et al.* (1980). Fra(X) studies are recommended in all cases of Down syndrome with seriously retarded development and/or with a family history of mental retardation.

C36. EGF Receptor-Hyperproduction in Human Squamous Cell Carcinoma Lines and Their EGF-Insensitive Variants. Shinobu GAMOU, Masamichi HIRAI and Nobuyoshi SHIMIZU (Dept. Mol. Biol., Keio Univ. Sch. Med., Tokyo)

Increased levels of EGF receptor (EGFR) are often associated with human squamous cell carcinomas (SqCC) and their derived cell lines. In most cases, EGFR gene amplification was found responsible for the increased EGFR levels. Peculiarly, growth of the receptor-hyperproducing cells is inhibited by EGF. To investigate the mechanism of EGF-mediated inhibition of cell growth, we attempted to isolate EGF-insensitive variants from two SqCC lines, NA and Ca9-22, both having high numbers of EGFR and the amplified EGFR gene. The variants ER6 and ER11 which were isolated from NA cells after several cycles of EGF treatment rather grew in an EGF-dependent manner. Scatchard plot analysis revealed the decreased levels of EGFR in these variants ($\sim 0.2 \times 10^6$ receptors/cell) as compared to the parental NA cells (3×10^6 receptors/cell). Southern blot analysis and RNA dot blot analysis showed that these variants had lost the amplified EGFR genes. Karyotype analysis showed the loss of a unique rearranged chromosome in these variants. The variant CER1 which were isolated from Ca9-22 cells grew well without being affected by EGF. Scatchard analysis revealed extremely high numbers of EGF receptor in this variant (4×10^6 receptors/cell) whereas EGFR gene copy number was similar to Ca9-22. Interestingly, down-regulation of the EGFR occurred in CER1 cells upon EGF exposure and the reduced receptor level was kept for a long period of time, suggesting an alteration in the endocytic mechanism. These data suggest two independent mechanisms by which EGF receptor-hyperproducing cells escape from the EGF-mediated growth inhibition: one mechanism is to lose the amplified genes and the other mechanism is to uncouple signal transduction from the receptor endocytosis.

C37. Chromosome Aberrations in Ovarian Cancer. Kimio TANAKA (Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima) **and J.R. TESTA** (Cancer Cent., Univ. Maryland)

Thirteen ovarian cancer specimens (7 ascites and 6 tumors) derived from 9 patients were analyzed cytogenetically. The types of their disease included 3 endometrioids, 2 serous cystomas adenocarcinomas, 2 mucinous cystomas adenocarcinomas, 1 carcinosarcoma, and 1 unclassified tumor. Three patients had a hypodiploid modal chromosome number, 2 were hyperdiploid, and 4 near-triploid to tetraploid. Extensive and complex numerical and structural abnormalities were seen in all patients. One case had double minute chromosomes with a modal chromosome number of 53. Karyotypic heterogeneity within a tumor was very common. Aberrations of chromosomes 1,3,6,7 and 10 were observed in 7, 5, 6, 5 and 5 patients, respectively; but no specific rearrangements were observed. The translocation between chromosomes 6 and 14, as previously reported in papillary type ovarian tumors, was not detected in our specimens. Breakpoints frequently involved in the rearrangements were at bands 1p34, 3p14, 6q15, 6q21, 7p12, 8p21, 12q14 and 21q12. The bands on chromosomes 1, 6 and 7 nearly correspond to the loci of the oncogenes c-*src*, c-*ros*, c-*myb*, *mcf*-3 and c-*erb*. Among the patients in whom chromosome aberrations were examined at two different sites (ascites and tumor), ascites had more complex karyotypes than tumors. In one patient studied twice (*i.e.*, before and during treatment), the degree of structural abnormalities was significantly increased in the second sample. Our findings indicate that karyotypes in ovarian tumors are extremely complex, and that the extent of chromosome change correlates with tumor progression.

C38. Chromosome Analyses of Tumor Tissues from Patients with Familial Polyposis Coli. Mitsuaki A. YOSHIDA, Tatsuro IKEUCHI, Akira TONOMURA (Dept. Cytogenet., Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo), **Michiko MIYAKI** (Tokyo Metropol. Inst. Med. Sci., Tokyo), **Takeo IWAMA and Yoshio MISHIMA** (Dept. 2nd Surg., Tokyo Med. Dent. Univ., Tokyo)

Familial polyposis coli (FPC) is a cancer-predisposing disease characterized by autosomal dominant inheritance of adenomatous polyps in the colon and rectum. Affected individuals have a high incidence of colon and other various tumors. In the present study, chromosome analyses were performed on tumor tissues from patients with FPC by the application of enzymatic disaggregation method. The tumor materials were obtained from 4 patients, including 3 cases of colon cancer (Cases 1, 2 and 4) and one case of duodenal papillary cancer (Case 3). The tumor tissues were usually transplanted into athymic nude mice to establish the cell lines, and chromosomes were successfully analyzed in 2 primary tumors and 4 tumors developed in nude mice. Modal chromosome number was near-

diploid in Cases 1 and 4, and near-tetraploid in Case 2. Case 3 showed a normal karyotype in the nude mouse transplanted tumor. Detailed analyses of Q-banded chromosomes demonstrated various structural changes; in Case 1, t(6;7), t(8;13), t(15;17), 10p+, 13q+, 19q+ and del(6q) were identified, and 1p−, 7p+ and 12p+ in Case 4. Case 2 showed abnormalities including i(13q) and i(17q). Of interest was the finding that, in Case 1, double minutes were frequently observed in both the primary and transplantable tumor cells.

C39. Quantification of the Frequency of "Spontaneous" SCEs in Bloom's Syndrome Fibroblasts. **T. KURIHARA,[1] K. TATSUMI[2] and M. INOUE[1]** ([1]Cent. Res. Lab., Kanazawa Med. Univ., Ishikawa; [2]Dept. Molec. Oncol., Kyoto Univ., Kyoto)

Cells from Bloom's syndrome (BS) patients show a high frequency of spontaneous mutation, and DNA-chain maturation is lower in BS cells than in normal cells. In addition, it has been reported that the extremely increased SCEs in BS lymphocytes were spontaneous. However, there are some reports that most of the SCEs observed in BS lymphoid B-cell lines were induced by the BrdU incorporated into the parental DNA strands. In the present study, the frequency of spontaneous SCEs in BS fibroblasts was examined by using a new method of experimental rationale. The frequencies of SCEs observed on the second metaphase chromosomes after BrdU substitution during just the first or the second cell cycles were defined to "A" and "B", respectively. The frequencies of reciprocal and non-reciprocal SCEs on the third metaphase chromosomes during successive three cell cycles in the presence of BrdU were also defined to "Q" and "P", respectively. An equation obtained from the method, $(B-2Q)(A-B+2Q)/4Q$, expresses the frequency of spontaneous SCEs per single strand per cell cycle. From the calculation of above equation, the spontaneous SCEs per two cell cycles in BS cells were 49.6 and 53.6 at 15 and 3 μM of BrdU (the baseline SCEs were 63.5 and 60.4), respectively. This result suggests that most of the baseline SCEs in BS fibroblasts are spontaneous SCEs, and extremely high frequency of the spontaneous SCE formation may reflect an intrinsic defect in BS cells.

C40. A Japanese Girl with Bloom Syndrome Suffering from Malignant Lymphoma. **Satoshi ISHIKIRIYAMA, Takaaki SHIKANO, Masato OOKAWA and Kenji FUJIEDA** (Dept. Pediatr., Sch. Med., Hokkaido Univ., Sapporo)

She was small for date at birth (1,140 g, 40 w). Afterwards, she has been stunted. She developed malignant lymphoma at six years of age. She is now under chemotherapy. She didn't experience frequent infectious diseases and erythemas or bullae after exposure

to sunlight. At seven years of age, her height was 96.6 cm (−4.8 SD), and her weight 10.2 kg (−3.3 SD). There were a lot of cafe-au-lait spots on the body and subtle telangiectasia on the cheeks, which might be due to steroid therapy. The left leg was larger than the right one. She had partial syndactyly on the left foot. Her peripheral lymphocytes exhibited an increased frequency of sister chromatid exchanges, 76.1±33.70/metaphase (control: 4.9±3.53/metaphase). Immunoglobulins were all within normal range. It is said that photosensitivity is relatively mild in girls and in the Japanese. We could also find only minimum change in the skin. Including our case, a total of nine patients belonging to eight families have been reported in Japan. Only one of them was a product of consanguineous marriage. Those facts suggest that Bloom syndrome is more frequent in the Japanese than in other non-Jewish groups. Bloom syndrome is important as a differential diagnosis for short stature in Japan.

C41. Dicentric and Monocentric Structure of an Isochromosome for the Long Arm of Chromosome 17, i(17q), in Blast Crisis of Chronic Myelogenous Leukemia.
Shinichi MISAWA, Masafumi TANIWAKI, Tatsuo ABE and Tatsuro TAKINO (3rd Dept. Med., Kyoto Pref. Univ. Med., Kyoto)

An isochromosome for the long arm of chromosome 17 was studied using C-banding as well as high-resolution G-banding in four patients with chronic myelogenous leukemia at blast crisis. The diagnosis of one patient is provisional, because B cell acute leukemia can not be ruled out. The i(17q) observed in two patients was noticed to be dicentric with G-banding and was confirmed with C-banding. The breakpoint was assigned at 17p11.2 in these two cases. The i(17q) in the remaining two patients appeared monocentric with G-banding. C-banding studies showed a single C-band in these two cases. The breakpoint was considered to be within the centromere. These results disclosed morphological heterogeneity of i(17q), dicentric and monocentric, and the breakpoint differs from case to case within a narrow range of 17cen-17p11.2.

C42. Chromosome Analyses in 477 Patients with Acute Nonlymphocytic Leukemia.
Yasunobu YOKOYAMA, Hiroko SATOU, Keiko TAKAHASHI, Yoshimori ISHIHARA and Toshimi GUNJI (Div. Cell Morphol., Spec. Ref. Lab. Co., Hachioji)

A total of 477 patients with acute nonlymphocytic leukemia (ANLL) have been studied cytogenetically by G- and Q-banding methods during a period from 1984 to 1986. The ANLL patients were divided into 24 separate groups from the types of chromosome aberration according to the modification of the First International Workshop on Chromosomes

in Leukemia. Among the 477 patients, 218 cases could be diagnosed as one of the subtypes M1-M6 by the FAB classification. Some clinical-cytogenetic correlations were established as follows. 1) Chromosome aberrations were found in 57.3% (125/218) of subtypes M1-M6. 2) Translocation t(8;21) was found in 26.1% (12/46) of M2 cases, and in one case of M3-variant type. 3) Translocation t(15;17) was found in 79.3% (46/58) of M3, including one case which showed 15q+ and i(17q−). 4) Translocation t(16;21)(p11;q22) was found in 11.9% (5/39) of M4 cases. 5) Rearrangement of 21q22 was found not only in t(8;21) but also in 3 types of translocations: t(16;21)(p11;q22), t(3;21)(p14;q22) and t(3;21)(q26;q22). 6) inv(16) was found in M2, M4 and M5 cases. Especially in M4, it was found in 17.9% (7/39). 7) Rearrangement of 11q23 was found in 18.5% (5/27) of M5 cases: t(9;11) in two cases and t(11;19) in one case, *etc.* 8) No specific chromosomal aberration was found in M6, but hypodiploid cases seem to be more frequent. 9) Trisomy 22 and 7q− were more frequent as an additional aberration in cases with inv(16). 10) Translocation t(7;11) was found in 4 cases, including 2 cases of M2. 11) Translocation t(6;11) was found in 7.7% (3/39) of M4 cases. 12) Monosomy 7 was found as a sole abnormality in only one case of M1. 13) In the t(8;21) and inv(16) groups, there was an excess of males (M38/F21) and (M9/F4), respectively.

C43. Cytogenetic Studies on Childhood Acute Lymphoblastic Leukemia. Toshiro NISHIDA, Akira YAMAGISHI, Keiko WAKUI, Masaaki YAMADA (Div. Lab., Saitama Child. Med. Cent., Saitama), **Yasuhide HAYASHI, Masahiro NAKASHIMA, Toshiya INABA, Ryoji HANADA and Keiko YAMAMOTO** (Div. Hematol. Oncol., SCMC, Saitama)

Using G and Q banding techniques, chromosomal analyses were made on peripheral blood or bone marrow aspirate from 15 patients with acute lymphoblastic leukemia (ALL). The immunologic studies indicated that 2 cases were of T cell origin, 3 cases of B cell origin, and the remaining 10 cases of non-T non-B cell origin. In both the T-cell leukemias an interstitial deletion between q21 and q25 of the long arm of No. 6 was found. A t(8;14)(q24;q32) was found in all the cases of B cell origin. A t(11;19)(q23;p13) was found in 3 cases with non-T non-B marker. Two of them expressed myeloid antigen, My 7 and My 9, simultaneously. We consider that the t(11;19)-associated leukemia had biphenotypic characteristics. Four cases with hyperdiploid chromosome abnormality (>50) have been alive for 5 to 18 months. We consider that the hyperdiploid (>50) cases have a good prognosis. Two cases with a ring chromosome died after a short period. A case with Ph^1 chromosome was found to bear both lymphoid and myeloid antigens, and died 13 months later.

C44. Cytogenetic Analysis of Lymphoid Cell Lines. Takashi ABE, Kanji SUGITA, Kazuyoshi NISHINO, Shinpei NAKAZAWA (Dept. Pediatr., Keio Univ., Tokyo), **Yasuhide HAYASHI and Keiko YAMAMOTO** (Div. Hematol. Oncol., Saitama Child. Med. Cent., Saitama)

Cell lines with specific chromosomal abnormalities are important for molecular genetic studies because they can provide the basic material that could elucidate the genetic mechanisms involved in neoplasia. We reported here some interesting chromosomal abnormalities in 11 cell lines. Five cell lines were established from patients with Burkitt's lymphoma/leukemia (KOBK-96, KOBK-101, KOBK-130, KOBK-134, KOPB-Y1); one was from a patient with non-Burkitt's type B-ALL (KOPB-26); three were from patients with common ALL (KOPN-1, KOPN-K, KOPN-32). KOCL-22 was originated from a patient with congenital leukemia who underwent morphological change from FAB-L2 at diagnosis to M5b at relapse. The translocation of t(8;14)(q24;q32) was found in KOBK-96, KOBK-130 and KOBK-134. The abnormal chromosome of 14q+ was found in KOPB-Y1, but the origin of the translocation segment could not be determined. KOBK-101 had the t(2;8)(p11;q24). KOPB-26 had an abnormal chromosome, der(11)t(11;?)(q23;?). All three cell lines established from patients with common ALL had the deletion and/or translocation of 17p. KOPN-1 and KOPN-32 had the terminal deletion 17p11, and KOPN-K had the t(12;17)(p12;p11). The 12p12 breakpoint which was found in KOPN-K was previously reported as the nonrandom involvement in chromosome abnormalities of non-T non-B ALL by Dorothy Williams. Both KOCL-22 and its original leukemic cells had the same translocation, t(11;19)(q23;p13). A-122, a normal B cell line derived from the peripheral blood of a patient with CML and transformed by EBV, had an abnormal chromosome, del(6)(q11).

C45. Human Lymphoblastoid Cell Lines Established by Esptein-Barr Virus and Ciclosporin (Cyclosporin A). Ikuko KONDO,[1] Ichiro KANAZAWA[2] ([1]Dept. Hum. Genet., [2]Dept. Neurol., Univ. Tsukuba, Ibaraki) **and Kohtaro YAMAMOTO** (Dept. Cytogenet., Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo)

Recent advances in molecular genetic techniques for diagnosis of genetic disorders and studies of genetic pathology have stimulated the need to store materials from large numbers of individuals with various genetic disorders and their relatives. *In vitro* transformation of human lymphocytes by Epstein-Barr virus (EB virus) has become a standard method for generating human cell lines. However, the initiation of B cell growth for establishment is not so easy that the rates of success have been 50 to 80% in various laboratories. Recently, Bird and coworkers (1981) reported that cyclosporin A (ciclosporin: CYA) might facilitate *in vitro* outgrowth of EB virus-transformed B cell lines, and Anderson and Gusella

(1984) have investigated the potential for using CYA to increase the efficiency with which EB virus-transformed human lymphoblastoid lines can be prepared. To prevent the biohazard of EB virus from investigators, we modified their methods. Lymphocytes were separated from 2 to 4 ml of blood samples using Ficoll, and were treated with EB virus and CYA (2 μg/ml) for 3 to 4 hr. Then, cells were cultured in RPMI 1640 medium with 20% FCS and 2 μg/ml CYA for 1 week and incubated in the maintenance medium for 1 month. The rates of success in establishing cell lines were 100 and 83% for EB virus and CYA treated cultures from 66 individuals and for treatment with EB virus alone in 256 individuals, respectively. Duration from the initiation of culture to harvest of cell lines ranged from 14 to 30 days. These results have permitted the efficient banking of a large number of lymphoblastoid cell lines from families with genetic disorders or from a general population to provide a permanent source of genetic materials for molecular genetic investigation.

C46. Lymphoblastoid Cell Lines Established from Fanconi Anemia Heterozygotes Showed Hypersensitivity to Mitomycin C. **Tomoko HASHIMOTO,[1] Kiyoshi NAKAMURA,[1] Atsuko OGAWA,[1] Masafumi HANDA,[1] Masahisa HAGIWARA,[1] Yoshihiro YAMAMOTO,[1] Osamu MIKAMI,[1] Seiji KINOSHITA,[2] Keiichiro YOSHIOKA,[2] Tomoko KAWATA,[3] Shinichiro UEHARA[3] and Jun-ichi FURUYAMA[1]** ([1]Dept. Genet., Hyogo Coll. Med., Nishinomiya; [2]Dept. Pediatr., Osaka Natl. Hosp., Osaka; [3]Dept. Pediatr., Saint Maria Hosp., Himeji)

The detection of heterozygotes with Fanconi anemia (FA) is necessary to genetic councelling when a FA patient is diagnosed, because FA is one of the autosomal recessive diseases. The propositi were FA2NI and FA6NI. The sister of FA2NI died of pancytopenia and the parents of FA6NI were cousins. These familial histories suggested that in both families parents were FA-heterozygotes. The hypersensitivity to mitomycin C (MMC) is one of the most important characteristics of FA cells, then the sensitivity to MMC of the FA parent cells were studied cytogenetically. The frequency of chromosomal aberrations was scored using peripheral blood lymphocytes (PBLs) (96 hr-treatment of 50 ng/ml of MMC) and lymphoblastoid cell lines (LCLs) (72 hr-treatment of 50 ng/ml of MMC). The MMC-induced frequency of chromosomal aberrations per cell was as follows; FA-PBLs:0.30–11.2, FA-parent-PBLs:0.16–0.18, normal control PBLs:0.04–0.20, FA-LCLs: 3.7–4.2, FA-parent-LCLs:1.1–1.9, and normal control LCLs:0.05–0.51. FA-parent LCLs showed intermediate sensitivity to MMC between FA and normal control LCLs, although FA-parent PBLs and normal control PBLs showed similar sensitivity to MMC. These results indicate that detection of hypersensitivity to MMC cytogenetically using LCLs could be helpful to diagnose FA heterozygotes.

C47. Telomeric Fusion of Chromosomes in T-Cell Colonies. H. SHIMBA,[1] Y. KODAMA[1], A. AWA,[1] M. HAKODA[2] and M. AKIYAMA[2] ([1]Genet., [2]Radiat. Biol., RERF, Hiroshima)

In the course of the chromosome study on somatic mutation assay for 6-TG resistant T lymphocytes in the peripheral blood of A-bomb survivors and their controls, we had an opportunity to detect two colonies with high incidence (15–45%) of telomeric fusion (TF). One was derived from 6-TG resistant colonies from a male survivor, and the other from non-resistant colonies from a male control. The present report describes the results of chromosomal analyses on 296 TF chromosomes obtained from 2 colonies. One colony showed to have four abnormal chromosomes of 5q−, 7q−, 15q− and 17q+ in all cells. The other had no such abnormal chromosomes, although 87 out of 118 cells analyzed showed a dic(11;14)(q13;pter) in the second preparation. The number of TF's varied from one to four pairs in these metaphases. In the ordinary staining preparations, TF chromosomes appeared to take a form of a usual dicentric shape. Analysis by G-banded metaphases showed that most of these dicentrics were made up of end-to-end fusion between two chromosomes. Constantly for several passages at intervals of 1–2 weeks, TF's were observed. The results of G-banding analyses showed that terminal regions of all chromosomes could be participated in the TF formation. There was a tendency that no. 8, no. 14 and no. 15 chromosomes were involved more frequently than the others in a variety of combinations, while no. 7 and X chromosomes were thought to be involved with a low frequency.

C48. Immunogenetic Study of Mite-Allergic Bronchial Asthma. Hitoshi MATSUOKA, Hisamitsu UNO, Kiyohide KAWANO, Kazunori TSUDA (2nd Dept. Intern. Med., Miyazaki Med. Coll., Miyazaki) **and Akira ISHII** (Dept. Parasitol., Okayama Univ., Okayama)

Bronchial asthma is a hypersensitive state to environmental antigens. Many factors such as genetic and environmental factors are related to the disease. Among those, genetic factor is assumed as a predisposition rather than a cause. We studied the immunogenetic factors involved in the development of asthma. Dermatophagoides pteronyssiums, Dp, are common in house dust and make a major contribution to the allergen content of house dust, and one of major allergen of bronchial asthma. Major allergen activity of Dp is pointed to exist in low molecular weight component less than 30,000. To isolate major allergen component, Dp-body extract was fractionated by gel filtration using IgE binding activity to the pooled serum from Dp-allergic patients. Allergen positive fraction, termed Dp2, has a molecular weight of 15,000. Frequency distribution of Dp2 specific IgE and IgG antibodies was different in between patients and controls, suggesting that specific IgE

and IgG antibody production was controlled separately. Lymphocyte proliferation response to Dp2 was observed only in asthmatics. Asthmatics who respond to Dp2 did not respond to candida allergen. Thus, this response was specific to Dp2. Grade of lymphocyte response did not correlate to specific IgE or IgG titers. Frequency of HLA-A11 and Bw61 in patients with high IgE titer was, though not significant, slightly higher than in controls. Frequency of HLA-Bw62 in patients with high lymphocyte response was higher significantly ($p<0.05$) than in controls. It was suggested that the lymphocyte which proliferated to Dp2 might not control the production Dp2 specific IgE antibody.

C49. Serum Lipids and Genetic Epidemiology: a Gerontological Research on Aging Twins. K. HAYAKAWA (Dept. Public Health, Kinki Univ., Osaka)

A total of 87 pairs of adult twins aged over fifty years were studied on their serum lipids (Apo A-I, Apo A-II, Apo B, Apo C-II, Apo C-III, E, HDL cholesterol, total cholesterol, Non-HDL cholesterol) from the view point of genetic epidemiology. All of the serum lipids showed a higher intraclass correlation coefficient in the monozygotic twins than in the dizygotic twins. HDL cholesterol showed the highest intraclass correlation among the variables and indicated strong heritability. In the monozygotic pairs discordant in occupation, the blue-collar workers showed a significantly higher level than the white-collar workers in Apo B, total cholesterol and Non-HDL cholesterol. In the monozygotic pairs discordant in alcohol consumption, the higher consumers within the pair showed a significantly higher level in Apo A-I and HDL cholesterol, and a lower level in Apo B. In the monozygotic pairs discordant in cigarette smoking, the higher consumers within the pair showed a significantly lower level in Apo C-III. In the monozygotic pairs discordant in fatness, the heavier twins within the pair showed a higher level in Non-HDL cholesterol, total cholesterol, Apo B, Apo C-II and Apo C-III.

C50. Experimental Study on the Inheritance of Rat Dermatoglyphics by Mating Inbred Strains. Michio OKAJIMA (Dept. Forens. Med., Tokyo Med. Dent. Univ., Tokyo) **and T. S. YOSIDA** (Natl. Inst. Genet., Mishima)

Inheritance of dermatoglyphic trait on the palmar III interdigital pad of the rat was studied by mating two inbred strains, WKS and ACI/N. The WKS strain predominantly presents whorl patterns, while the ACI/N is characterized by triradial configurations. In total, 54 F_1, 88 F_2 and 52 backcross offspring were produced from each 4 of parent strains. The F_1 and F_2 hybrids showed a wide range of pattern types, consisting of whorls, loops, cusps, arches, and triradial patterns. The patterns were more evenly distributed in the F_2 than the F_1 hybrids. Patterns in each backcross offspring showed a shift towards the

characteristic patterns of the parental inbred strain. The size of patterns in the F_1 hybrids were intermediate between the both parental strains. Similar results were obtained in the mating between the ACI/N strain and another inbred strain presenting characteristic concentric whorl patterns. It is suggested that there is a genetic basis for the occurrence of dermatoglyphic traits of the rat but the manifestation of patterns is influenced by environmental factors, especially in the F_1 hybrids.

C51. 先天性偏側性多嚢腎と考えられる姉妹例. 安田寛二・山崎嘉久・西田 隆・長澤宏幸・近藤富雄 (大垣市民病院・小児), **国枝篤郎・二村敦朗・堀部 廉・広瀬敏勝・河田 良** (国立療養所長良病院・外科) **Sister Cases of Congenital Unilateral Multicystic Kidney.** K. YASUDA, Y. YAMAZAKI, T. NISHIDA, H. NAGASAWA, T. KONDO (Ogaki Municipal Hosp., Gifu), A. KUNIEDA, A. FUTAMURA, R. HORIBE, T. HIROSE and R. KAWADA (Nagara Natl. Child. Hosp., Gifu)

先天性嚢胞腎は従来より，肉眼的所見，組織像，病因などに基づいて数多くの分類がなされている．そのなかで代表的な疾患の遺伝性については，多発性嚢胞腎 (polycystic kidney) の成人型は常染色体優性遺伝，乳児型は劣性遺伝，多嚢腎 (multicystic kidney) は遺伝性なしとされている．われわれは最近，左側に水腎症を合併した右側低形性嚢胞腎の姉妹例を経験し，右摘出腎の病理組織像は，正常ネフロンに乏しく線維性結合織に富み，一部に軟骨組織の混入を示していた．以上の所見から，この姉妹例は先天性偏側性多嚢腎にもっとも近いと考えられる．本症は，本邦ではこれまでに126例の報告があるが (泌尿紀要30巻3号)，われわれの症例は初の家族発生例と思われる．本症は現在 renal dysplasia に分類されるが，病因は議論が多く一定していない．われわれの姉妹例から本症の発生機序に遺伝的要因の関与を推定でき，先天性嚢胞腎全体の分類や病因論上貴重な症例と考えられる．