chromosome 5, we introduced a whole or truncated human chromosome 5 into murine hepatoma cell line, 7R1 and constructed microcell hybrids, BG15-6 and BG15-9, containing a whole human chromosome 5 and a truncated human chromosome 5 (5pter-q23), respectively.

We found that 5q31-qter region of human chromosome 5 possessed the ability to suppress the tumor formation in nude mice, and that the proximal region of 5q23, where the FPC gene was located, could dramatically reduce the colony formation in soft agar.

3) The role of the loss of human chromosome 5 in the process of malignant transformation in colorectal carcinomas were investigated by introducing a chromosome 5 into a human colorectal carcinoma cell line, SW620, which possessed a deletion of long arm of chromosome 5. We found that introduced human chromosome 5 suppressed the growth rate of SW620, further suggesting that tumor suppressor gene may locate on chromosome 5.

シンポジウム II. 優性遺伝性疾患への実験的アプローチ

Symposium II. Experimental Approaches to Autosomal Dominant Disorders

Chairpersons: Zenichi OGITA (Toyama) and Ichiro MATSUDA (Kumamoto)

SII-1. APPROACHING GENETIC DISEASES BY "REVERSE GENETICS." Yusuke NAKAMURA (Dept. Biochem., Cancer Inst., Tokyo)

Development of genetic linkage maps of human chromosomes, with markers based on RFLPs (restriction fragment length polymorphisms), has led to localization of genes responsible for many genetic diseases. The conventional approach to studying genetic mutations causing hereditary diseases is to identify an abnormal protein or metabolic product first and then to isolate the gene in order to characterize the mutations at the DNA level. For most genetic diseases, however, the biochemical abnormalities have not been identified; linkage mapping makes it possible to begin the process of identifying a mutation from the other direction, or "reverse genetics." Genetic diseases such as adenomatous polyposis coli (APC), multiple endocrine neoplasia types I and II (MEN I and II), or von Recklinghausen neurofibromatosis (NF I), for example, have so far defied efforts to identify the abnormal gene products. However, as polymorphic DNA markers are able to distinguish two cytogenetically identical chromosomes which have been inherited by a given individual from each parent, one can examine the pattern of co-segregation between the unknown gene causing the phenotype (*i.e.*, affected or unaffected for genetic diseases) and genotype (alleles for RFLP markers). Because primary maps of markers are now available for almost all chromosomes, this approach can localize an unknown gene to a particular chromosomal region as a first step toward its isolation; when the gene is cloned and its mutation(s) characterized at the molecular level, the function of its product and the biochemical consequences of mutation can be determined.

I have been using reverse genetics to approach the isolation of the genes responsible

for APC and MEN IIa. I will describe our recent progress on these diseases and introduce general strategies for isolating a gene after the first linkage is detected with DNA markers on the genomic map.

SII-2. AN APPROACH BY THE CHROMOSOME STUDY. Shin-ichi SONTA (Inst. Develop. Res., Aichi Pref. Colony, Kasugai)

In cases with an unknown disease of dominant inheritance, chromosomes of the patient are usually analyzed at first, because cases with a certain chromosome abnormality always show abnormal phenotypes. The abnormal region of DNAs which causes genetic disorders may be various in size. They are, for instance, abnormal arrangements of DNAs, deletion of genes, and duplication of chromosome segments. The chromosome abnormalities are all morphological changes of segments distinguishable by optical microscope. The size of chromosome segments distinguishable as abnormal ones became very small by the recently improved techniques such as the high resolution banding techniques. However, individuals even with an addition or deletion of a very tiny segment of the chromosome, with the exception of a part of sex chromosomes and heterochromatic segments, have some phenotypical expression different from normal phenotypes.

Most living individuals with "balanced" structural rearrangements, which were either transmitted from the parent or occurred *de novo*, usually have no abnormal phenotype. Only a few persons with such rearrangements, however, very often show some abnormal phenotype.

Using experimental animals, we can obtain cases with "balanced" chromosome rearrangements by X-irradiation. In such "balanced" rearrangements, they may accompany the structural abnormality of DNAs and a gene at the breakpoint. If this is true, we could use the rearranged chromosome as a marker of the presence of abnormalities on DNAs and genes. The results of chromosomal observation of gametes, embryos and offspring from experimental animals with X-irradiation indicated that some cases with "balanced" rearrangements arrested at various developmental stages and some live offspring with such rearrangements evidenced some abnormal phenotypes. Furthermore, the results also indicated that some cases homozygous for "balanced" rearrangements were recessive lethal, whereas the heterozygotes have no abnormal phenotype.

These results suggest that some of the "balanced" structural rearrangements accompany abnormalities of a tiny invisible segment of the chromosome, genes or DNAs at the breakpoint and the neighboring region. The difference between dominant and recessive expression may well be due to a difference of the gene or the part of gene affected by X-irradiation.

SII-3. USE OF TRANSGENIC MICE FOR DISSECTING THE MOLECULAR MECHANISM OF AMYLOID DEPOSITION IN FAMILIAL AMYLOIDOTIC POLYNEUROPATHY. K. YAMAMURA,[1] S. WAKASUGI,[1] S. YI,[2] F. TASHIRO,[1] T. IWANAGA,[1] S. MAEDA,[3] K. TAKAHASHI[2] and K. SHIMADA[3] ([1]Inst. Med. Genet., [2]Dept. Pathol., and [3]Dept. Biochem. Kumamoto Univ. Med. Sch., Kumamoto)

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant disorder characterized by extracellular deposition of amyloid fibrils and by prominent peripheral and