A COMPARATIVE STUDY OF THE DIVERSITY OF GENE EXPRESSION IN BRAIN
B.B. KAPLAN, A.E. GIOIO, C. PERRONE CAPANO and A. GIUDITTA
Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA and
International Institute of Genetics and Biophysics and Department of
General and Environmental Physiology, Naples, Italy

ABSTRACT
Results of previous RNA-DNA hybridization experiments have demonstrated that the mammalian brain expresses 2- to 5-fold more of the haploid genome than other somatic tissues or organs. The striking complexity of gene expression in brain raises fundamental questions regarding the ultimate function of this large amount of genetic information and the degree to which it participates in the development and maintenance of tissue-specific structure and function. Here, we review our recent results obtained from a comparative study of the diversity of gene expression in brain. In this work, RNA-DNA saturation hybridization was used to estimate the sequence complexity of nuclear and polysomal RNA from rat, goldfish and squid brain. Additionally, the data were compared to the complexity of RNA from a typical non-neural tissue of each of these animal species. Our findings suggest that, as is the case in mammals, the diversity of gene expression in the CNS of teleosts and cephalopod mollusks is greater than in non-neural tissue. Importantly, however, the differences in the complexity of goldfish and squid brain RNA relative to that of non-neural tissue is significantly less than that observed in several mammalian species.

INTRODUCTION
The sequence complexity of RNA in various mammalian organs has been estimated by RNA-DNA saturation hybridization. In these experiments, single-copy DNA (scDNA) is hybridized to large excesses of nuclear or cytoplasmic RNAs, yielding a direct measure of the amount of the genome transcribed. In general, the results of these studies show that the mammalian brain expresses 2 to 5 times more of the haploid genome than other somatic tissues or organs (for review, see ref. 1-3). For example, mammalian brain nuclear RNA hybridizes to 16 to 24% of the scDNA, whereas liver, kidney and spleen RNA are complementary to 4 to
10% of the single-copy genome (4-7). Assuming asymmetric transcription, the sequence complexity of rodent and sheep brain nuclear RNA is $5.9-6.3 \times 10^8$ nucleotides (nt), a value sufficient to code for 140,000 different nuclear RNAs averaging 4500 nt in length.

Consistent with the nuclear RNA findings, mammalian brain polysomal RNA is complementary to significantly more scDNA than mRNA from other organs (see for example, ref. 8,9). The striking diversity of gene expression in brain is generally interpreted as reflecting the extensive heterogeneity of cell types in the tissue. However, data obtained from the analysis of several clonal cell lines of neuroectodermal origin suggest that, like the brain itself, neural cells express an unusual amount of the genome (6,8).

In the past, comparisons have been made of the sequence complexity of nuclear RNA from several brain regions differing markedly in cell composition, structure, and function (6-8). Results of these studies show that the great majority of nuclear RNA transcribed in whole brain is also present in the major brain regions. However, unlike the regional distribution of nuclear RNA sequences, the diversity of brain cytoplasmic RNA seems to reflect the summation of regional RNA populations of somewhat lower complexity (8,9). Taken together, these findings call attention to three important features of gene expression in brain. First, that each brain region, regardless of cell composition or function, utilizes a remarkable amount of genetic information. Second, that information necessary for region-specific function is encoded in a relatively small minority of the total genes expressed. Third, that post-transcriptional regulatory mechanisms may play an important role in the elaboration of region-specific structure and function.

In view of the profound functional and evolutionary implications of the above observations, we have begun a phylogenetic comparison of RNA sequence complexity in neural tissue. As a working hypothesis, we postulated that the diversity of gene expression in brain would increase during phylogeny, correlating with the evolutionary development of the organ. It bears emphasis, however, that there is no a priori reason to believe that the evolution of the mammalian brain results directly from the expression of a large number of new gene "sets." Rather, evolution