SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HL 00002-03 LBG

PERIOD COVERED
July 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Morphine Receptors as Regulators of Adenylate Cyclase

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Marshall Nirenberg	Chief, Lab. of Biochemical Genetics	LBG NHLI
OTHER:	Arthur Lampert	Staff Fellow	LBG NHLI
	Werner Klee	Research Chemist	LGCB NIMH

COOPERATING UNITS (if any)

Laboratory of General and Comparative Biochemistry, NIMH

LAB/BRANCH
Laboratory of Biochemical Genetics

SECTION
Section on Molecular Biology

INSTITUTE AND LOCATION
NHLI, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives are to elucidate the mechanisms of dependence upon opiates and of tolerance to these compounds and to define the normal functions of the newly discovered endogenous opiate peptides.

PHS-6040
(12-75)

Project Description:

Major Findings: Clonal cell lines with morphine receptors were found and were used to study the mechanism of action of narcotics. Morphine and other narcotics were found to affect adenylate cyclase in two ways, mediated by the opiate receptor: (1) narcotics inhibit adenylate cyclase activity, and (2) when cells are cultured in the presence of morphine for 12 to 48 hours an increase in adenylate cyclase activity is observed which compensates for the inhibition of enzyme activity by morphine. Cells then have normal cAMP levels and appear tolerant to morphine because the increase in adenylate cyclase activity is approximately equal to the inhibition of enzyme activity by morphine. However, the cells then are dependent upon morphine to maintain normal cAMP levels. Withdrawal of morphine, or displacement of the narcotic from the opiate receptor by the antagonist, naloxone, reverses the inhibition and results in the synthesis of abnormally high levels of cAMP. Thus, dual regulation of adenylate cyclase by narcotics accounts for narcotic dependence and tolerance. The recently discovered endogenous opiate peptides, Met-enkephalin and Leu-enkephalin, also were shown to be potent inhibitors of adenylate cyclase. These results show that the endogenous opiate peptides and narcotics act as pleiotropic regulators of other species of receptors which are coupled to the activation of adenylate cyclase. In this way, the opiates alter the perception of neurons to incoming messages.

Significance to Biomedical Research: The biochemical basis for narcotic dependence and tolerance has been established and the mode of action and the normal role of the endogenous opiate peptides have been clarified.

Proposed Course: Further studies on the mechanism of dual regulation of adenylate cyclase are in progress.

Publications:

1. Sharma, Shail K., Klee, Werner A. and Nirenberg, Marshall: Dual regulation of adenylate cyclase accounts for narcotic dependence and tolerance. Proc. Natl. Acad. Sci. USA 72: 3092-3096, 1975.