ing how the brain processes sensory input. "The [brain] cortex is like a patchwork quilt," Mishkin says. Each patch performs a computation and sends the result on to the next station.

As Mishkin, Leslie Ungerleider, and other colleagues traced area-by-area the parts of the visual system that are used to identify objects, they were led from the back of the brain forward to the low, outside region called the temporal lobe. Other sensory systems have a similar organization. For the olfactory, gustatory, auditory and tactile systems, signals also travel station-to-station, eventually reaching areas in or adjacent to the temporal lobe.

The function of each area of the brain is determined by assessing monkeys' performance on specially devised tasks, before and after the area is surgically removed. In a revealing test for "recognition memory," the animal is asked to distinguish a novel object from an object it has seen once before.

"Monkeys are incredibly good at this," Mishkin says. A normal monkey correctly selects the novel item more than 90 percent of the time.

The experiments revealed functional connections between the cortex, the outer and evolutionarily newest portion of the brain, and two underlying structures, the hippocampus and the amygdala. These structures are part of the limbic system.

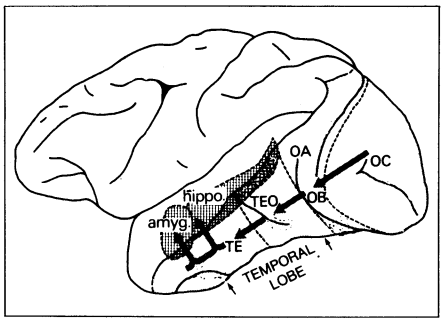
A monkey lacking both amygdala and hippocampus on both sides of the brain shows a severe deficiency in the recognition memory task. This finding was surprising because removal of either the amygdalas or the hippocampal structures had little effect.

The limbic system's role is not limited to visual-information recall, Mishkin and colleague Elisabeth Murray find. If the recognition memory task is performed in the dark, allowing the monkey to touch rather than see each object, the monkey selects accurately unless both amygdala and hippocampus have been removed.

In addition, the limbic system appears to be a site where information stored by different sensory systems can be combined. To test "cross-modal association," Mishkin and Murray presented monkeys with the series of objects in the dark, so the memories were established from tactile information. Then the monkeys made their choice in the light, without handling the objects.

While normal monkeys and monkeys lacking any hippocampus scored about 90 percent correct, monkeys lacking any amygdala were correct only 55 percent of the time, hardly better than chance. "In the absence of the amygdala, the brain can lay down both tactile and visual memories, but it can't compare them," Mishkin says.

The hippocampus serves as a different type of selector, Mishkin now proposes.



Mishkin

Visual information enters the brain cortex at the back (OC) and is processed by a series of stations (OB, OA, TEO, TE). It then travels deeper into the brain to the amygdala and hippocampus.

It provides associations between memories of objects and of positions. In the visual system, for example, a series of cortex stations, distinct from those that run along the temporal lobe, process information about spatial relations.

Mishkin and John Parkinson of NIMH devised a task to test the combined use of spatial and object memory. In step 1, a monkey is shown an object in a given position on a tray. In step 2, the monkey is presented with two copies of that object and is rewarded for selecting the one in the same position as the object in step 1. Normal monkeys, and monkeys without amygdalas, succeed about 80 percent of the time. But monkeys lacking any hippocampus choose correctly in only about 55 percent of their attempts.

The hippocampus and the amygdala share a common ability to store information but differ in which representations they can connect, Mishkin concludes.

What's beyond the limbic system? Connections run in both directions between the hippocampus and the amygdala and another group of deep-brain structures called the basal forebrain cholinergic system. The destruction of these structures in Alzheimer's disease (see story, this page) and other brain disorders may underlie the characteristic memory loss. The basal forebrain structures produce a neurotransmitter called acetylcholine. Mishkin and his colleagues find that a monkey's performance on the recognition memory task can be improved by a drug that increases the amount of acetylcholine available in the brain, and can be decreased by a drug that blocks the acetylcholine receptor.

In recent experiments Mishkin, Thomas Aigner of NIMH and Donald Price of Johns Hopkins University in Baltimore used a chemical to selectively destroy the cells of monkeys' basal forebrains. This treatment impaired the monkeys' ability to recognize whether an object is novel. Mishkin speculates that the basal forebrain plays a role in memory storage, perhaps relating it to emotional context. He says, "We're on the way to begin to think about higher level memory processes." *—J.A. Miller*

On the trail of the Alzheimer's tragedy

It is a tragic disease of mysterious cause — with no known cure and no apparent way to stop its progressive loss of mental acuity. For the estimated 2 million people in the United States who suffer from senile dementia of the Alzheimer type, the brain has inexplicably gone haywire.

Increasing scientific interest in the disease, which is not limited to the aged, has yielded strong evidence indicting abnormalities in the neurotransmitter network in certain areas of the brain (SN: 10/6/84, p. 221). Now, recent research findings offer more etiologic evidence, as well as a new *in vivo* diagnostic approach and a possible new treatment.

According to a report in the Dec. 6 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), a group of researchers led by Duke University Medical Center staff members in Durham, N.C., analyzed the concentration of the hormone corticotropin-releasing factor (CRF) in brains from Alzheimer patients. Using radioimmunoassay techniques, they measured CRF in nine brain regions using postmortem brain tissue from 13 patients who had died of Alzheimer's and from 13 age- and sex-matched controls with no evidence of such disease.

Compared with controls, the Alzheimer brains showed a marked reduction of CRF concentrations in three regions: about 50 percent reduction in the frontal and temporal cortex, and 70 percent in the caudate nucleus. The report apparently is the first to point out CRF deficiencies in Alzheimer's, but the significance of the findings remains unclear. Still, the results suggest that CRF-containing neurons degenerate in Alzheimer's disease, joining the previously described somatostatinergic and cholinergic neuronal damage as possible contributors to the disease's pathology.

Signs of neuronal damage found by microscopic evaluation of postmortem brain tissue are needed to confirm the difficult clinical diagnosis, which still depends on physical examination and psychometric testing. Those parameters may be replaced, at least in part, by a new *in vivo* approach utilizing single-photon emission computed tomography (SPECT), according to another report in the Dec. 6 JAMA by a team from Harvard Medical School and Massachusetts General Hospital in Boston and George Washington University Medical Center in Washington, D.C.

Using radioactive iodine-labeled compounds injected intravenously and a special camera to produce three-dimensional brain images, the researchers studied specific neurotransmitter receptor binding function in a 56-year-old Alzheimer patient. The noninvasive technique revealed a unique and "profound" decrease in blood flow to certain regions of the brain, a phenomenon previously observed using other techniques. Although the SPECT study also corroborates earlier descriptions of specific receptor site distribution based on other methods, the real significance of these findings, despite the very small sample size, may be the eventual introduction of an important diagnostic tool that may provide earlier diagnosis.

Neuronal biochemistry is also the scientific springboard for a search by scientists at Yale Medical School in New Haven, Conn., for drugs to ameliorate cognitive deficits like those associated with Alzheimer's disease, such as memory loss. Attempts to find a drug for age-related cognitive disorders have not produced sudden success stories (SN: 5/7/77, p. 292; 10/27/84, p. 263). Nonetheless, Amy F. T. Arnsten and Patricia S. Goldman-Rakic of Yale report in the Dec. 13 SCIENCE that a different approach may produce results — one that uses drugs affecting catecholamine transmission in the brain rather than the more commonly utilized acetylcholine transmission. Both neurotransmitter systems deteriorate in the aging brain.

Using five aged rhesus monkeys ranging from 17 to over 30 years of age, the 18-month study tested their performance in memory tests following injection of varying doses of various drugs that affect catecholamine transmission, alternated with doses of a saline placebo. The monkeys' performance with the placebo averaged 64 percent correct during the course of the study, with individuals showing a wide range of memory ability.

Specific doses of the drug clonidine, an antihypertensive agent, produced "near-perfect performance" in four of the five animals, with the oldest monkey showing the most marked improvement. Arnsten and Goldman-Rakic found higher doses of clonidine had a sedative effect on the animals, which apparently developed a tolerance to this side effect over a period of time. The researchers caution that clonidine's sedative effects may obscure its beneficial actions and should be considered if the drug is used in human clinical trials. *— D. D. Edwards*

Strategic defense of X-ray laser initiative

Nuclear explosions produce a lot of X-rays. That makes them a good place to start attempts to make X-ray lasers, and the Lawrence Livermore (Calif.) National Laboratory (LLNL) has done just that. "I can tell you that X-ray lasers exist. That is as far as I am allowed to go." Thus spake Edward Teller, associate director emeritus of LLNL, at last week's meeting of Lasers '85 in Las Vegas, Nev.

Teller's firm and categorical affirmative seemed to be at least partly a response to recent speculations in the press, which, he says, contain much that is untrue about Project Excalibur, as the effort is called. Some of these reports have suggested that the X-ray laser may not exist, or, if it exists, that it may not ever be good enough for its purpose, the Strategic Defense Initiative (SDI). They have also hinted that the resignation of Roy E. Woodruff, former associate director of defense systems at LLNL, was related to these difficulties. The laboratory officially denies any such suggestions.

To make a laser requires a "population inversion." Atoms emit radiation when they possess more energy than is required in their lowest possible energy state, their ground state. Each kind of atom can occupy a spectrum of energy states above the ground state. Usually when a large group of atoms shares a given amount of energy, statistically most of the energy should be shared by atoms in fairly low energy states, close to the ground state. Only a few atoms will be in high energy states. If, contrary to statistical expectations, a large number of atoms are brought to the same, high energy state, usually by some kind of resonant pumping, a population inversion exists. If these high-energy atoms can then be triggered to radiate in chorus, coherently, a laser exists.

The energy states that produce X-rays are those belonging to the innermost electrons of a heavy atom or to the nucleus itself. It may be that a nuclear explosion produces a fleeting population inversion in its own fuel, or it may be that X-rays from the explosion are used to pump up a population inversion in some other substance, which then does the lasing. The latter would be a very elegant application of a nuclear explosion. There has been mention of devices to focus X-rays. Such devices have been part of the triggering mechanisms of thermonuclear bombs as long as this variety of explosive has existed, and it could be that some derivative of them is used to focus X-rays on a lasing material.

All this is, of course, the rankest speculation, and Teller might say it was all wrong. But, as he himself points out, by keeping such things secret the government denies information only to its own citizens, not to potential enemies. Teller says he believes that the Soviet Union is ahead of the United States in research of the SDI sort, which includes this nuclear X-ray laser project. He calls for openness and sharing of information in matters of this kind. "We should be scientists and not alchemists. We should be for openness in the name of science, of the unity of the world, and in the name of the defense of the United States." But he refuses to try to change the rules by breaking them.

Another object that might go with an X-ray laser is a mirror for specular reflection of X-rays. A laser that is pumped and then emits is a one-pass device. As soon as they have one, experimenters try to put mirrors on the ends of it and reflect the radiation back and forth. In multiple passes radiation stimulates more of the same and so amplifies itself greatly. Most practical lasers have mirrors. The reason for not putting them on is that they are impossible or at least highly impractical.

Mirrors for X-rays in the wavelength range of those from nuclear explosions, roughly in the tens of angstroms, have been impossible up to now. Visible light, infrared and radio waves are easy to reflect. X-rays, because of their extremely short wavelengths and great penetrating power, are extremely difficult to reflect, particularly in the specular or near-perpendicular mode. Development of a substance that would reflect them specularly would be a technological achievement of very high magnitude and many possible uses.

However, for wavelengths in the few hundreds of angstroms, such specular reflectors do exist. Products of fairly recent technology, they are composed of thin layers of different substances that collaborate with one another in such a way as to reflect a good portion of the incident radiation. In this wavelength range two experiments demonstrated lasing a little over a year ago (SN: 11/3/84, p. 278). At Lasers '85 the leaders of both, Szymon Suckewer of the Princeton (N.J.) Plasma Physics Laboratory and Dennis L. Matthews of LLNL, detailed numerous extensions of their experiments, including use of such multilayered reflectors to make multiple-pass amplifiers.

Although SDI hangs in the background — and, in the case of the nuclear-explosion laser, drives the research — lasers of this wavelength range have many other potential applications. Matthews lists the study of biological cell structures, materials science, microelectronics, atomic physics and studies of laser physics itself. Holograms of small structures are among the methods of these studies, and Matthews expects soon to begin collaboration with AT&T Bell Laboratories to do some surface holography. A very short X-ray laser, if it is more than just a nuclear explosion, could have similar uses.

— D. E. Thomsen