graph all fluorescent slides. The barrier filters employed and the exposure times for photography were varied according to the intensity of fluorescence. The photographs of Figs. 1 and 2 were obtained under exactly comparable conditions of exposure.
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Cerebrospinal Fluid Production: Stimulation by Cholera Toxin

Abstract. *Large increases in the production of cerebrospinal fluid have been observed after the intraventricular administration of cholera toxin. Because cholera toxin stimulates adenylate cyclase, the data suggest that adenosine 3',5'-monophosphate plays a role in cerebrospinal fluid production.*

The ability of adenosine 3',5'-monophosphate (cyclic AMP) to mediate hormonal responses in various secretory epithelia, including the kidney, salivary glands, intestinal epithelia, pancreas, and thyroid, has been well documented (*1*). Purified cholera toxin serves as a specific adenylate cyclase–cyclic AMP probe. After it is introduced to the luminal side of epithelia, it stimulates adenylate cyclase production of cyclic AMP and subsequent electrolyte transport in the gut (*2, 3*) and the kidney (*4*). Recent studies have also shown that cholera toxin can stimulate endolymph production in the inner ear (*5*).

Cerebrospinal fluid (CSF) is secreted by the choroid plexus and associated ventricular structures and absorbed primarily through the arachnoid villi (*6*). This secretion has been directly correlated with transepithelial flux of electrolytes; however, the biochemical mechanism is still poorly understood. We have now demonstrated the ability of intraventricularly administered cholera toxin to stimulate cerebrospinal fluid secretion, ostensibly through stimulation of an adenylate cyclase–cyclic AMP pathway in the choroid plexus and periventricular compartment.

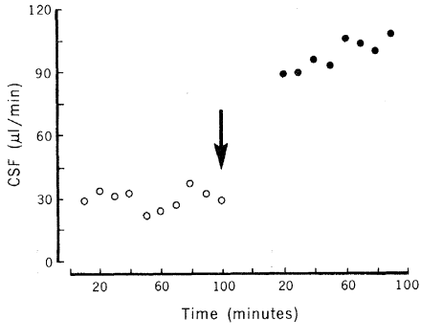

Fig. 1. Production of CSF in a representative experiment before (○) and after (●) the intraventricular administration of cholera toxin. The arrow indicates the time the toxin was introduced into the ventricle. There was a 2-hour incubation period before the perfusion was started again. Production of CSF was determined by inulin dilution.

Experiments were performed on mongrel dogs weighing 20 to 25 kg, anesthetized with pentobarbital, and maintained on positive pressure ventilation. Arterial pressure, heart rate, intracranial pressure, body temperature, p_{O2}, and p_{CO_2} (the partial pressures of O_2 and CO_2, respectively) were constantly monitored and stabilized. Cerebrospinal fluid secretion was measured through the use of a modification of the method of Pappenheimer *et al.* (*7*). Both lateral ventricles were perfused with Elliotts B artificial CSF containing 2 μc of [^{14}C]carboxyinulin (New England Nuclear) per 100 ml at a rate of 0.15 ml per minute per ventricle; a pump (Harvard model 2219) and two 50-ml syringes in parallel were used. The outflow catheter was placed at zero pressure with respect to the ear so that bulk collection of fluid represented CSF production plus the volume of the perfusate less the amount absorbed. Cerebrospinal fluid production was calculated by the indicator dilution method (*8*). After the values of normal CSF formation were determined for each dog, the perfusion was stopped and 250 μl of purified cholera toxin (100 μg per milliliter of normal saline), heat-inactivated cholera toxin, or saline was injected into each lateral ventricle. Cholera toxin was prepared as previously described (*5*). After 2 hours of incubation, the perfusion was again started and CSF formation was again measured. Statistical analyses were made between baseline and experimental values with *t* tests.

The effects of cholera toxin on CSF production by a typical dog are shown in Fig. 1. Figure 2 shows a significant difference ($P < .001$) between control production (47.0 ± 7.0 μl/min) and secretion after cholera toxin challenge (102.0 ± 8.0 μl/min); however, no significant difference was observed between control rates (59.0 ± 6.0 μl/min) and rates after exposure to saline (59.0 ± 6.0 μl/min) or between control rates (57.0 ± 4.0 μl/min) and production after incubation with heat-inactivated cholera toxin (68.0 ± 7.0 μl/min). Measurement of the volume of CSF released from the cisternal catheter showed similar increases after cholera toxin challenge, as was also seen in the isotope dilution technique; these results indicate that cholera toxin did not change brain permeability to inulin. Control secretion was 17.0 ± 6.0 μl/min, and secretion after cholera toxin challenge was 73.0 ± 7.0 μl/min. There was no significant change in the volume from the cisternal catheter after incubation with saline or with inactivated cholera toxin.

Normal values reported for CSF formation in this report are similar to those shown previously with the inulin-dilution technique. The higher production found with inulin dilution as compared with bulk flow at the cisternal catheter is a function of CSF absorption through normal pathways and inulin diffusion into the brain (*9*). Inactivated cholera toxin was used as a control to demonstrate that injected protein does not significantly contribute to increased fluid production (Fig. 2). The possibility that cholera toxin was absorbed and acted system-

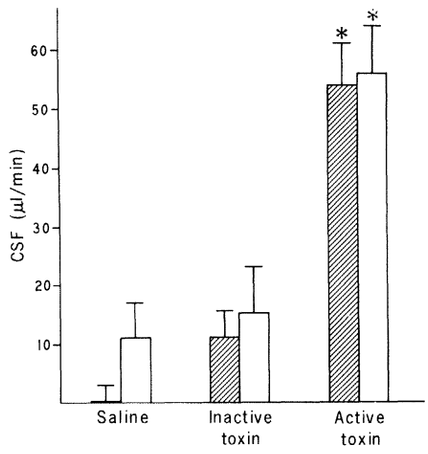

Fig. 2. Differences between baseline and experimental CSF production after intraventricular administration of saline, heat-inactivated cholera toxin, and active cholera toxin. Shaded bars represent change in CSF formation calculated according to the inulin dilution technique, and open bars represent the change in bulk collection at the cisterna magna outflow catheter. Brackets represent the standard errors of the mean; $N = 5$ in all groups. Asterisks indicate a significant difference ($P < .001$).

ically cannot be excluded, although the small dose administered, the low outflow perfusion pressure, and the high binding coefficient of cholera toxin would make such a result unlikely (*10*).

There was no change in the concentrations of sodium, potassium, or chloride in CSF after cholera toxin administration in unperfused and perfused animals. This absence of change in fluid composition has been noted in intestinal fluid and endolymph when their secretion was stimulated by cholera toxin (*3, 5*).

Rudman (*11*) has suggested that cyclic AMP plays a role in the pathogenesis of increased intracranial pressure associated with brain trauma. Except for questionable stimulation of CSF production with ouabain and spironolactone (*12*), cholera toxin appears to be the most potent activator known to increase the brain's fluid production. Although there is considerable flexibility in the amount of fluid that can be passively handled by the arachnoid villi, the restrictions imposed by the Monro-Kellie doctrine (a rigid skull with a constant total CSF, brain, and blood volume) call for a biochemical mechanism for fluid production control. Our data implicate cyclic AMP as a mediator of brain ventricular fluid production control.

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Visual Search in the Pigeon: Hunt and Peck Method

Abstract. *Pigeons pecked at small forms displayed on an oscilloscope screen under computer control. The birds were required to find a small o amid varying numbers of x forms. A photocell glued to the bird's beak provided a signal to the computer when the beak approached a form, and the computer recorded the time and target of the response. As in some similar studies with human subjects, errors and reaction times increased with number of x forms displayed. The method appears promising for further studies of search and of other processes related to perception and information-processing in birds.*

Rapid, accurate search of the visual environment is necessary to the survival of many species; search also appears to be one of the more informative varieties of the pattern recognition problem. The pigeon seems an appropriate subject with which to extend and generalize search findings from experiments with humans (*1*). Some aspects of form identification have been studied in pigeons, and something is known of their basic visual functions (*2, 3*); also important, for the present method, is their strong tendency to peck at visual targets that signal presentation of food (*4*).

This report summarizes a method for studying search in pigeons and presents data on the effect of visual noise on the speed of search. The pigeon subject searched for a small o displayed under computer control on an oscilloscope screen set in the wall of an experimental chamber (Fig. 1). The o was often accompanied by a number of x's of the same size as the o (4-mm diameter). Although all the forms seemed to be continuously present during search, they actually appeared in rapid sequence about 150 times per second (*5*). A small photocell, glued to the bird's beak, sent signals via a connecting wire and amplifier to the computer whenever the beak approached one of the forms. When the input signal exceeded a set threshold, the computer recorded the type and location of the form being displayed at that instant; this information specified the time and target of the peck response.

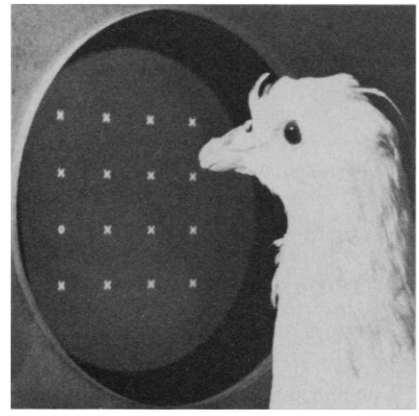

Fig. 1. One of the search displays and a pigeon with a photocell (visible as a lump on the beak). During experimentation, the only illumination came from the display.

Three food-deprived White Carneaux pigeons were trained by standard methods to eat from a grain feeder located below the display screen, and to peck at the target o when it appeared on the screen. For several hundred presentations, one or more x forms appeared along with the o, and presentation of food followed only pecks at the o; the birds quickly learned to peck only at the o. The final search procedure was then introduced. On each trial, the o first appeared alone in the center of the screen; this served to position the bird for the subsequent display. When pecked, the o vanished and 0.2 second later the search display appeared. This display comprised one o (the target) and either 0, 1, 3, 7, or 15 x (noise) forms. Each form was located at one of the 16 positions defined by 4 × 4 matrix 7 cm square, subtending a visual angle of approximately 50 deg. The search display continued until the bird pecked at one of the forms. Then a rectangular blanking stimulus appeared briefly in each position and, unless reinforcement occurred, the next trial was initiated 0.5 second later. If the bird pecked the o in the search display, food was presented with a probability of .083, and the next trial started 0.5 second after the end of food presentation. If the bird pecked an x, no food appeared, and the same display was repeated on the next trial. Except for such correction trials, the o was located randomly within the matrix, with the restriction that within 80-trial blocks it appeared in each location just five times, once under each of the five noise conditions. The x elements had random positions with respect to the 15 remaining matrix locations. Each bird received at least 25,000 trials with this procedure, in daily sessions of 800 or 880 trials (*6*).

The data from six 880-trial sessions were pooled for each bird, with the omission of responses on error and correction trials and on the first 80 trials of each session. Reaction time, defined as time from search display onset until the peck response, was determined for all birds and