from 0 to 30 seconds. The average response time for each 2-hour session was computed from these totals.

Although the correct position was such that the bird was not required to stand perfectly still but could move its head somewhat while remaining within bounds, the task proved a difficult one. Well-trained birds stood for an average of only 5 to 6 seconds before they moved away. While standing, they appeared to be very excited and commonly made slight pecking movements.

In testing sessions, the drug or control water dose was administered intramuscularly 10 minutes before the experimental session began. The results of a series of sessions with two birds are shown in Fig. 1. Dose-response curves for chlorpromazine, a widely used tranquilizer, and pentobarbital, a hypnotic, appear together, with their associated water controls. The average response times during three sessions at each dosage are connected by lines, while individual sessions appear as separate dots. Dosage, in milligrams per kilogram, is shown on the abscissa.

It is evident that chlorpromazine substantially lengthened the response time that these birds were able to sustain, while pentobarbital reduced the response time (*5*). Since the birds were highly excited, one may appreciate at a common-sense level why a "tranquilizer" might enable the bird to "stand still" for an extended time. Neither drug, it should be noted, was given in doses large enough to produce gross behavioral effects such as ataxia. The difference in the direction of effect of the two drugs is of some interest, because these drugs have produced effects in the same direction (though of different magnitude) both in conditioned avoidance and in discrimination experiments (*1, 3*). It remains to be seen whether other tranquilizers will produce effects similar to those of chlorpromazine, or whether such effects will be matched by drugs not ordinarily classed as tranquilizers. If the promise of the initial results is borne out, it may prove profitable to study other varieties of "continuous" responding and perhaps to investigate the effects of tranquilizers in other areas that do not involve "anxiety" or "fear."

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6 November 1957

Hormone-Induced Ovarian Development in Mosquitoes

The common house mosquito, *Culex pipiens* L., is said to be anautogenous in that the adult female requires a blood meal to form eggs. A closely related form, referred to as *Culex molestus*, is autogenous; these females are able to produce a small batch of eggs without having imbibed blood or any other food.

It has been stated that a blood meal or some blood fraction is necessary to initiate egg formation in some mosquitoes (*1*).

Twohy and Rozeboom (*2*) have shown that *C. molestus* contains more nutritional reserves than *C. pipiens* if the two species are reared under comparable conditions, but they agree with Clements (*3*) that nutritive conditions per se are not responsible for initiation of autogenous ovarian development. However, the possibility that the ovarian development of mosquitoes, like that of some other insects, is controlled by hormones has been suggested. The experiments that are reported here (*4*) were specifically designed to clarify this issue.

The undeveloped ovaries of *C. pipiens* were removed 5 to 7 days after the females had emerged [Fig. 1 (3)] and were transplanted into recently emerged *C. molestus* females. Four days later the *C. molestus* females were dissected, at which time the transplanted ovaries were seen to be fully developed [Fig. 1 (4)]. Undeveloped ovaries of *Aedes aegypti* (also an anautogenous mosquito) which had been transplanted into recently emerged *C. molestus* females also were shown, on dissection, to have become completely developed after 4 days. On the other hand, ovaries of *C. pipiens* or *C. molestus*, when transplanted into *C. pipiens* females, do not develop if the hosts are denied a blood meal. Hence, the factors responsible for initiation of development are not inherent in the ovary.

It has been shown for a number of insects that ovarian development is controlled by hormones and that a hormone produced by the corpora allata is involved (*5*). In the light of these findings, the corpora allata were removed from *C. molestus* females within 24 hours after emergence and transplanted into 5- to 7-day-old female *C. pipiens*. This operation is technically rather difficult but was successful on five occasions. These females were dissected 5 days after the transplantation and, in each case, contained fully developed eggs [Fig. 1 (1, 2)]. The evidence thus suggests that ovarian development is induced by a gonadotropic hormone secreted by the corpora allata. The young *C. molestus* female is apparently able to release this hormone without taking a blood meal, while *C. pipiens* needs to ingest blood for the release of the allatum hormone.

Ligature experiments by Detinova (*6*), Clements (*3*), and Gillette (*7*) and by me have provided evidence that a factor in the brain, presumably hormonal in nature, is also involved in the maturation of the ovary. The evidence presented here indicates that the corpora

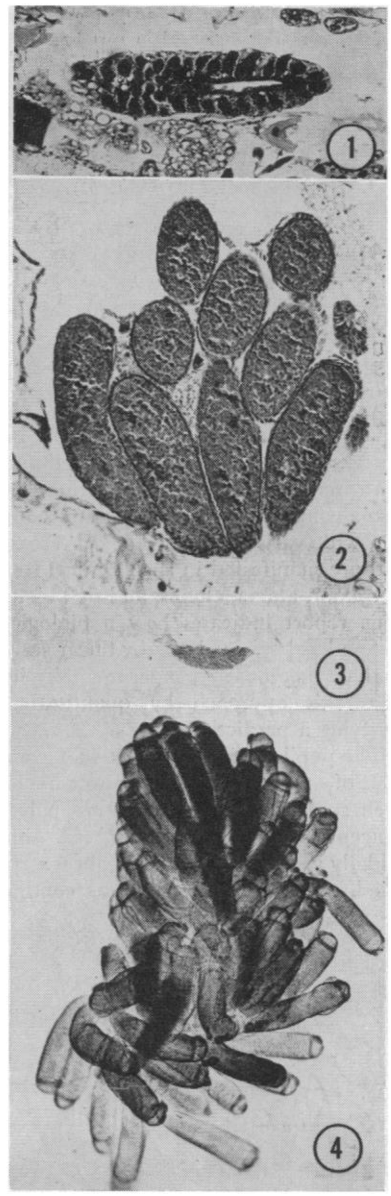

Fig. 1. (1) Section through ovary of a 2-day-old adult *C. pipiens*, showing condition of resting ovary in adult mosquito not fed on blood. (2) Section through part of adult *C. pipiens* ovary, showing fully developed eggs 5 days after corpora allata transplantation. (3) Total mount of ovary of a 5-day-old adult *C. pipiens* not fed on blood, showing size of ovary at time of transplantation. (4) *Culex pipiens* ovary 4 days after transplantation into a 24-hour-old *C. molestus* host. Note fully developed eggs. Compare with ovary in (3).

allata are also a link in the humoral cycle initiating ovarian development in mosquitoes.

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19 November 1957

Testing a Servoanalytic Hypothesis for Pupil Oscillations

Oscillations are a common and important instance of the malfunctioning of a servomechanism. Oscillations are also a common pathological abnormality in a wide variety of neurological diseases and are manifested in such clinical signs as tremor, ataxia, clonus, and nystagmus. This report indicates how a biological system has been analyzed by linear servoanalytic methods and experimentally justifies this approach by quantitatively verifying a prediction.

The pupil response to light—an example of neurological servosystem—has been studied by means of servoanalytic concepts and techniques (*1*). A sinusoidally varying intensity of light was applied, and the pupil area was continuously recorded. When intensity increases, the pupil contracts. The resultant effect of light falling on the retina can be resolved into two factors: (i) an increase due to increase in applied intensity and (ii) a decrease due to contraction of the pupil. System gain is here defined as the ratio of (ii) to (i). An open-loop transfer function

$$G(s) = 0.16e^{-0.18s}/(1+0.1s)^3$$

was computed from data graphically displayed in Fig. 1. This, the Nyquist diagram, is a vector plot of the relationship between gain and phase shift at various frequencies. For example, at 1.2 cy/sec, the gain is 0.12, with a phase lag of 180°. This gain means that the pupil compensates for 12 percent of the change in applied light intensity.

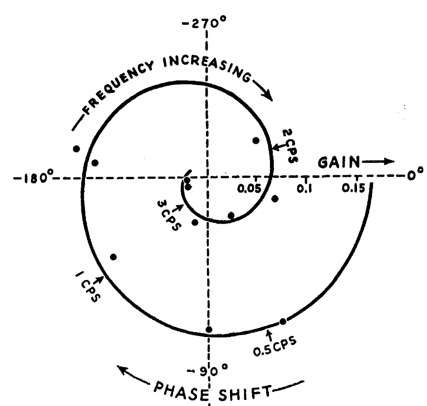

Fig. 1. Nyquist diagram of pupil response. This is a vector plot of gain and phase shift. The scale of the modulus is shown, and a few frequencies are indicated. The curve is derived from fitted lines from gain and phase frequency-response graphs, while the points are experimental.

If the gain were to be increased to 1.0 or more, the system would become unstable, and the pupil would oscillate at its natural frequency—that is, the frequency at which the phase lag is 180°. From the figure we see that this frequency is 1.2 cy/sec. Thus, from our servoanalysis of the normal, low-gain, stable pupil system, we are led to predict that a large increase in gain would produce sustained oscillations and that the frequency of these oscillations would be 1.2 cy/sec (72 cy/min). A test of the validity of the servoanalytic method would be the production of pupil oscillations in this manner and at the predicted frequency. Observations which comprise such a test are already available for evaluation.

Clinical studies have been reported in which sustained oscillations of the pupil have been produced and in which the frequency of the oscillations has been measured. Stern (*2*) pointed out that a series of oscillations of the pupil could be induced by imaging a small point of light just on the margin of the pupil. This causes the iris to contract, and all the light is cut off in the early phase of contraction. The iris therefore redilates, and full light intensity again enters the eye. The gain is thus increased to more than 1.0, and sustained oscillations result. Campbell and Whiteside (*3*) made a careful study of parameters affecting this induced pupil oscillation, using quantitative techniques on a group of normal subjects. A third report is that of Wybar (*4*), who studied a large number of normal subjects and also patients with multiple sclerosis (*5*). In Table 1 the frequencies of the sustained oscillation observed are summarized.

Table 1. Observed frequencies of pupil oscillations (references in parentheses).

Group studied	Mean frequency (cy/min)
10 Normal subjects (*2*)	80
1 Normal subject (*3*)	71
37 Normal subjects (*3*)	69
34 Normal subjects (*4*)	62
Patients with multiple sclerosis: 70 pupils (*4*)	41
Predicted value (*1*)	72

There is good agreement between the frequency of pupil oscillations observed in normal subjects and our prediction. Further experiments have been carried out by Stark and Baker (*6*) in which the transfer function of the pupil system has been altered by drugs. For example, when the 180°-phase cross-over frequency was changed from 1.5 to 0.9 cy/sec, the high-gain oscillation frequency shifted in a parallel fashion from 1.5 to 1.0 cy/sec (*6*).

The qualitative value of the servoanalytic approach is demonstrated by the clarification introduced through explanation of the nature of these pupil oscillations. The quantitative nature of the method is illustrated by the accuracy of the prediction (*7*).

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4 November 1957

Preparation of an Apoprotein from Ceruloplasmin by Reversible Dissociation of Copper

The blue copper-protein of plasma, ceruloplasmin, with a molecular weight of 151,000, contains eight atoms of copper per molecule (*1*). The physiologic significance of this protein, while not clear, has usually been implicitly associated with its oxidase activity (*2–5*). On the other hand, the possibility that reversible binding and release of copper by the protein may be the basis of its