HEREDITARY AND DRUG-INDUCED TUMBLING IN PIGEONS

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by

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I hereby recommend that the thesis prepared under my supervision by Richard Kent Entrikin

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be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

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To my beautiful wife, Maureen, for her patience, love and encouragement during the course of my graduate training.

Tumbling in pigeons is "...one of the most remarkable inherited habits or instincts ever recorded..."

Charles Darwin, 1897, in
Animals and Plants under
Domestication

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This dissertation would have been much more difficult, and certainly less enjoyable, had it not been for the help and encouragement of many persons. With this in mind, I would like to mention as many of these people as possible in a short space, and thank them for their contributions.

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So many times I have told family and friends that "I don't have time" to spend with them, and for this I apologize. These fine people deserve a great deal of credit for their continued understanding and encouragement. To them I extend my love and thanks.

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the sacrifices she has made.

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I. INTRODUCTION

Tumbling in pigeons consists of paroxysms of rapid, consecutive backward somersaults, and is commonly observed only in pigeons of the Tumbler and Roller strains. At rest Tumbler pigeons are indistinguishable from common street pigeons (Fig. 1), but when the former move suddenly or attempt to fly, tumbling occurs. This phenomenon has been known since 1600 A.D. (Levi, 1965) and has recently been found to be an autosomal recessive trait (Entrikin, 1971; Entrikin and Erway, 1972).

Fig. 1 Tumbler Pigeons At Rest.

Numerous hypotheses to explain the physiological mechanism of tumbling have been proposed, but most of these have not been tested in a systematic manner. Mowrer (1940) stated that the inner ear morphology of Tumbler pigeons was normal and that blindfolded Tumbler pigeons would not tumble. Since Mowrer's findings left many questions unanswered, a more detailed study was undertaken by Entrikin and Erway. We examined thoroughly the organization of the vestibular apparatus, with special emphasis upon the cristae and maculae, but could not distinguish between inner ears of control and Tumbler pigeons by light microscopy (Entrikin, 1971; Entrikin and Erway, 1972).

We also repeated Mowrer's "blindfold" experiment and found, contrary to Mowrer's results, that blindfolded Tumbler pigeons would still tumble (Entrikin, 1971; Entrikin and Erway, 1972). The reason for this discrepancy is unknown, but one possibility is that our testing procedure was different from that used by Mowrer. It is very difficult to stimulate a blindfolded pigeon to tumble in response to the usual auditory or visual stimuli. If, on the other hand, a blindfolded pigeon is dropped from a height, or in some other way forced to move suddenly, tumbling will occur. It appears then that visual input is necessary for tumbling only insofar as it causes the pigeon to move suddenly. Our finding is supported by Gilbert's observation that blind Tumbler pigeons will tumble in response to an appropriate stimulus (Gilbert, 1947).

Mowrer (1940) also suggested that tumbling might be a form of myotonia or epilepsy, or that it might be caused by an abnormality of the cerebellum. Of these possibilities, epilepsy is the only one that has

received any attention from the scientific community. Lange (1952) reported that pentobarbital and trimethadione, but not diphenylhydantoin, "slightly decreased" the severity of tumbling. He concluded that tumbling is not a form of epilepsy and that the drug effects resulted from general depression of the central nervous system, and not from specific anticonvulsant activity.

This Dissertation provides new information regarding the potentially important physiological mechanism of tumbling, as well as a detailed description of the component motions involved in tumbling. Skeletal muscles and the central nervous system (CNS) of Parlor Tumbler pigeons have been examined by means of electrophysiological, pharmacological, and anatomical techniques.

II. DESCRIPTION OF TUMBLING

A. Definitions. One of the recurrent questions regarding tumbling concerns the actual movements that occur during a tumbling episode. It is known that Tumbler pigeons always somersault in a backward direction, but early attempts to film tumbling failed to reveal the specific component movements that occur during tumbling (Levi, 1969). In addition to satisfying one's intellectual curiosity, knowledge of the tumbling motions might aid in determining the physiological mechanism of tumbling.

As many as 40 different variations of tumbling behavior have been described (Gilbert, 1947) in the 22 known strains of Tumbler pigeons (Levi, 1965), but it is generally agreed that tumbling reaches its highest expression in Parlor Roller pigeons. The term "Parlor" indicates that after learning to fly normally during the first few weeks of life, these pigeons tumble so frequently as adults that every attempt at flight results in tumbling on the ground. In other words, Parlor pigeons cannot fly at all after a certain age is reached. In fact, the term "Parlor" is applied to these pigeons since they were often kept indoors as pets during the 19th Century. Rolling is a term that is sometimes used interchangeably with tumbling, but is usually reserved to describe only the more violent, prolonged episodes of backward somersaulting. The tumbling pigeons used in this research would be classified as Parlor Rollers by pigeon fanciers since these birds are incapable of flight and somersault backwards at high velocity for a distance of from five to twenty feet in a single "roll". In this thesis I have chosen to refer to all backward somersaulting as tumbling since rolling

is technically defined as rotational movement about the longitudinal body axis, and the backward somersaulting by pigeons is rotation about the transverse body axis.

Pigeon fanciers and researchers alike use number of somersaults per unit time, duration of a tumbling episode, and ease of provocation of tumbling to categorize the performance of Tumbler pigeons (Entrikin, 1971; Entrikin and Erway, 1972; Gilbert, 1947; Lange, 1952; Mowrer, 1940). In terms of ease of provocation, a severely-affected Tumbler pigeon will somersault with each mild provocation such as the approach of an investigator or a snap of the fingers. Less severely-affected Tumblers may simply run from the investigator, and may somersault only in response to a loud hand clap or to release from a height.

B. High-Speed Cinematography. Since tumbling occurs with such extreme rapidity that visual observation of the component motions is impossible, it was decided to produce a high-speed film of the normal flight of a Racing Homer pigeon and characteristic tumbling episodes by Parlor Tumbler pigeons. A summary of this endeavor has recently been published (Entrikin and Bryant, 1974).

Six Parlor Tumbler pigeons and one Racing Homer pigeon were filmed at 2000 frames per second. During each filming period one hand-held pigeon was released from a height of 0.3 meters above a flat surface. Just prior to each "drop", four 1,000 watt quartz iodine lamps were activated, followed immediately by activation of the high-speed 16 mm movie camera (Model 41-0004 Hycam Camera, Redlake Corporation, Santa Clara, California). The main objective was to capture on film the initial

tumbling motions, but the one-two second filming period permitted filming of an additional 5-10 somersaults by each pigeon.

C. Analysis of Tumbling Motions. Analysis of the film involved taking notes from comments tape-recorded during stop-frame and 16-frame-per-second viewing of each film segment. Sketches from representative frames with corresponding elapsed time from release in milliseconds (ms) are shown in Figure 2. These particular frames were chosen because they illustrate the major changes in body posture and position that occur after release of a pigeon. The actual number of frames between each sketch can easily be calculated from the time scale indicated directly beneath each sketch number (2 frames per ms).

Figure 2a shows that the Homer pigeon raises its wings and extends its feet upon release, and lands on the feet with the wings extended forward. During the descent the head, body and tail remain in line with one another and parallel to the surface below. Frames 4-7 in Fig. 2a illustrate the initial flying motions, consisting of phasic wing beats accompanied by a forward shift of the body mass, that result in flight less than 200 ms later. As during the descent, the head, body and tail remain in line as the pigeon ascends.

The severely-affected Tumbler pigeon in Figure 2b raises the wings and extends the feet upon release (frames 1 and 2) as does the normal pigeon (Fig. 2a) but the head and body of the Tumbler are not parallel to the surface below. Also the tail of the Tumbler forms an acute angle with the rest of the body. This angle is formed within 15 ms after the Tumbler is released (not shown) and this abnormal relationship between the tail and body is maintained throughout the tumbling episode. The

severely-affected Tumbler lands with feet and wings extended forward (frame 3) but the feet and wings do not contact the underlying surface due to the backward rotation that has positioned the pigeon abnormally. The initiation of the somersault is seen in Figure 2b (frame 3), where the pigeon has begun to rotate backwards (nose-up pitching) as the wings move forward. A cycle for a single wing beat in the severely-affected Tumbler pigeon and in the normal pigeon lasts 100-125 ms; the head and body remain aligned in both, but the tail is elevated only in the Tumbler. Subsequent somersaults are stereotyped and occur at a rate of 8-10 per second, with one wing beat per somersault.

Figure 2b also shows that movements other than rotation in pitch occur during tumbling. These are rotation about the longitudinal body axis (rolling) and rotation about a dorsoventral body axis (yawing) that cause the pigeon to land in a position different from that expected after a simple 360° motion in pitch. Comparison of frames 3 and 7 in Figure 2b illustrates the effect of these superimposed motions upon the ultimate position of the pigeon.

Figure 2c represents a mildly-affected Parlor Tumbler. The wings and feet are again extended, and the tail elevated within 15 ms after release (frame 2). After 45 ms the pitching motion has positioned the pigeon abnormally, but the head and body remain in line with one another (frame 3). The first evidence of tumbling is seen in frame 3 as the forward wing stroke begins; 140 ms later the somersault ends in an awkward landing as the cycle is completed (frame 6). The effects of the rolling and yawing motions are illustrated in frames 4 and 5.

All the Tumbler pigeons that were filmed had apparently normal wing motions. The force was supplied by the forward wing stroke, during which the feathers appeared tightly interlocked. During the back-stroke the wing feathers separated and sliced through the air with little apparent resistance. Furthermore, the position of the wings relative to the body was the same in Homer and Tumbler pigeons. The feet did not seem to contribute to tumbling; their position varied from one somersault to the next, and no pushing movements of the feet were observed. In fact, in some cases the feet seemed to decrease the tendency to tumble by exerting a dragging force opposite in direction to the characteristic motion in pitch.

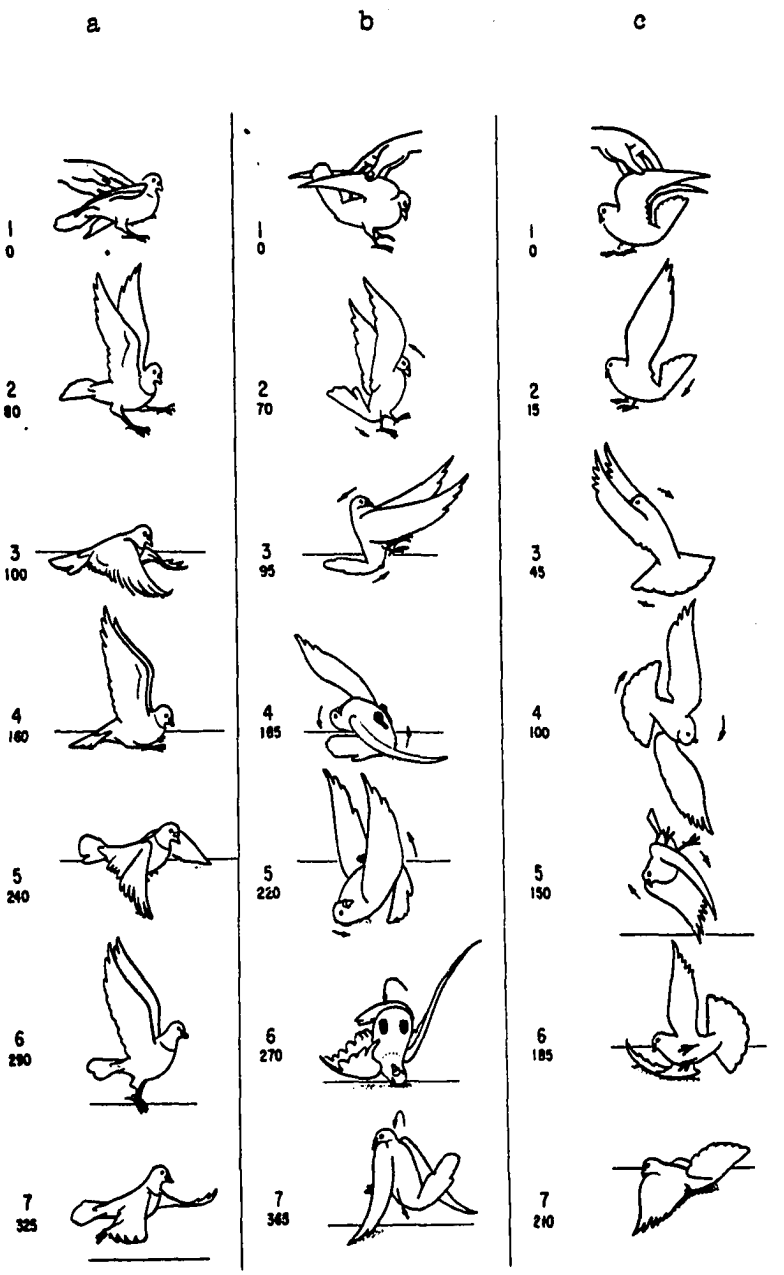

Fig. 2. Movements of Homer and Parlor Tumbler pigeons in response to release 0.3 m above flat surface. (a) Homer, (b) severely affected Parlor Tumbler, (c) mildly affected Parlor Tumbler. Each pigeon was released at 1. Numbers 1-7 are successive frames. Time in milliseconds from time of release is given below each frame number.

D. Discussion. Analysis of the film has shown that within 15 msec after a Parlor Tumbler pigeon is released from a height, abnormal dorsiflexion of the tail occurs. After this abnormal tail movement the pigeon rotates backward during the descent (nose-up pitching). Subsequent wing movements appear appropriate for flight, but the abnormal posture maintained during tumbling causes the wing motions to propel the pigeon backwards.

It seems probable, although not yet proven, that the dorsiflexion of the tail also occurs during the "natural" course of tumbling. That is, tumbling is usually induced by forcing the pigeon to move suddenly from a position of rest on a solid surface, and not by releasing the bird from a height. The pigeons were dropped from a height during the filming sessions since this procedure always induces tumbling. This was considered necessary to eliminate the possibility that a pigeon would not tumble, which would have resulted in a great deal of wasted film.

In support of the theory that dorsiflexion of the tail occurs during the natural course of tumbling, one is reminded of the maneuver known as "tail-sitting" that occurs in young Tumbler pigeons. This maneuver can be observed in Tumbler pigeons that have not yet begun to tumble frequently. These birds fly normally but at variable intervals make several slow, powerful wing strokes and extend the wings as if to glide. As the wings are extended in an upward position, the pigeon does not glide, but falls toward earth. During this time the pigeon rotates backward (nose-up pitching) and the tail becomes parallel to the ground. This position is indistinguishable from that in frame 2 of Figures 2b

and 2c. With time the young Tumbler pigeon makes flying motions with the wings during tail-sitting, and tumbling occurs.

The precise neural pathways involved in dorsiflexion of the tail are unknown, but the fact that this movement occurs in Tumbler pigeons within 15 ms of release is consistent with neural transmission of impulses for a stereotyped movement. This tail movement appears to be an active process that involves the dorsiflexor muscles of the tail, the levator caudae. It must also be mentioned though, that decreased tone in muscles antagonistic to the levator caudae would likely result in the same tail movement. This movement possibly arises from the abnormal function of a sensory input, a central or feedback mechanism, or some aspect of the motor output. As stated earlier, the only aspects previously examined in a systematic way involved inner ear histology and the effects of anticonvulsant drugs upon tumbling. Elements of the motor system and the central nervous system are considered in the remainder of this thesis.

III. SKELETAL MUSCLE FUNCTION

A. Isolated Biventer Cervicis Muscles.

1. Introduction. The biventer cervicis muscles of pigeons are paired muscles on either side of the midline of the dorsal aspect of the neck (George and Berger, 1960), and extend from the posterior part of the skull to the lower cervical vertebrae (Fig. 3). These muscles were chosen for study since they seemed to be involved in the tumbling motions, were well-suited for electrophysiological experiments, and could be easily dissected.

This section describes experiments designed to determine the electrical properties of biventer cervicis muscle fibers and secondly, to determine whether or not these muscles are abnormal in Tumbler pigeons. Cable properties and excitability characteristics of the muscle fibers were measured with intracellular microelectrodes, and the contractile response of isolated biventer cervicis muscles to acetylcholine was measured in organ baths.

2. Methods.

a. Animals. Adult pigeons (0.3-0.5 Kg) of the Homer (standard-flying controls), Helmet (standard-flying controls), and Parlor Tumbler strains were used for these studies. These pigeons were chosen in random fashion from the flock of pigeons maintained by the Department of Laboratory Animal Medicine at the University of Cincinnati College of Medicine. All these birds were fed a standard diet of Purina pigeon grain (Ralston-Purina, St. Louis) ad libitum, received fresh drinking water each day, and were in good health at the time of each experiment.

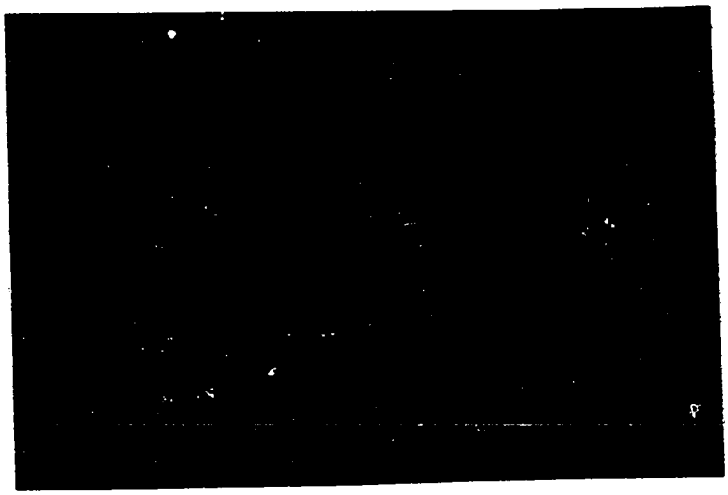

Fig. 3. Biventer Cervicis Muscles In Situ.

b. Anesthesia and muscle preparation. Pigeons were sacrificed by intraperitoneal injection of 40-80 mg/Kg pentobarbital sodium (Nembutal, Abbott). A dorsal midline incision was then made from the base of the skull caudally for about 8 cm to expose both biventer cervicis muscles, which were subsequently removed in the manner of Ginsborg and Warriner (1960). In all experiments the muscles were immediately placed in a physiological solution of the following composition (mM): NaCl 160; KCl 4.5; $CaCl_2$ 2.0; $MgCl_2$ 1.0; NaH_2PO_4 0.44; $NaHCO_3$ 12.0; and glucose 5.5. This solution (pH 7.1) was maintained at 38-40°C and gassed with 95% O_2, 5% CO_2 during all experiments. The muscles were stretched under slight tension in a shallow plexiglas chamber and connective tissue was removed under a stereomicroscope (Fig. 4a). The time from injection of pentobarbital to completion of connective tissue removal was less than 30 minutes.

c. Cable parameters. After connective tissue removal one muscle was selected, placed in a plastic chamber, and spiralled one-half turn under slight tension on a clear, plastic rod (Fig. 4b). The muscle was illuminated from below by reflected light and viewed from above through a stereomicroscope. Two capillary-glass microelectrodes filled with 3 M KCl were then inserted into the same muscle fiber. These microelectrodes had tip diameters of 0.5 μm or less and resistances of 15-20 Megohms. The current electrode passed hyperpolarizing constant-current square wave pulses (10 ms duration) and the voltage electrode recorded the resultant electrotonic potential (Fig. 5). Current and voltage traces were displayed simultaneously on a cathode-ray oscilloscope (Tektronix, type 502 A)

and recorded photographically (Grass Instrument Company, Model C4 Camera). Voltage measurements were made intracellularly at two distances (0.05 mm and 0.45-1.20 mm) from the current electrode. These interelectrode distances were estimated with an ocular micrometer to within 0.01 mm. (For

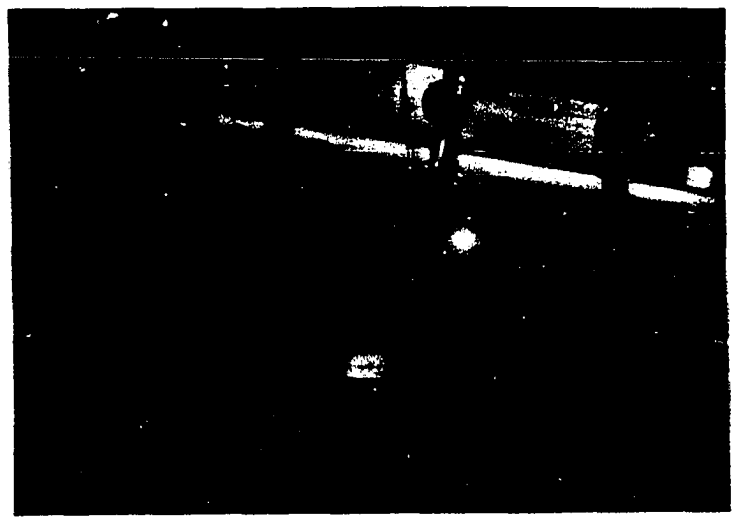

Fig. 4. a) Upper: Biventer Cervicis Muscle in Dissection Chamber.

b) Lower: Isolated Biventer Cervicis Muscle Prepared For Electrophysiological Measurements.

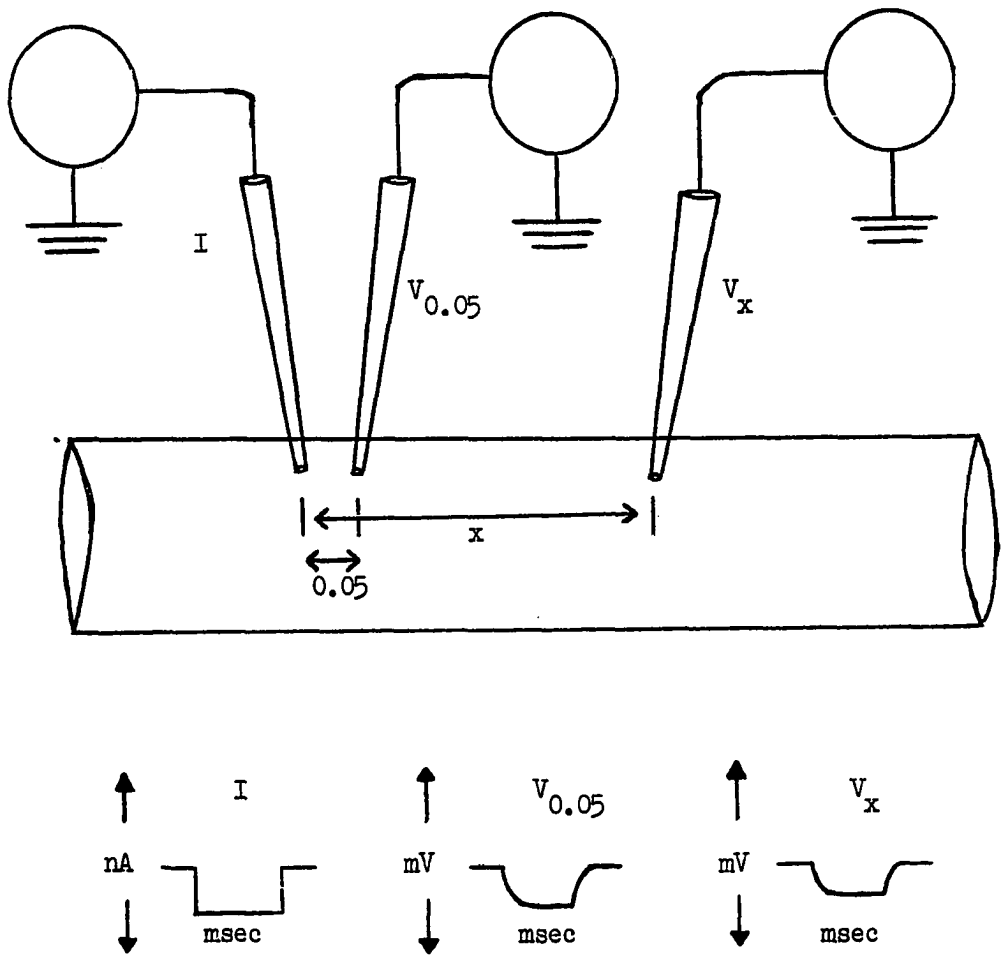

Fig. 5. Recording Arrangement for Cable Measurements.

Upper: Diagrammatic representation of skeletal muscle fiber. I = current electrode; $V_{0.05}$ = voltage electrode at first position; V_x = voltage electrode at 2nd position.

Lower: I = current pulse (nA); $V_{0.05}$ = voltage trace recorded at 1st electrode position; V_x = voltage trace recorded at 2nd position (mV).

further details of the recording procedure(see Bryant, 1969). Data were obtained by analysis of the film with a film-reader and the subsequent calculations were performed on a digital computer.

Figure 6 is an electrical model of the skeletal muscle fiber membrane and is the basis for the following cable parameter measurements. Standard techniques for determinations of R_{in}, λ, and R_i appear in the literature (Bryant, 1969; Fatt and Katz, 1951). The experimentally determined input resistance, R_{in} ($M\Omega$); space constant, λ (mm); time constant, τ (ms); and myoplasmic resistivity ($\Omega \cdot cm$) were used to calculate fiber diameter, D_{calc} (μm); membrane resistance, R_m ($\Omega \cdot cm^2$); and membrane capacitance, C_m ($\mu F/cm^2$). Membrane capacitance determined in this study was assumed to be the sum of surface membrane and tubular capacitances. Values were obtained from a number of individual fibers from 3 Homer, 4 Helmet, and 6 Tumbler biventer cervicis muscles. Calculations were based on the following relationships (Bryant, 1969; Freygang, Rapoport and Peachey, 1967):

$$r_i = 2 R_{in}/\lambda \quad (1),$$

$$r_m = 2 R_{in} \cdot \lambda \quad (2),$$

$$c_m = \tau/r_m \quad (3),$$

$$R_i = A \cdot r_i \quad (4),$$

$$D_{calc} = (4 R_i/\pi r_i)^{1/2} \quad (5),$$

$$R_m = \pi D_{calc} \cdot r_m \quad (6),$$

$$\text{and } C_m = c_m/\pi D_{calc} \quad (7),$$

where r_i = longitudinal resistance of the fiber, Ω/cm; r_m = membrane

resistance, $\Omega \cdot cm$; c_m = fiber capacitance, $\mu F/cm^2$; and A = cross-sectional area of the fiber, μm^2.

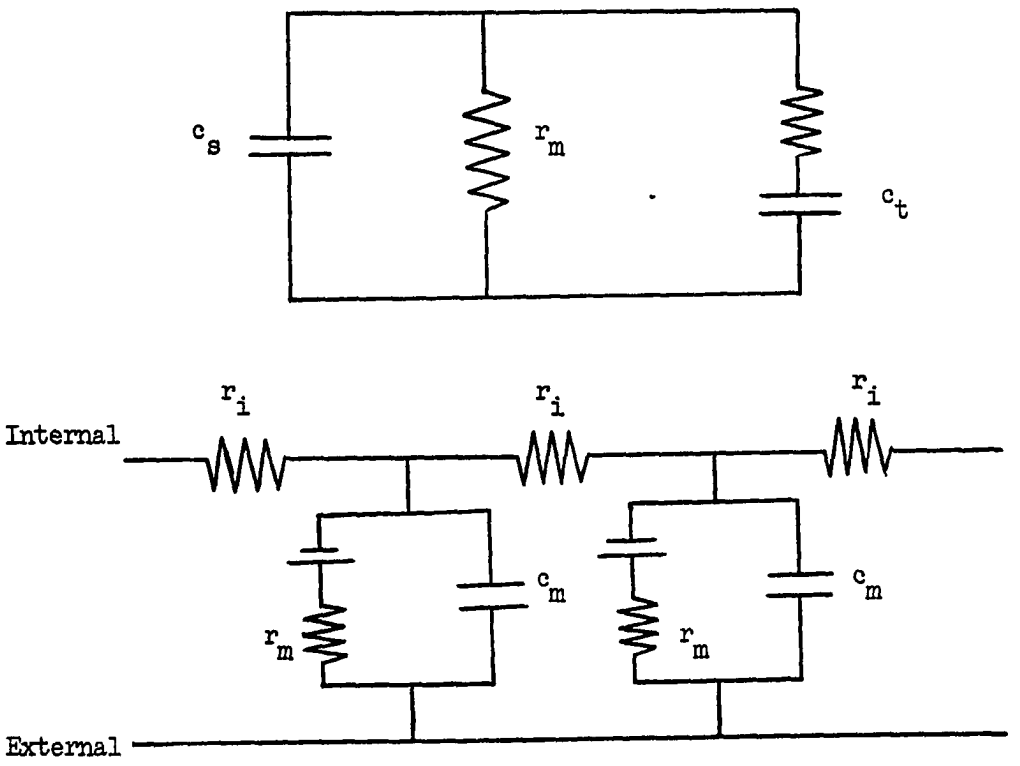

Fig. 6. Cable Models of Skeletal Muscle Fiber Membrane.

Upper: Two time-constant model (Falk and Fatt, 1964).

Lower: One time-constant model in which surface and tubular capacitances are combined.
r_i = longitudinal resistance of the fiber;
r_m = membrane resistance; c_m = total membrane capacitance;
c_s = capacitance of surface membrane alone;
c_t = capacitance of tubular system membrane.

Individual fiber cross-sectional areas were not determined in these multifiber preparations because the fiber edges were not sufficiently distinct to allow reliable estimation of fiber diameter using the ocular micrometer of the microscope. Instead a mean fiber cross-sectional area was calculated from hematoxylin-eosin stained cross-sections of each muscle. The area from these sections (A) and the mean longitudinal resistance (r_i) determined electrophysiologically from fibers of the same muscle were used to calculate a mean myoplasmic resistivity (R_i) using equation 4. That this procedure is valid is supported by the finding that the mean of $1/r_i$ covaries with the mean cross-sectional areas of different muscles and that the slope of the regression line closely approximates the mean R_i for all the preparations, the line passing close to the origin (see Bryant, 1969). R_i can thus be assumed to be constant for biventer cervicis fibers from the same strain of pigeons.

From the mean R_i a calculated diameter, D_{calc}, was determined for each fiber in a given preparation by equation 5, and the specific membrane parameters, R_m and C_m, were then calculated from equations 6 and 7. The calculated diameter seems to be a reasonable estimate of the diameter of a right cylinder of myoplasm electrically equivalent to the muscle fiber. Since the mean R_i's for Helmet (79 Ω·cm), Homer(185 Ω·cm), and Tumbler (116 Ω·cm) muscle fibers were significantly different, the corresponding R_i was used to determine the calculated diameter for each strain.

The time constant, τ, was calculated from the 50% rise time of the steady-state electrotonic potential at the second voltage-electrode position from the following equation:

$$\tau = t_{50} / [0.2275 + 0.5\ (x/\lambda)] \qquad (8),$$

where t_{50} is the time to rise to one-half the steady-state potential at a distance, x, and λ is the fiber space constant.

Cable parameters and fiber diameters for each muscle are expressed as the mean ± the standard error of the mean. Summary values for Helmet, Homer, and Tumbler muscles are expressed as the mean ± the standard error of the mean, giving equal weight to each fiber.

d. Excitability Characteristics. Each muscle was prepared and positioned on the plastic rod as in the cable experiments. The voltage deflection to 50 ms depolarizing constant-current pulses was recorded through an intracellular microelectrode inserted within 50 μm of an intracellular current electrode. The following parameters were recorded (see Fig. 7): minimum current intensity that would elicit a single action potential (rheobasic current, I_o); maximal latency from the beginning of the current pulse to the critical membrane potential (T_u); resting potential (RP); critical membrane potential (CMP); and the action potential amplitude (AP).

e. Contractile Response to Acetylcholine Bromide. The muscles for these experiments were obtained in the same manner as were those used in the cable and excitability experiments, but fine dissection of connective tissue was kept to a minimum. For each experiment paired biventer cervicis muscles were removed from a single pigeon and suspended under one gram tension in separate double-walled organ baths. The bath solution had the composition described above, was maintained at 38-40°C, and was gassed with 95% O_2, 5% CO_2.

The upper belly of the muscle was connected via a short length of thread to a force-displacement transducer (Grass FT03C).

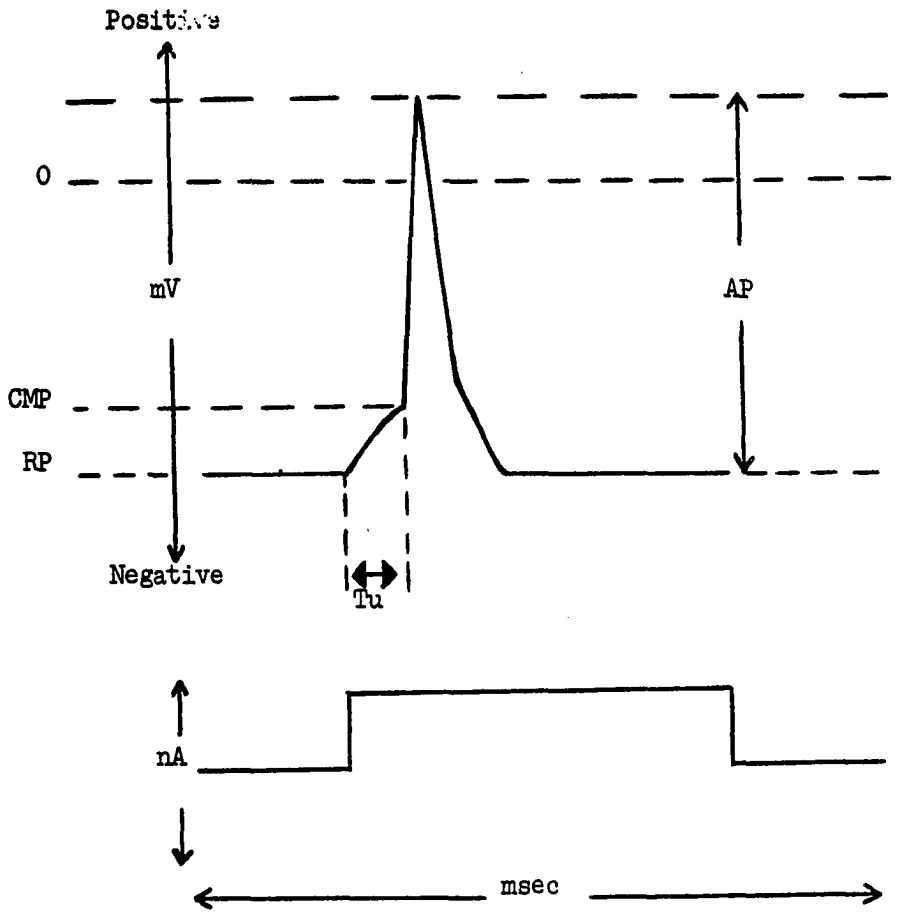

Fig. 7. Diagrammatic Representation of Excitability Characteristics as Components of a Single Action Potential. I_o = rheobasic current; Vm = membrane potential; RP = resting potential; CMP = critical membrane potential; AP = action potential amplitude. 0 indicates zero membrane potential. Units for current are nanoamps (nA); for voltage they are millivolts (mV); time scale is in milliseconds (ms). Tu, latency from initiation of current to initiation of action potential is measured in ms

The muscles were allowed to equilibrate for 30 minutes, acetylcholine bromide solution ($\leq$ 0.25 ml) was then added directly to the bath, and the tension recorded on a Grass polygraph (Model 5). Cumulative concentration-response curves were obtained from 6 Helmet and 6 Tumbler muscles by raising the bath concentration of acetylcholine from 10^{-7} to 10^{-2} M. Each successive addition of acetylcholine was made when the tension to the previous concentration of acetylcholine had reached a plateau. The amount of acetylcholine added to the bath was calculated in such a manner that each addition would increase the bath concentration by the factor $\sqrt{10}$.

f. Histology. Muscle fiber dimensions were calculated from 731 fibers. These fibers were from 11 biventer cervicis muscles that had previously been fixed in 10% formalin, paraffin-embedded, stained with hematoxylin and eosin, and sectioned on a microtome. A representative section from the midpoint of each muscle was projected onto plain paper and the outlines of 60-80 fibers were drawn. Since it was assumed that the fiber cross-section could be approximated by an ellipse, the best estimates of the major axis (a) and minor axis (b) were measured and recorded for each fiber. Fiber cross-sectional areas were calculated by equation 9 and multiplied by 2.02 to correct for histological shrinkage (Bryant, 1969).

$$A = \pi \cdot a \cdot b/4 \qquad (9)$$

g. Statistics. Student's t test was used to test for statistically significant differences among mean values of cable and excitability characteristics of Helmet, Homer, and Tumbler pigeon muscle fibers.

With respect to acetylcholine, the percent response at each bath concentration was transformed to probits for each of the 12 biventer cervicis muscles. The probit value versus log concentration at each point was subjected to a least-squares linear fit, and the slope and EC_{50} determined for each of the 12 curves. The EC_{50} is the bath concentration of acetylcholine that produced 50% of maximal tension development. From these values a mean EC_{50} and mean slope were calculated for the 6 Helmet and 6 Tumbler muscles. Student's t test was used to test for statistically significant differences between Helmet and Tumbler means.

3. Results

a. Cable Parameters. The calculated values of R_i for the three strains of pigeons are shown in Table 1. It can also be seen from that Table that the r_i's are similar among the three strains, and that R_i of the different strains varies with cross-sectional areas of the muscle fibers.

Table 2 summarizes the cable properties of 4 Helmet, 3 Homer, and 6 Tumbler muscles. Compared to Helmet fibers, Tumbler fibers have significantly smaller R_{in}, R_m, and λ, and larger D_{calc}. Compared to Homer fibers, Tumbler fibers have smaller R_{in}, R_m, τ, and D_{calc}, and larger C_m. Compared to Helmet fibers, Homer fibers have larger R_m, τ, and D_{calc}, and smaller C_m and λ. Mean values for Helmet, Homer, and Tumbler fibers, respectively, are: R_{in}, 0.40, 0.38, and 0.32 MΩ; R_m, 450, 556, and 386 $\Omega \cdot cm^2$; C_m, 4.2, 3.9, and 4.5 $\mu F/cm^2$; and D_{calc}, 30, 43, and 37 μm.

b. Excitability Characteristics. Table 3 summarizes the excitability characteristics of 86 fibers from 5 Homer muscles, and 67 fibers from 5 Tumbler muscles. Mean values of RP, CMP, and AP are slightly lower for the Tumbler fibers, but none of these differences is significant at the $P \leq 0.05$ level. The mean T_u for Tumbler fibers, 2.6 ± 0.11 ms, is significantly lower than the Homer T_u, 3.1 ± 0.15 ms ($P < 0.025$). Likewise I_o of Tumbler fibers, 58.6 ± 2.4 nA, is lower than the value for Homer fibers, 77.4 ± 2.7 nA ($P < 0.05$).

c. Acetylcholine Response. Plots of mg tension developed versus molar bath concentration on a log scale are shown in Figure 8. In Figure 9 the percent of maximal response is plotted against molar bath concentration of acetylcholine. The Helmet and Tumbler curves have the same general shapes and slopes, and maximal responses range from 1000 to 1490 mg in 11 of the muscles. One Tumbler muscle had a maximum response of only 415 mg.

The calculated EC_{50} and slope for each of the 12 curves are shown in Table 4. Neither the differences between the mean EC_{50} of Helmet (0.55×10^{-4}M) and Tumbler (1.41×10^{-4}M) muscles, nor the differences between the mean slope of Helmet (1.222 probits per log unit) and Tumbler (1.435 probits per log unit) concentration-response curves is statistically significant.

An additional finding was that Tumbler muscles sometimes maintained tension longer than did the Helmet muscles. Three of the Tumbler muscles maintained near-maximal tension to acetylcholine in spite of repeated washes with fresh physiological solution. This resulted in a longer time to reach 50% relaxation in Tumbler muscles compared to Helmet muscles.

Table 1. Myoplasmic Resistivities of Pigeon Biventer Cervicis Muscle Fibers.

Preparation		r_i (MΩ/cm)	A (μm^2)	R_i (Ω·cm)
Helmet	A	15.4 ± 3.0 (10)	550.9 (75)	84.6
	B	16.8 ± 4.6 (9)	687.1 (75)	115.6
	C	11.5 ± 0.6 (12)	530.5 (71)	60.9
	D	11.5 ± 3.7 (3)	489.2 (76)	56.4
			Mean	79.38 ± 13.58
Homer	E	19.7 ± 2.5 (8)	1103.8 (60)	217.6
	F	12.8 ± 1.6 (14)	1315.6 (69)	167.7
	G	12.8 ± 1.1 (11)	1315.6 (69)	168.9
			Mean	184.74 ±16.41
Tumbler	H	8.6 ± 0.7 (8)	944.0 (80)	81.3
	I	12.3 ± 1.2 (15)	1074.3 (71)	131.6
	J	11.1 ± 1.3 (15)	991.0 (75)	109.7
	K	10.4 ± 0.9 (17)	1117.2 (80)	115.9
	L	11.9 ± 0.8 (16)	1031.6 (-)	112.6
	M	13.3 ± 1.2 (15)	1031.6 (-)	137.1
			Mean	116.35 ± 8.12

r_i = mean longitudinal resistance; A = mean fiber cross-sectional area; and R_i = mean myoplasmic resistivity. Numbers in parentheses refer to number of fibers measured in each preparation.

Table 2. Cable Parameters of Pigeon m. biventer cervicis

Prep.	n	D_{calc} (μm)	R_m ($\Omega \cdot cm^2$)	C_m ($\mu F/cm^2$)	D (μm)
		HELMET, R_i = 79 Ω·cm			
A	10	30.7 ± 3.8	424 ± 83	4.4 ± 0.8	26.5
B	9	28.2 ± 2.3	403 ± 60	4.5 ± 0.6	29.6
C	12	30.6 ± 0.9	495 ± 43	4.0 ± 0.3	26.0
D	3	32.3 ± 4.7	496 ± 94	3.6 ± 0.5	25.0
Mean	(34)*	30.14 ±1.33	449.9 ±33.2	4.21 ±0.30	27.01 ±0.28
		HOMER, R_i = 185 Ω·cm			
E	8	35.7 ± 2.1	446 ± 70	3.9 ± 0.2	38.6
F	14	45.1 ± 1.9	656 ± 58	3.6 ± 0.2	41.3
G	11	43.9 ± 1.7	510 ± 28	4.2 ± 0.3	41.3
Mean	(33)	42.47 ±1.26	556.4 ±34.2	3.87 ±0.14	40.65 ±0.20
		TUMBLER, R_i = 116 Ω·cm			
H	8	42.0 ± 1.8	399 ± 29	4.6 ± 0.4	34.7
I	15	36.7 ± 2.2	405 ± 50	5.1 ± 0.2	37.0
J	15	38.8 ± 2.1	341 ± 21	4.6 ± 0.4	35.5
K	17	39.4 ± 1.7	343 ± 20	4.3 ± 0.3	38.6
L	16	36.0 ± 1.2	436 ± 41	4.2 ± 0.4	----
M	15	33.1 ± 2.2	403 ± 25	4.1 ± 0.3	----
Mean	(86)*	37.34 ±0.82	386.4 ±13.9	4.45 ±0.15	36.75 ±0.20
Tumbler vs. Helmet	P	<0.001	<0.05	NS	<0.001
Tumbler vs. Homer	P	<0.005	<0.001	<0.005	<0.001
Helmet vs. Homer	P	<0.001	<0.05	NS	<0.001

Prep. refers to each muscle; n is the number of fibers studied in each muscle; and D is the mean fiber diameter determined histologically. Other column heading abbreviations are defined in the text. The P's are probability values and NS refers to $P > 0.05$. * For C_m: Prep. B, n = 8; prep. H, n = 7; Prep. J, n = 13.

Table 3. Excitability Characteristics of Pigeon m. biventer cervicis

Prep.	n	RP (mV)	CMP (mV)	AP (mV)	T_u (msec)	I_o (nA)
			HOMER			
P	13	-69 ± 3.2	-46 ± 2.6	97 ± 2.6	3.2 ± 0.4	99.5 ± 7.2
Q	14	-68 ± 1.4	-48 ± 0.8	85 ± 2.5	3.5 ± 0.4	75.9 ± 6.5
R	27	-67 ± 1.1	-49 ± 1.0	86 ± 2.0	2.8 ± 0.2	70.6 ± 4.2
S	15	-72 ± 1.4	-46 ± 0.7	95 ± 3.3	2.7 ± 0.2	88.9 ± 6.9
T	17	-75 ± 0.6	-48 ± 0.4	75 ± 1.7	3.7 ± 0.4	62.9 ± 2.8
Mean	(86)	-69.9 ±0.75	-47.7 ± 0.54	86.9 ±1.33	3.13 ±0.14	77.4 ±2.71
			TUMBLER			
U	9	-60 ± 1.3	-47 ± 1.2	78 ± 2.9	2.5 ± 0.3	43.3 ± 7.9
V	10	-70 ± 1.8	-47 ± 1.1	97 ± 3.4	2.2 ± 0.3	68.5 ± 6.4
W	11	-65 ± 2.3	-45 ± 2.0	81 ± 2.4	2.5 ± 0.2	67.3 ± 5.6
X	15	-73 ± 1.3	-48 ± 0.9	94 ± 2.5	2.3 ± 0.2	57.9 ± 5.2
Y	22	-69 ± 0.9	-45 ± 0.8	80 ± 1.3	3.0 ± 0.2	56.6 ± 3.1
Mean	(67)	-68.2 ± 0.80	-46.2 ± 0.55	85.7 ±1.38	2.6 ±0.11	58.6 ±2.41
P		NS	NS	NS	<0.025	<0.05

Prep. refers to each muscle and n to the number of fibers studied in each muscle. Other abbreviations are defined in the text. NS refers to $P > 0.05$. Prep. W, n = 9 for AP.

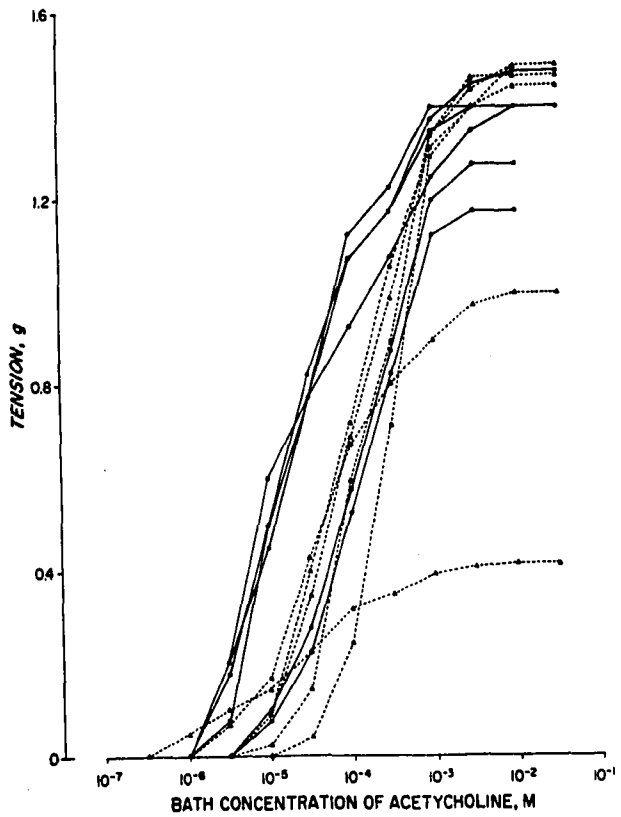

Fig. 8. Absolute Tension Developed vs. Bath Concentration of Acetylcholine. Pigeon biventer cervicis muscles, 38-40°C. Homer (control) muscles are represented by solid lines; Tumbler muscles by broken lines.

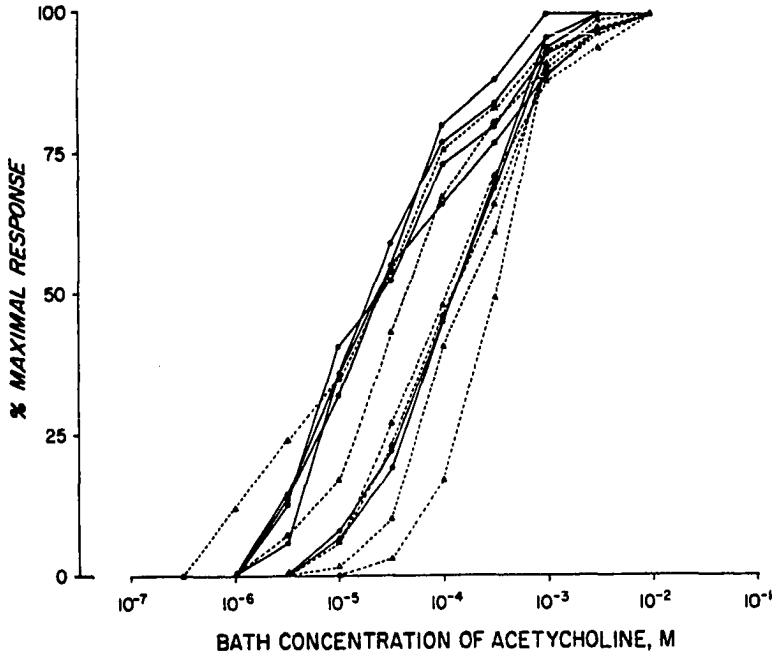

Fig. 9. Percent of Maximal Response vs. Bath Concentration of Acetylcholine. Pigeon biventer cervicis muscles, 38-40°C. Homer (control) muscles are represented by solid lines; Tumbler muscles by broken lines.

	HELMET			TUMBLER	
	EC_{50}(M)	Slope*		EC_{50}(M)	Slope*
1.	0.26×10^{-4}	1.08	7.	1.38×10^{-4}	1.25
2.	0.29×10^{-4}	1.35	8.	1.82×10^{-4}	1.65
3.	1.05×10^{-4}	1.59	9.	0.53×10^{-4}	1.10
4.	1.07×10^{-4}	1.44	10.	0.21×10^{-4}	0.90
5.	0.36×10^{-4}	0.92	11.	1.62×10^{-4}	1.76
6.	0.29×10^{-4}	0.94	12.	2.88×10^{-4}	1.95
Mean ±	0.553×10^{-4}	1.222		1.407×10^{-4}	1.435
S.E.M.	0.161×10^{-4}	0.114		0.391×10^{-4}	0.168
P				> 0.05	> 0.05

Table 4. EC_{50} and Slope for Helmet and Tumbler Pigeon Acetylcholine concentration-Response Curves. S.E.M. is the standard error of the mean; P is the probability value for statistically significant differences between means of Helmet and Tumbler values.

*Slope units = probits per log unit.

4. Discussion.

a. Avian Muscle. Cable properties of avian muscle are summarized in Table 5. The pigeon biventer cervicis has a membrane resistance much lower than that of the chicken anterior latissimus dorsi (ALD), but only slightly lower than that of the posterior latissimus dorsi (PLD) of the chicken. If a value for R_i = 160 Ω ·cm had been used in the present studies, as in those of Fedde (1969), the differences between R_m of chicken PLD and pigeon biventer cervicis would be even less. The membrane capacitance of pigeon muscle (3.9 - 4.5 $\mu F/cm^2$) is also lower than that of chicken muscle (6.0 - 8.2 $\mu F/cm^2$), but the pigeon membrane capacitance approaches 7.0 if one takes τ as the 83% rise time as did Fedde (1969).

The differences between cable properties of chicken and pigeon muscle can, therefore, be increased or decreased according to choice of R_i and τ. The reasons for taking τ as the 50% rise time in the studies of pigeon muscle are discussed in detail elsewhere (Entrikin and Bryant, in press). The choice of the appropriate value for R_i is usually of little concern in electrophysiological experiments, since only one strain of animal is usually used. The finding that three highly inbred strains of pigeons have different R_i's and fiber diameters suggests that the intracellular contents of the muscles of the three strains are different. R_i should vary inversely with ionic concentration in the myoplasm and the three strains might, therefore, have different myoplasmic ion concentrations. Another possibility (suggested by Fatt, 1964) is that the mobility of the myoplasmic ions decreases with the protein concentration. The

larger fibers, muscular appearance, and relatively large R_i of Homer pigeons are consistent with the possibility of increased protein concentration in muscles of that strain.

Another consideration when comparing cable properties of fibers from different muscles is the type of innervation of the fibers. Chicken muscles have the following types of innervation: ALD, multiple; PLD, focal; and biventer cervicis, mixed, but mainly multiple (Ginsborg and MacKay, 1960; Hess, 1961). Apparently the type of innervation of pigeon biventer cervicis muscle fibers has not been determined, but cable parameters are similar to those of focally innervated chick PLD fibers. If the majority of the pigeon biventer cervicis fibers are multiply innervated, the fiber sampling methods used were unbiased, and the cable parameters of chicken and pigeon muscle are similar, the cable properties of the pigeon biventer should be similar to those of the multiply innervated ALD fibers of the chicken. This apparent discrepancy cannot be resolved by the experiments reported here, but could be due to a relatively high percentage of focally innervated fibers in the pigeon biventer or to a generally much lower R_m in pigeon muscle than in chicken muscle.

Two additional comparisons are noteworthy. Values of resting potential, critical membrane potential, and action potential of pigeon biventer fibers are similar to those of the chicken PLD (Albuquerque and Warnick, 1971), and concentration-response curves of pigeon muscle to acetylcholine (Figs. 8 and 9) are similar to those of chicken biventer muscles (Baldwin and Lesser, 1971; Marshall, 1971; Snyder et. al., 1973).

		n	R_i ($\Omega \cdot cm$)	R_m ($\Omega \cdot cm^2$)	C_m ($\mu F/cm^2$)
Albuquerque and Warnick, 1971					
Chicken PLD, 23°C		52	180*	606	6.0**
Fedde, 1969					
Chicken ALD, 20-23°C		9	160*	4388	8.2**
Chicken PLD, 20-23°C		12	160*	561	7.0**
These experiments					
Pigeon Biventer Cervicis,					
38°C	Helmet	34	82	450	4.2
	Homer	33	185	556	3.9
	Tumbler	86	115	386	4.5

Table 5. Cable Parameters of Avian Muscle. n = number of fibers studied. Other abbreviations are defined in the text.

*R_i assumed.

**Calculated from time constant measured as theoretical rise time of electrotonic potential at $< 0.3\ \lambda$ from current source.

Table 2 shows that there are also differences in cable properties among the three strains of pigeons. The significantly lower R_{in} and R_m of Tumbler fibers compared to Helmet and Homer fibers indicates a higher resting membrane conductance in Tumbler fibers. The specific ionic conductances that are increased in Tumbler fibers have not been determined, but it has been shown that 90% of resting membrane conductance in Homer biventer cervicis muscles is due to chloride ion (Morgan, Entrikin, and Bryant, unpublished observation).

Differences in fiber diameters between Helmet and Homer muscles, and between Tumbler and Homer muscles, is not surprising since the size and weight of Helmets and Tumblers (275-300 gm) are quite different from those of Homers (425-500 gm). The highly significant difference between Helmet (30 μm) and Tumbler (37 μm) fiber diameters suggests hypertrophy of Tumbler fibers, possibly related to the more frequent contraction of Tumbler fibers due to tumbling. In general, the differences in muscle fiber cable properties are as great between the two control strains as they are between the Tumblers and either control strain.

b. Tumbling Phenomenon. From these studies one can draw some conclusions regarding the possible relationship between tumbling and the proposed myotonia of Tumbler pigeon neck muscles. It is clear that if myotonia exists in Tumbler pigeon muscles that it is not similar to that found in muscle from either goats or people with myotonia congenita (Bryant, 1973; Lipicky, Bryant and Salmon, 1971). In congenital myotonia there is an increased membrane resistance of about three-fold, a decreased rheobase of about the same magnitude, and a greatly prolonged maximal

latency for spike initiation. In addition, muscle fibers in congenital myotonia fire in an abnormally repetitive fashion with occasional after-discharges. Muscle fibers from Tumbler pigeons resemble myotonic fibers only with respect to the decreased rheobase, and even this small difference from control can be explained on the basis of the smaller size of Tumbler fibers compared to Homer fibers.

The concentration of acetylcholine that produced a contractile response 50% of maximum was similar in Helmet and Tumbler pigeon muscles. This finding also does not support the hypothesis that Tumbler fibers are myotonic in the usual sense since it is known that myotonic fibers respond differently to acetylcholine than do control fibers (Brown and Harvey, 1939).

Whether or not there is a myopathy of Tumbler fibers is not clear, but the muscles appear somewhat pinker during dissection, and light microscopic examination of the stained cross-sections used to obtain fiber dimensions reveals a relatively large number of central nuclei (Entrikin and Bryant, in press). As suggested earlier any of the abnormalities of Tumbler muscle found in these studies could be due to physiological adaptation to the more vigorous contractions these muscles appear to undergo during tumbling. Regardless of the cause of these differences between control and Tumbler pigeon biventer cervicis muscles, it is difficult to imagine how such minor changes could be causally related to such grossly abnormal movements as occur during tumbling.

B. In Vivo Administration of Drugs Known to Affect Skeletal Muscle Function.

1. Introduction. In conjunction with studies of isolated pigeon muscle, it was decided to investigate the effects of certain drugs upon tumbling behavior, and upon the motor behavior of control (Homer) pigeons. A number of drugs with prominent effects upon peripheral nerve or skeletal muscle were injected into Racing Homer and Parlor Tumbler pigeons, and the subsequent behavior of the pigeons was observed. The drugs used were: dantrolene sodium, d-tubocurarine, procainamide, and anthracene-9-carboxylic acid.

Dantrolene (Dantrium^{R}, Eaton) is a hydantoin derivative (Snyder et al., 1967) that is currently receiving widespread attention as a therapeutic agent for spasticity (Chyatte, Birdsong and Bergman, 1971; Chipman and Kaul, 1972; Chipman, Kaul and Lambie, 1974; Gelenberg and Poskanzer, 1973; Mayer, Mecomber and Herman, 1973; Sheplan and Ishmall, 1975). Dantrolene is unique among skeletal muscle relaxants by virtue of its direct action on skeletal muscle fibers (Ellis and Carpenter, 1972; Heald and Matsumoto, 1971; Honkomp, Halliday and Wessels, 1970). Present evidence indicates that dantrolene uncouples the excitation-contraction process in skeletal muscle by decreasing calcium release from the transverse tubular system (Ellis and Bryant, 1972; Ellis and Carpenter, 1974; Ellis et al., 1973; Putney and Bianchi, 1974).

Tubocurarine is the classic non-depolarizing neuromuscular blocking agent (Koelle, 1970). It will produce skeletal muscle relaxation

and paralysis in a variety of species and in isolated nerve-muscle preparations. In birds it has been used to decrease movement artifacts of skeletal muscle contraction during electroencephalographic and electromyographic recording (Holliday et al., 1965; Ookawa, 1973).

Procainamide (Pronestyl, Squibb) is a local anesthetic that is often used clinically in the therapy of cardiac arrythmias (Ritchie, Cohen and Dripps, 1970). Like other local anesthetics it blocks sodium conductance in peripheral nerve (Taylor, 1959), has anticholinergic effects at high doses (Harvey, 1939; Jaco and Wood, 1944; Steinbach, 1968), and has anticonvulsant effects at low doses (Bernard and Bohm, 1965). In terms of skeletal muscle function, procainamide, by an unknown mechanism, produces subjective and objective relief of clinical signs of myotonia in people (Munsat, 1967).

Anthracene-9-carboxylic acid (ACA) is one of many agents that causes skeletal muscle stiffness reminiscent of myotonia when injected into mice, rats, and goats, (Bryant, 1973). The ACA effect of skeletal muscle is considered a pharmacological model for myotonia, since the natural course of the disease and the membrane action of ACA are both characterized by decreased resting chloride conductance and by abnormal repetitive firing in skeletal muscle fibers (Bryant and Morales-Aguilera, 1971).

None of these agents has previously been used in the study of tumbling behavior, but it seemed reasonable to assume that at least one of them would affect tumbling if the condition were due to an abnormality of peripheral nerve or skeletal muscle. Dantrolene, tubocurarine, and procainamide might be expected to depress skeletal muscle function, and

thereby decrease the severity of tumbling. ACA should induce myotonia in pigeons as it does in mammals and chicks, and permit comparison of tumbling to myotonia. If tumbling is a form of myotonia, one might expect tumbling to be worsened by ACA.

2. Methods. Dantrolene, tubocurarine, procainamide, and anthracene-9-carboxylic acid were administered on a mg/Kg basis to Racing Homer and Parlor Tumbler pigeons weighing 0.3-0.5 Kg. Different pigeons were used for different drugs except in those cases where the interval between administration of different drugs was greater than one week. Prior to drug administration, injections of 0.13, 0.18, 0.26, and 0.52 cc of 0.9% sodium chloride USP (Abbott) were given intraperitoneally (i.p.) to five Homer and five Tumbler pigeons to determine whether the solvent alone would affect tumbling behavior. Each drug was then administered to Homer and Tumbler pigeons. The behavior of each pigeon was observed 20 minutes pre-injection and every 20 minutes post-injection for a period of two hours. Tumbling was tested at these times by dropping each pigeon twice in succession from a height of 2 m above a foam cushion, at which time the pattern and duration of tumbling were noted.

A saturated solution of dantrolene sodium in 0.9% NaCl was injected i.p., ($\leq$ 0.5 cc) in 4 doses at 30 minute intervals. After successive injections, the total dose administered was 10, 20, 40, or 80 mg/Kg. Gelatin capsules (# 5, Parke-Davis) containing dantrolene and lactose USP (Merck 71590) were administered orally three times daily (t.i.d.) to two Racing Homer and two Parlor Tumbler pigeons. The total daily

oral dose was 5 mg/Kg for days 1-5, 10 mg/Kg for days 6-10, 20 mg/Kg for days 11-15, and 40 mg/Kg for days 16-20.

Tubocurarine chloride (Abbott) was dissolved in 0.9% NaCl (10^{-3} g/ml) and injected into the wing veins of 8 Homer and 6 Tumbler pigeons. Two Homer and two Tumbler pigeons received each dose of tubocurarine. The dose administered to any one pigeon was 15, 30, 60, or 120 µg/Kg.

Procainamide hydrochloride injection (100 mg/cc) USP (Pronestyl, Squibb) was injected i.p., (≤ 0.35 cc) in 5 doses at 30-minute intervals into 5 Homer and 10 Tumblers. After successive injections the total dose administered was 4, 8, 16, 32, or 64 mg/Kg.

Anthracene-9-carboxylic acid (Aldrich, A 8940-5) was dissolved in 0.9% NaCl (4 mg/ml)and injected i.p., (≤ 0.8 cc) in 4 doses at 30-minute intervals to 10 Homers and 5 Tumblers. After successive injections the total dose administered was 2, 4, 8, or 16 mg/Kg. Since ACA is only slightly soluble in aqueous solution, the mixture was swirled in a flask under warm water to aid in formation of a solution.

3. Results. When procainamide was first administered to Tumbler pigeons it seemed to decrease the severity of tumbling. Further studies revealed that this was an incorrect interpretation. When the initial studies with procainamide were performed, the testing procedure consisted of dropping each pigeon 10 times in rapid succession from a height of one foot. Each series of 10 "drops" was made at 20-minute intervals, and any time a pigeon reached the floor 5 consecutive times without tumbling the height for the next series of drops was increased by one foot. After two hours of this testing procedure, several Tumbler pigeons that

had received procainamide could fly to the floor 10 consecutive times from a height of six feet without tumbling. This was an exciting finding, but close examination revealed that pigeons injected with procainamide were less severely-affected prior to drug administration than were those which had been injected with an equal volume of saline.

To resolve this confusion, the procainamide experiments were repeated. This time the less severely-affected Tumbler pigeons were injected with saline and the more severely-affected Tumblers were injected with procainamide. The result was disappointing, but intriguing. The animals injected with saline could fly without tumbling at the end of two hours, while the severely-affected pigeons injected with procainamide did not show a decrease in tumbling. These observations necessitated a change in the testing procedure to that outlined in the preceding Methods section. With this modified testing procedure, dantrolene, procainamide, and tubocurarine did not decrease the severity of tumbling. All Homer and Tumbler pigeons were noticeably weakened by tubocurarine at doses of 30 μg/Kg or greater (Table 6) and by procainamide at doses of 8 mg/Kg or greater (Table 7), but tumbling behavior was not changed. When spontaneous motor activity of the pigeons was decreased by high doses of procainamide ($\geq$ 32 mg/Kg), tumbling was slowed and it was more difficult to elicit tumbling. The most prominent effect of tubocurarine was a squatting posture, presumably due to weakness of the legs; the most prominent effect of procainamide was violent vomiting by all pigeons within 10 minutes after injection of an 8 mg/Kg dose.

Dantrolene sodium injections had minimal effects upon behavior of Homer and Tumbler pigeons (Table 8). Lethargy and decreased motor activity were the major effects, and these were first evident at a dose of 10 mg/Kg. The decreased motor activity was characterized by a squatting posture, presumably due to weakness of the leg muscles, and was first observed in Tumbler pigeons at 20 mg/Kg. Decreased motor activity was observed in all Tumbler pigeons at 20 mg/Kg, but in only three Racing Homers (60%) at a dose of 80 mg/Kg. Duration of tumbling was not decreased by dantrolene, but the velocity and violent nature of tumbling were reduced at doses (20-40 mg/Kg) that decreased spontaneous motor activity. It was also more difficult to elicit tumbling at these doses.

Oral dantrolene (Table 8) caused only vomiting. This effect was first observed at daily doses of 20 mg/Kg in Homer and Tumbler pigeons, and was especially prominent on days 16-20 when the daily dose was 40 mg/Kg. Tumbling was not changed in pigeons receiving oral dantrolene.

Anthracene-9-carboxylic acid had profound effects upon motor behavior of Homer pigeons, but did not induce tumbling in these animals (Table 9). The first sign of ACA-induced myotonia in the pigeon was a prolonged, quivering closure of the eyelids at the end of an eye-blink. This effect was observed in Homer and Tumbler pigeons after 4 mg/Kg of ACA. At the next higher dose (8 mg/Kg) slight myotonia of the legs and feet was observed following sudden movement. The highest dose of ACA, 16 mg/Kg, produced continuous stiffness of the legs and feet, and generalized myotonia upon sudden movement. The time course of the appearance of myotonic rigidity was related to the dose of ACA injected. The higher the

dose, the more rapidly the effects were observed. Most effects were evident within 5 to 10 minutes after injection.

The generalized, or "complete", myotonic attack in pigeons has features common to myotonia in mammals and chicks. These are: rigidity upon sudden movement, a "warm-up" phenomenon, and a refractory period during which a second myotonic attack cannot be elicited. Rigidity in the pigeon first affects the feet, in which the toes are curled inward, and the legs, which are extended. When such an attack is induced by forcing a pigeon to move suddenly, the bird will immediately become rigid, and may even fall over if caught off balance. Within seconds the rigidity decreases (warm-up) and the bird will walk away with a stiff-legged gait. Full recovery occurs within several minutes, but at high doses ($\geq$ 16 mg/Kg) rigidity may last for five minutes or longer. During a severe myotonic attack, the pigeon is prostrate, the head is retracted (opisthotonus), the legs are rigidly extended in abduction, and the tail is spread and held in line with the body. Interestlingly, the flight muscles are relatively unaffected. During an attack, a normal pigeon cannot attain flight on its own accord, presumably due to the position of the legs. An animal so-affected can fly normally if dropped from a height, but cannot land due to the curling of the toes and position of the legs.

Myotonia in Tumbler pigeons had the same general characteristics and progression as that in Homer pigeons. In a myotonic Tumbler pigeon the initiation of tumbling was unaffected, but the duration of tumbling was greatly reduced. In all five Tumblers injected with ACA, the first

somersault could be provoked in the usual manner, but the intervention of myotonic rigidity caused cessation of tumbling. When this occurred, the Tumbler pigeons still beat their wings, but the body and tail were in line with one another, and the legs were extended in abduction. While in this position Tumbler pigeons, like Racing Homers, could move about by lifting the body on extended wing tips and lurching forward. If dropped from a height before recovery from the myotonic attack, Tumbler pigeons could sometimes fly without tumbling.

Table 6. d-tubocurarine in Pigeons

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
15 μg/Kg	1 injection, i.v.	2 Homers, 2 Tumblers	None	Slight leg weakness.
30 μg/Kg	2 injections, i.v.	2 Homers, 2 Tumblers	None	Leg weakness more evident; birds have assumed squatting posture.
60 μg/Kg	1 injection, i.v.	2 Homers, 2 Tumblers	None	Cannot stand; respiratory difficulties.
120 μg/Kg	2 injections, i.v.	2 Homers	----	Both animals died within 3 minutes after injection

Table 7. Procainamide in Pigeons

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
4 mg/Kg	1 injection, i.p.	5 Homers, 5 Tumblers	None	None
8 mg/Kg	1 injection, i.p.	5 Homers, 5 Tumblers	None	All vomited within 10 minutes after injection.
16 mg/Kg	1 injection, i.p.	5 Homers, 5 Tumblers	None	All vomited; apparent weakness of the legs.
32 mg/Kg	2 injections, i.p.	5 Homers 5 Tumblers	Slower tumbling more difficult to elicit tumbling.	All vomited; leg weakness more severe; birds are lethargic and do not move about from place to place.
64 mg/Kg	3 injections, i.p.	5 Homers 5 Tumblers	Slower, less violent tumbling; more difficult to elicit tumbling.	All vomited; severe leg weakness; squatting posture; no moving from place to place.

Table 8. Dantrolene Sodium in Pigeons

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
5 mg/Kg	t.i.d., Orally for 5 days	2 Homers 2 Tumblers	None	None
10 mg/Kg	t.i.d., Orally for 5 days	2 Homers 2 Tumblers	None	None
20 mg/Kg	t.i.d., Orally for 5 days	2 Homers 2 Tumblers	None	Vomiting
40 mg/Kg	t.i.d., Orally for 5 days	2 Homers 2 Tumblers	None	All birds vomited daily.
10 mg/Kg	1 injection i.p.	5 Homers 5 Tumblers	None	Homers: none Tumblers: lethargic, squatting posture.
20 mg/Kg	2 injections i.p.	5 Homers 5 Tumblers	Tumbling slower and less violent.	Homers: 1 lethargic; 4 unchanged. Tumblers: decreased spontaneous activity; squatting posture with eyes closed.
40 mg/Kg	3 injections i.p.	5 Homers 5 Tumblers	More difficult to elicit tumbling; tumbling slower	Homers: lethargic; awkward staggering gait. Tumblers: decreased spontaneous activity; move about only if perturbed.
80 mg/Kg	4 injections i.p.	5 Homers	----	3 Homers have decreased motor activity.

Table 9. Anthracene-9-carboxylic acid in Pigeons

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
2 mg/Kg	1 injection, i.p.	10 Homers, 5 Tumblers	None	None
4 mg/Kg	2 injections, i.p.	10 Homers 5 Tumblers	None	3 Homers and 4 Tumblers have prolonged closure of eyelids after an eye-blink.
8 mg/Kg	3 injections, i.p.	10 Homers 5 Tumblers	None	Homers: 6 have myotonia of legs and feet upon sudden movement. Tumblers: 1 has myotonia of legs and feet upon sudden movement.
16 mg/Kg	4 injections, i.p.	10 Homers, 5 Tumblers	All Tumblers still tumble but duration is decreased greatly	Homers: all have spontaneous myotonia of feet and legs 10 minutes after injection. Tumblers: all 5 have spontaneous myotonia of feet and legs; generalized myotonia occurs during each tumbling episode.

4. Discussion. The lack of similarity between hereditary tumbling and ACA-induced myotonia, and the studies of isolated biventer cervicis muscles described in Section IIA, strongly indicate that tumbling in pigeons is not a form of myotonia. It has been shown previously that iodide ingestion produces myotonia in pigeons (Grieve, Entrikin and Bryant, 1974). The behavior of pigeons after iodide ingestion is indistinguishable from that induced by parenteral injection of ACA.

Drug-induced myotonia of the pigeon is interesting since it does not appear to significantly affect the wing muscles. The wing movements necessary for flying and tumbling still occur, but both flying and tumbling are profoundly altered. The difficulty encountered by ACA treated Homer pigeons when attempting to fly from the ground appears to be related to rigidity of the legs alone, since such pigeons can fly during a myotonic attack if dropped from a height. Tumbling by myotonic Tumbler pigeons seems to be antagonized in a physiological sense by ACA. That is, ease of provocation of tumbling is not changed by ACA, but the duration of tumbling is drastically reduced, presumably by rigidity of the muscles involved in tumbling. The importance of the acute angle formed between the tail and body of a pigeon during tumbling is supported by the ACA experiments. During a myotonic attack the body and tail remain in line with one another, as during normal flight, and no tumbling occurs. If a Tumbler pigeon is released from a height at this time it will not tumble.

The lack of wing involvement during a myotonic attack in the pigeon cannot be explained on the basis of these studies. It seems likely that

the electrical properties of the wing muscles are different from those of the muscles involved in myotonic rigidity of the pigeon,but these properties have not yet been determined. There seems to be a definite progression of muscle systems affected by ACA, the feet and leg muscles being most sensitive, and one would anticipate finding a high dose of ACA that would also cause rigidity of the wing muscles.

The effect of ACA upon hereditary tumbling allows one to predict the effects of other classes of drugs upon tumbling. Tumbling appears to be a clonic movement superimposed on a tonic phase of other muscles, mainly those of the tail and back. It seems reasonable, therefore, that those drugs that antagonize contraction of certain muscles of the tail and back would prevent formation of the acute angle between the body and tail of the Tumbler pigeon. Based on earlier observations in the high-speed cinematography studies of tumbling, one might expect such drugs to antagonize tumbling. It has been shown in this study that ACA causes the body and tail to be held in line with one another, and pigeons affected in this manner do not tumble. This suggests that other drugs that cause tonic rigidity would also decrease tumbling.

The fact that neither procainamide nor d-tubocurarine, even in high doses, greatly altered tumbling indicates that tumbling is not due to a peripheral abnormality. Procainamide does affect the central nervous system, but only at doses that also cause severe respiratory depression (Moe and Abildskov, 1970). Respiratory depression was not observed in procainamide-treated pigeons, and it is likely that the major effect of procainamide in the present study was depression of

peripheral nerve function. The fact that nerve trunks are not blocked by procainamide (Moe and Abildskov, 1970) further supports the possibility that tumbling involves the central nervous system. The high doses of tubocurarine severely depressed respiration, and actually caused the death of two Homer pigeons. The legs were so weakened that the pigeons could not stand, yet tumbling was unaffected. This finding supports the earlier observation that leg movements are relatively unimportant for tumbling.

Since dantrolene slowed tumbling only at doses that also decreased spontaneous motor activity, its effect on tumbling may simply be related to general depression of the nervous system or to muscular weakness. The relative contributions of CNS depression and muscular weakness to the dantrolene effect on tumbling have not been determined. One of the early concerns was that dantrolene might not uncouple the excitation-contraction mechanism in avian muscle. I have recently learned that dantrolene does block contraction of the isolated pigeon biventer cervicis muscle (Kenneth Dretchen, personal communication).

An important finding is that the amount of tumbling decreases when a pigeon is forced to tumble numerous times in rapid succession, even in the absence of drug administration. The reason for this decrease is not clear, but it seems unlikely that it is due to "learning". If it were due to "learning", one would expect a pigeon to tumble less on successive days after repeated forced rumbling. This was not the case. In fact, untreated pigeons tumbled the same on consecutive days even if successful flight had been attained on the previous day. This suggests

that frequent tumbling in rapid succession causes "fatigue"of some system essential to tumbling. Whether this process involves depletion of a naturally occurring neurotransmitter, or production of some inhibitory substance cannot be resolved at this time. Whatever the mechanism, one cannot ignore the effects of repeated activity upon tumbling.

The next section examines the possibility that tumbling is due to an abnormality of the central nervous system.

IV. CENTRAL NERVOUS SYSTEM

A. Drug Experiments.

1. Introduction. This section deals with the possibility that certain drugs might modify hereditary tumbling or induce tumbling in standard-flying pigeons, and thereby provide a clue to the physiological basis of tumbling. The only previous investigation of this type was that of Lange (1952). To test the "epilepsy" hypothesis of tumbling, Lange administered trimethadione, diphenylhydantoin, and pentobarbital to 15 Parlor Tumblers and 12 common pigeons. He observed decreased tumbling activity after trimethadione and pentobarbital, but not after diphenylhydantoin. Lange concluded that the decrease in tumbling was related to depression of the CNS, and not to specific anticonvulsant activity of any of these drugs.

Lange should be credited for being the first to systematically investigate the physiological basis of tumbling, but certain aspects of his experimental procedure can be criticized. First, he injected only one dose of each drug: 250 mg/Kg trimethadione, 5 mg/Kg pentobarbital, and 20 mg/Kg diphenylhydantoin, and therefore, could not show that the alterations in tumbling were dose-dependent. Second, each drug was administered in a single intramuscular injection and the tumbling behavior observed at 20-minute intervals for the next 80 minutes. This procedure is questionable since one may not see beneficial effects in people for a period of days or weeks after initiation of chronic anticonvulsant therapy (Toman, 1970). It should be possible to achieve a therapeutic

response earlier in the course of therapy, but larger initial doses would be required and unwanted effects would be more troublesome. Lange reported no side effects at the doses he used, and one must question whether or not the single intramuscular dose was large enough. Third, at each 20-minute testing interval each pigeon was forced to tumble 6 times, with only a 3-minute interval between successive tumbling episodes. This means that after being injected with a drug, each pigeon was forced to tumble 24 times in a 60-minute period. In this respect one is forced to consider the possibility that alterations in tumbling might have resulted from "fatigue" or conditioning, and not from effects of drugs. Such a possibility is supported by the observation in the preceding section that tumbling decreased during forced, repeated tumbling in non-treated Tumbler pigeons. Fourth, the manner in which tumbling was quantified is disturbing. In each of the 24 tumbling episodes, a pigeon was dropped from a height of six feet by the investigator and the number of tumbles executed during the descent was visually counted by the investigator. The greatest decrease observed in number of somersaults was from a pre-injection value of 11.9 to an 80-minute post-injection value of 8.9 in the trimethadione group. It is inconceivable to me that such a difference can be detected by unaided vision. As described in the "Description of Tumbling" section, tumbling occurs at a rate of 8-10 somersaults per second. If Lange's pigeons tumbled at a similar rate, the number of tumbles he counted would have occurred in approximately one second.

One dilemma when working with an hypothesis such as epilepsy is the validity of extrapolation from human data to animal data (and

vice-versa). This is especially important with drug studies since one does not know if a drug will have similar effects or mechanisms of action in members of different species. One might wonder then if drugs effective in therapy of convulsive disorders in people are also effective as antagonists of convulsions in pigeons.

In 1974 Kuenzel and Rubenstein reported on studies of a seizure syndrome in chickens known as paroxysm. Those seizures can be spontaneous or induced by electrical stimulation of the brain, and consist of four phases: alert, clonic, tonic, and recovery. Since repetitive high amplitude EEG spikes were recorded from the brains of affected chickens during seizures, the authors considered the possibility that the seizures were epileptiform in nature, and that they might be antagonized by anticonvulsant drugs. Both diphenylhydantoin and pentobarbital antagonized seizures. Also, epileptiform seizures in chickens are prevented by diphenylhydantoin, trimethadione, and diazepam (Johnson, Crawford and Fedoroff, 1973). Since drugs have been shown to be effective antagonists of these seizures in chickens, it seems reasonable to assume that they would also antagonize certain seizures in pigeons.

Whereas modifying hereditary tumbling by means of drugs might aid in classifying the nature of the abnormality, it would also be of interest to induce seizures in normal pigeons by administration of convulsant drugs. This type of experiment would at least provide a standard seizure pattern to which one could compare hereditary tumbling. Electroencephalographic effects of pentylenetetrazol have been demonstrated in chicks (Spooner and Winters, 1966) and in adult chickens

and pigeons (Ookawa, 1973). The behavioral patterns accompanying these EEG changes have not been reported, and since there are no reports of "epilepsy" in pigeons, it has not been possible to state whether or not hereditary tumbling resembles a specific seizure pattern.

Drugs that have their major influence upon the function of the basal ganglia would also be of interest in the study of tumbling. L-dihydroxyphenylalanine (L-DOPA) and benztropine mesylate are used to treat people with Parkinsonism (Klawans, 1968; McDowell et al., 1970; Yahr and Duvoisin, 1972), but the effects of neither agent have been described in pigeons. A dopamine receptor agonist, apomorphine, has also been used on a limited basis in the treatment of Parkinsonism (Cotzias et al., 1970; Cotzias et al., 1972; Schwab, Amador and Lettvin, 1951), but in pigeons interest in apomorphine has centered around its use as an emetic agent. Effects of these drugs in normal and Tumbler pigeons would be of interest since according to Ariens Kappers (1960) motor control in pigeons is mainly a function of the basal ganglia.

Alteration of presumptive neurotransmitters other than dopamine can also be achieved by administration of certain drugs. There is currently a great deal of interest in these presumptive neurotransmitters since there is evidence that they are involved in a number of behavioral abnormalities. Serotonin and norepinephrine concentrations in the brains of normal pigeons have been determined (Bogdanski, Bonomi and Brodie, 1963;Brodie and Bogdanski, 1964) as have the concentrations of brain serotonin after peripheral administration of the serotonin precursor, 5-hydroxytryptophan (Aprison and Ferster, 1961; Aprison et al., 1962). Both of these amines are present in high concentrations

in chicken and pigeon brains, and the ratio (2:1) of serotonin to norepinephrine in the pigeon is nearly double that found in mammals (Brodie and Bogdanski, 1964).

There have been no reports of involvement of central biogenic amines in motor disorders of birds, but there is one known as Scotty cramp in Scottish Terrier dogs (Fox, 1965; Meyers, Padgett and Dickson, 1970). Affected dogs undergo periods of muscular hypertonicity during which they experience abnormalities of posture and locomotion. Severity of the episodes can be increased by p-chlorophenylalanine (p-CPA), an agent that depletes brain serotonin (Weitzman et al., 1968), and decreased by nialamide(a monoamine oxidase inhibitor) and 5-hydroxytryptophan (Meyers, Dickson and Schaub, 1973).

The remainder of this section describes the results of experiments during which a variety of drugs were administered acutely and chronically to Homer and Tumbler pigeons. These experiments were aimed at: 1) antagonizing hereditary tumbling with anticonvulsants and CNS depressants and; 2) inducing "tumbling" in otherwise normal pigeons (Homers) with convulsant drugs and CNS stimulants.

2. Methods. Drugs were administered acutely and chronically to Homer and Tumbler pigeons. Acute administration was by the intraperitoneal (i.p.) route in most cases; chronic administration involved force-feeding of drug-filled gelatin capsules.

A complete list of drugs used is shown in Table 10. Determination of proper dosage was a major problem since there are no published doses for use of most of these drugs in pigeons. In such cases a dose reported

for use in other species was used initially. Before administration of any drug to Tumbler pigeons, a relatively small dose was administered on a per kilogram basis to two or three Racing Homer pigeons. Once a safe dose had been determined, each drug was administered to both Homer and Tumbler pigeons. The number of animals that received each drug was rather small and was limited by the small number of Tumblers on hand. The upper dosage was approached cautiously, especially in Tumblers, since these animals are quite expensive and difficult to replace. The number of Tumblers available did not exceed 20 at any time.

Drugs administered on a chronic basis were prepared by thorough manual mixing of the drug with lactose USP (Mallinckrodt, St. Louis). Empty gelatin capsules (No. 5, Parke-Davis) were then filled with the powdered mixture to a predetermined weight. Since no data were available for such studies in pigeons, the total daily dose and the interval between doses was determined from studies in other species. Capsules were administered by holding the beak of a pigeon in an upward, open position with one hand and dropping the capsule into the oral cavity with the other hand. Each pigeon was then watched closely for several minutes to be certain that the capsule was not regurgitated. Drugs administered in this manner are listed in Table 11.

Drugs administered acutely are listed in Table 12. Most were injected i.p. in volumes not exceeding 0.5 cc; benztropine mesylate and d-amphetamine were administered by both the i.p. and i.v. routes. In some cases pre-mixed solutions of drugs were used. In other cases, the powdered or crystalline form of the drug was dissolved in saline for in-

Table 10. Drugs with Prominent CNS Effects Administered to Racing Homer and Tumbler Pigeons

GENERIC NAME	TRADE NAME	MANUFACTURER
amitriptyline injection	Elavil	Merck
amitriptyline tablets	Elavil	Merck
d-amphetamine	Dexedrine	Smith, Kline & French
apomorphine	Apomorphine USP	Mallinckrodt
benztropine mesylate	Cogentin	Merck
chlorpromazine HCl	Thorazine	Smith, Kline & French
diazepam	Valium, injectable	Roche
l-dihydroxyphenylalanine (L-DOPA)	Larodopa tablets	Roche
diphenylhydantoin sodium	Dilantin, ready-mixed	Parke-Davis
diphenylhydantoin	Dilantin capsules	Parke-Davis
ethosuximide	Zarontin powder	Parke-Davis
ethosuximide	Zarontin capsules	Parke-Davis
mephenytoin	Mesantoin	Sandoz
meprobamate	Equanil	Wyeth
pentobarbital sodium	Nembutal	Abbott
pentylenetetrazol	Metrazol	Bilhuber-Knoll
phenacemide	Phenurone	Abbott
phenobarbital	Phenobarbital, USP	Wyeth
picrotoxin	Picrotoxin solution	Abbott
propranolol HCl	Inderal	Ayerst
strychnine	Strychnine. USP	Merck
trimethadione	Tridione	Abbott

Table 11. Drugs Administered Orally to Pigeons on a Chronic Basis

DRUG	CAPSULES PER DAY	TOTAL DAILY DOSE	TOTAL DAYS
amitriptyline	2	0.36 mg/Kg	10
	2	0.72 mg/Kg	8
L-DOPA	2	7.00 mg/Kg	10
	2	14.00 mg/Kg	8
DPH-mephenytoin combination	DPH-3	6.00 mg/Kg	7
	mephenytoin--1	4.30 mg/Kg	7
	DPH-3	6.00 mg/Kg	7
	mephenytoin--1	8.60 mg/Kg	7
ethosuximide	2	20.00 mg/Kg	7
	2	40.00 mg/Kg	7
meprobamate	2	5.20 mg/Kg	10
	2	10.40 mg/Kg	8
phenacemide	3	7.00 mg/Kg	5
	3	14.00 mg/Kg	5
	3	28.00 mg/Kg	5
phenobarbital	2	0.13 mg/Kg	10
	2	0.26 mg/Kg	16
trimethadione	3	10.00 mg/Kg	7
	3	20.00 mg/Kg	14

Table 12. Drugs Administered Parenterally to Pigeons

DRUGS	DOSAGE RANGE	ROUTE OF ADMINISTRATION
amitriptyline HCl	2.5-10.0 mg/Kg	i.p.
d-amphetamine	0.25-4.0 mg/Kg	i.p., i.v.
apomorphine	0.1-3.2 mg/Kg	i.p.
benztropine	0.1-2.5 mg/Kg	i.p., i.v.
chlorpromazine HCl	5.0-20.0 mg/Kg	i.p.
diazepam	0.1-0.4 mg/Kg	i.p.
diphenylhydantoin	2.0-80.0 mg/Kg	i.p., i.v.
ethosuximide	50-400 mg/Kg	i.p.
pentobarbital	5-80 mg/Kg	i.p.
pentylenetetrazol	30-120 mg/Kg	i.p.
picrotoxin	1.0-4.0 mg/Kg	i.p.
propranolol	5.0-20.0 mg/Kg	i.p.
strychnine sulphate	0.25-4.0 mg/Kg	i.p.
trimethadione	125-500 mg/Kg	i.p.

jection. The number of pigeons that received each drug was usually quite small. In most cases 5 Homer and 5 Tumbler pigeons were injected with a particular drug. Any drug that produced significant changes in behavior was then administered to a second group of 5 Homer and 5 Tumbler pigeons. The number and type of pigeons that received each drug are shown in Tables 13-22.

The dose of each drug was increased by a specific numerical factor to achieve logarithmic increases in dosage with time. Successive injections were made in the same pigeon at 30-minute intervals to achieve a specific cumulative dose of injected drug. Although this injection schedule is far from ideal due to differences in absorption, distribution and elimination of different drugs, it did seem a valid means of comparison for similar drugs in different pigeons.

Each pigeon was observed 5 minutes before drug injection and at 20-minute intervals after each injection for a period of two hours. Initially an attempt was made to count the number of somersaults by each pigeon before and after drug injection. This procedure was quickly abandoned since it was not possible to accurately count the number of somersaults by unaided vision. Next an attempt was made to correlate the severity of tumbling with the time taken to tumble to the floor from a height. It seemed reasonable that the time to reach the floor would increase as the severity of tumbling decreased, since decreased tumbling would permit the pigeon to experience some periods of normal or near-normal flight during the descent. The time to reach the floor was recorded to the nearest tenth of a second with a stop-

watch, but was found to be an unreliable measure of changes in tumbling behavior. This became obvious when certain drugs would greatly increase the duration or increase the ease of provocation of tumbling without a change in time taken to reach the floor.

The procedure finally employed involved observation of the distance of tumbling on the ground during each tumbling episode and the ease of provocation of tumbling. Ease of provocation of tumbling was taken as a measure of "control" by the pigeon over the propensity to tumble. A pigeon with poor control would spontaneously tumble when placed gently on the floor and upon each approach by an investigator. A pigeon with average control would tumble in response to a loud handclap or to the sudden approach of an investigator. Good control indicated that the pigeon would tumble only when released a few cm above the floor. Most pigeons had average control and would tumble 4-6 feet during a single tumbling episode.

3. Results.

a. Anticonvulsants. None of the anticonvulsant drugs produced profound decrease in tumbling, nor did they produce any unexpected effects in control pigeons. The major finding was that trimethadione and ethosuximide increased the severity of tumbling. Relatively low doses of pentobarbital produced a similar effect.

Diphenylhydantoin (DPH) had unremarkable effects in Homer and Tumbler pigeons (Table 13). Some pigeons vomited after 20 and 40 mg/Kg doses, and tumbling was slowed in one Tumbler after 40 mg/Kg DPH. The only other effect was a side-to-side, writhing movement of the neck in

3 of 3 Homers and 3 of 4 Tumblers after 80 mg/Kg DPH. Even at high doses tumbling was unchanged from the pre-injection test period. The oral combination of DPH and mephenytoin likewise caused no noticeable change in tumbling (Table 14). By the end of drug-day 5, the only behavioral change was that the pigeons seemed less active. This effect persisted until Day 9, when one Homer and one Tumbler became unusually defensive. By Day 11 both Homer and Tumbler pigeons were defensive, and would peck at the investigator's hand when an attempt was made to capture a pigeon. The onset of this defensive behavior coincided with that of vomiting, which occurred after administration of drug on days 11-14.

Oral administration of phenobarbital produced dose-related lethargy in Homer and Tumbler pigeons (Table 15). This effect was first noticed in one Tumbler pigeon after the seventh day of phenobarbital ingestion, and by the 12th drug-day all pigeons were lethargic. This effect was most noticeable one to two hours after drug ingestion. During this time Tumbler pigeons still tumbled, but tumbling was more difficult to provoke, slower, and somewhat decreased in duration. An attempt was then made with another group of pigeons to determine whether the decreased severity of tumbling was related to the anticonvulsant action of phenobarbital or to the general decrease in activity. For this purpose, pentobarbital was injected into Homer and Tumbler pigeons.

Pentobarbital had variable effects upon tumbling, depending on the dose administered (Table 16). The lowest dose, 5 mg/Kg, increased the duration of tumbling and produced motor incoordination characteriz-

ed by opisthotonus and staggering gait. The increased duration of tumbling was most marked in two Tumbler pigeons which tumbled only four to five feet before injection of pentobarbital. After drug injection these two pigeons tumbled for distances of from 30-40 feet during each tumbling episode. Motor incoordination was usually observed within 20 minutes after 5 mg/Kg pentobarbital and coincided with the increase in severity of tumbling.

The next highest dose of pentobarbital, 10 mg/Kg, decreased the severity of tumbling. This effect was accompanied by decreased spontaneous motor activity, and was characterized by decreased ease of provocation and duration of tumbling. These effects were more prominent after 20 mg/Kg pentobarbital. Since all Tumblers were asleep within 15 minutes after 20 mg/Kg pentobarbital, higher doses were not administered.

The only noticeable behavioral effect of pentobarbital in Homer pigeons was dose-related sedation. This effect was first observed after 10 mg/Kg, and all Homers were asleep after 20 mg/Kg. Homer pigeons died after injection of 40 or 80 mg/Kg pentobarbital.

Chronic oral trimethadione (10-20 mg/Kg/day) produced no noticeable behavioral changes in Homer or Tumbler pigeons, but injection of 175-250 mg/Kg trimethadione produced motor incoordination in both strains (Table 17). At these doses Homer pigeons had difficulty walking, and would sometimes fall over. These birds were also reluctant to fly, and when dropped from a height, they flew aimlessly, often flying into stationary objects. In Tumblers the incoordination was accompanied

by increased ease of provocation and duration of tumbling.

Behavioral effects of ethosuximide (Table 18) were similar to those of trimethadione. Tumbling was worsened after doses that caused motor incoordination, but lower doses produced no behavioral changes. In addition to incoordination and increased severity of tumbling, ethosuximide also induced a peculiar posture in Homers and Tumblers. The pigeons' legs were in the usual upright position, but the head was held low and the tail was elevated. The head, body and tail were in line with one another, but the whole animal was slanted forward about 50°.

Chronic phenacemide administration produced motor incoordination and worsened tumbling (Table 19). This occurred at 14 mg/Kg daily, and was more noticeable at 28 mg/Kg. The lowest dose, 7 mg/Kg, produced no behavioral changes.

b. Convulsants. These drugs produced the most dramatic effects in the entire study of tumbling. Strychnine induced tonic convulsions in Homer pigeons, and antagonized hereditary tumbling. Picrotoxin and pentylenetetrazol induced "tumbling" in Homer pigeons and increased the frequency of tumbling episodes in Tumbler pigeons.

1. Strychnine. Strychnine induced convulsions in Homer pigeons at doses of 0.75-2.00 mg/Kg;in Tumbler pigeons at 0.50-0.75 mg/Kg (Table 20). The dose-effect curve for strychnine convulsions in Homer pigeons is shown in Figure 10. Complete data were not obtained for strychnine convulsions in Tumbler pigeons, but it is obvious from Table 20 that Tumbler pigeons were more sensitive to strychnine than

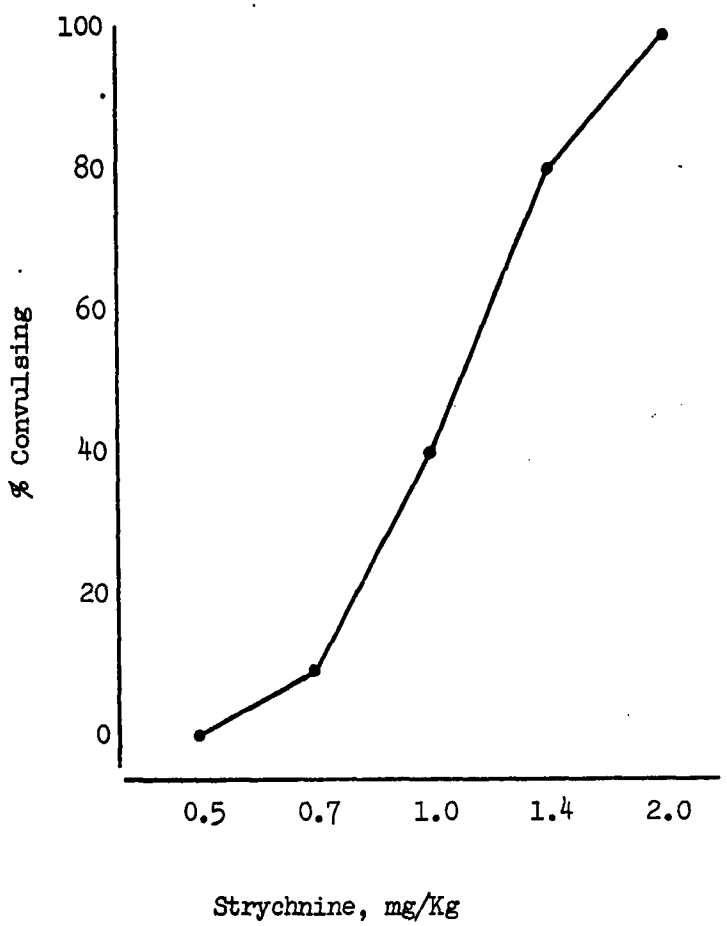

Fig. 10. Dose-Effect Relationships for Strychnine Convulsions in Homer Pigeons. One group of 10 Homer pigeons was used. If a pigeon convulsed at one dose, it was assumed that he would have also convulsed at a higher dose. Details presented in the text and in Table 20.

were Homers. For example 80% of the Tumblers convulsed after 0.5 mg/Kg, whereas none of the 10 Homers convulsed at that dose. Only after 1.5 mg/Kg did 80% of the Homers convulse.

Strychnine convulsions in both Homer and Tumbler pigeons were characterized by tonic extension of the limbs, and were indistinguishable from myotonic rigidity induced by ACA. The legs were extended in abduction, the tail was held in line with the body or vertically downward, and the wings were extended. Although the usual character of strychnine convulsions was tonic extension, there were occasional clonic movements of the feet and wings.

Strychnine greatly reduced the duration of tumbling and prevented normal pigeons from flying. After sufficiently high doses of strychnine, Tumbler pigeons could usually somersault once, but were then immobilized by the onset of a tonic strychnine convulsion. During a strychnine convulsion, Tumbler pigeons would not tumble. If dropped from a height during a convulsion, Homer and Tumbler pigeons would simply fall to the ground.

2. Picrotoxin. Dose-effect relationships for picrotoxin are described in Table 21 and plotted in Figure 11. These Figures show that Tumbler pigeons are much more sensitive to picrotoxin than are Homers, and that this increased sensitivity is expressed as frequent spontaneous tumbling episodes. In addition, sufficiently high doses of picrotoxin induce "tumbling" in Homer pigeons. This "tumbling" is similar to hereditary tumbling in that both consist of rapid consecutive backward somersaults that last for a matter of seconds. The experienc-

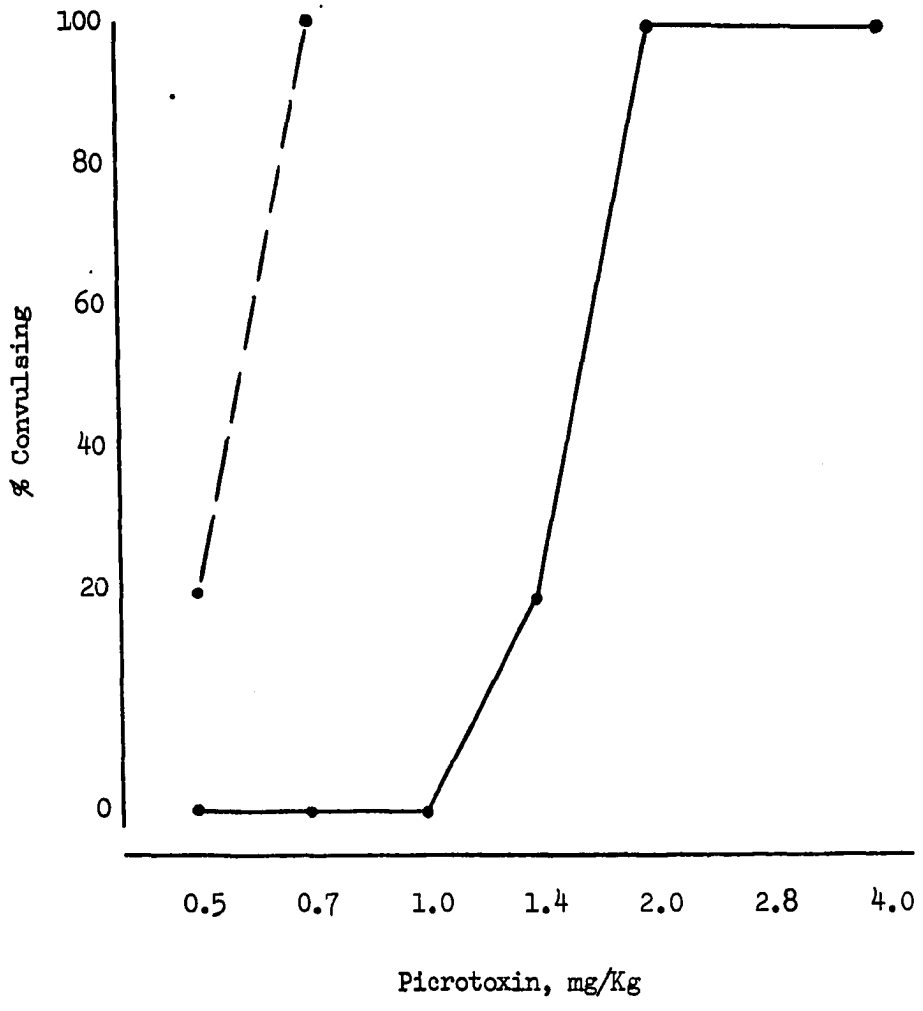

Fig. 11. Dose-Effect Relationships for Picrotoxin-Induced Convulsions in Homer and Tumbler Pigeons. Homers are represented by the solid line; Tumblers by the broken line. Details presented in the text and in Table 21.

ed observer can distinguish between these types of "tumbling", since drug-induced "tumbling" is accompanied by noticeable rigidity and hereditary tumbling is not. Furthermore, drug-induced "tumbling" was invariably followed by a tonic period during which the pigeon remained on its back for as long as two hours, and this was usually followed by death.

Picrotoxin effects follow a similar progression in Homer and Tumbler pigeons. Vomiting occurs first, then prolonged closure of the eyes after an eye-blink, jerking movements of the head, rapid "stomping" movements of the feet, rapid flexion and extension of the wings, and finally "tumbling". These effects are dose and time-dependent, and usually all the effects cannot be observed in a single pigeon after a single injection of picrotoxin. At low doses only vomiting may occur, and at high doses "tumbling" or tonic rigidity may be the only observable effect. In most cases gradual increases in the dose of picrotoxin from a relatively low initial dose were necessary to permit observation of all the behavioral effects. In spite of the variable expression of picrotoxin effects, the appearance of rapid movements of the head, feet and wings are assurances that a full-blown "tumbling" episode will soon follow.

3. Pentylenetetrazol. Pentylenetetrazol induces changes in behavior that are indistinguishable from those after picrotoxin. Effects of pentylenetetrazol are described in Table 22 and Plotted in Figure 12. The progression of behavioral changes with pentylenetetrazol is likewise similar to that produced by picrotoxin. The only major

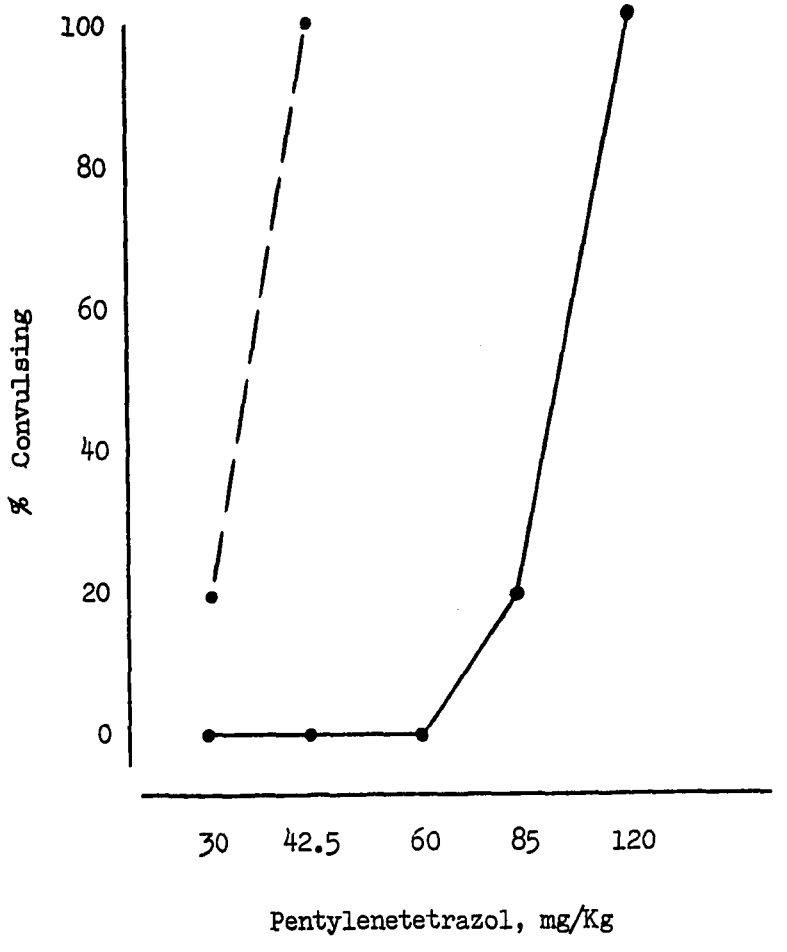

Fig. 12. Dose-Effect Relationships for Pentylenetetrazol-Induced Convulsions in Homer and Tumbler Pigeons. Homers are represented by the solid line; Tumblers by the broken line. Details presented in the text and in Table 22.

difference between these two drugs is that picrotoxin is about 40 times more potent in producing "tumbling".

4. Antagonism of Drug-induced "Tumbling". In the small number of animals tested, both trimethadione and pentobarbital antagonized drug-induced "tumbling". Figure 13 shows that both 10 mg/Kg pentobarbital and 125 mg/Kg trimethadione caused about a 2-fold shift to the right of the dose-effect curve for picrotoxin-induced "tumbling". Both antagonists seemed to afford some protection against all behavioral effects of picrotoxin, since vomiting, "tumbling", and death all required higher doses of picrotoxin than prior to administration of the antagonist. The progression of behavioral effects produced by picrotoxin was not changed by either antagonist, and all pigeons died after receiving a dose of picrotoxin that induced "tumbling".

Figure 14 shows that pentylenetetrazol-induced "tumbling" was also antagonized by pentobarbital. The evidence for antagonism by trimethadione is less convincing. As with picrotoxin, the progression and form of behavioral changes induced by pentylenetetrazol was not changed by either antagonist, but the dose required to produce these effects was increased.

c. Additional Drugs. Most of the drugs in this group were administered to only a few animals, but any drug that affected tumbling to a noticeable degree was investigated further. In general, drugs that decreased spontaneous motor activity, decreased tumbling, whereas those drugs that produced motor incoordination tended to increase the severity of tumbling. The most spectacular decreases in tumbling

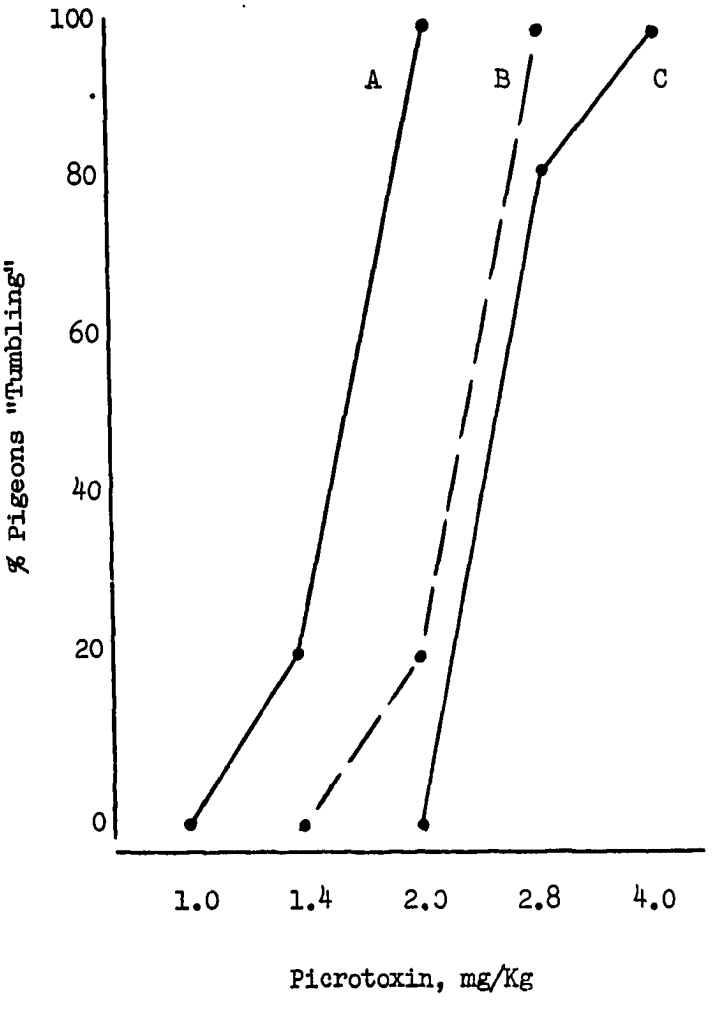

Fig. 13. Effects of Pentobarbital and Trimethadione on "Tumbling" Induced by Picrotoxin. (A) Picrotoxin alone, (B) Picrotoxin after i.p. injection of 10 mg/Kg pentobarbital, (C) Picrotoxin after i.p. injection of 125 mg/Kg trimethadione. All pigeons were standard-flying Racing Homers.

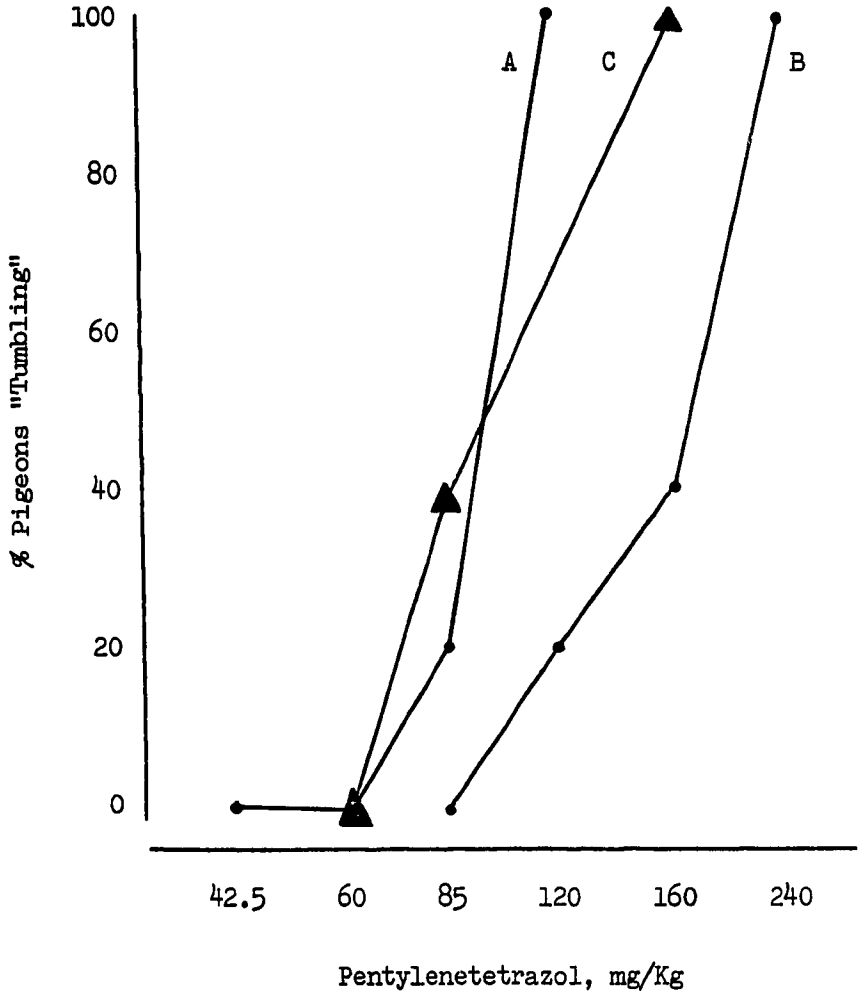

Fig. 14. Effects of Pentobarbital and Trimethadione on "Tumbling" Induced by Pentylenetetrazol. (A) Pentylenetetrazol alone, (B) Pentylenetetrazol after i.p. injection of 10 mg/Kg pentobarbital, (C) Pentylenetetrazol after i.p. injection of 125 mg/Kg trimethadione. All pigeons were standard-flying Hacing Homers.

occurred after injection of amitriptyline or apomorphine.

Meprobamate (5.2 or 10.4 mg/kg/day) administered orally for 18 days did not have a profound effect upon hereditary tumbling. By the 14th drug-day there was an obvious decrease in spontaneous motor activity, and the pigeons crouched close to the floor of the cage with their eyes closed most of the time. A similar decrease in spontaneous activity was observed within 10 minutes after injection of diazepam (150 or 300 μg/Kg). Prior to decreased motor activity, no change in tumbling was observed, but during periods of decreased activity it was more difficult to elicit tumbling. Tumbling was also slower and less violent than before drug injection.

Oral amitriptyline (0.36 or 0.72 mg/Kg/day) for 18 days decreased the ease of provocation and duration of tumbling, but no other effects upon motor behavior were evident. Intraperitoneal injections of 2.5-5.0 mg/Kg amitriptyline had an alerting influence upon Homer and Tumbler pigeons, and at no time was there any sign of drowsiness or decreased motor activity. In spite of the lack of decreased motor activity, the severity of tumbling was decreased after i.p. injection of amitriptyline.

Amphetamine (0.5 or 1.0 mg/Kg) had an alerting influence in Homer and Tumbler pigeons, but no changes in tumbling were observed. Parenteral injection of chlorpromazine (5-20 mg/Kg) increased the frequency of spontaneous tumbling at doses that produced motor incoordination. Propranolol, on the other hand, decreased spontaneous motor activity and decreased the ease of provocation of tumbling.

Apomorphine induced nearly continuous pecking activity in 5 of 5 Homer pigeons. This activity was first noted in two pigeons after 0.4 mg/Kg apomorphine, and was observed in all 5 pigeons after 1.6 mg/Kg. Two of the 5 Homers vomited after 0.2 mg/Kg, but three others did not vomit, even after 1.6 mg/Kg.

Apomorphine decreased the duration of tumbling in 6 of 10 Tumblers, but had no noticeable effect on motor behavior of 4 other Tumblers. The decrease in tumbling appeared to be dose-related in the six animals that showed improvement, and three of these animals could actually fly after the higher doses (1.6 and 3.2 mg/Kg) of apomorphine. Only two of the 10 Tumblers vomited after apomorphine, but 8 of the 10 exhibited the increased pecking behavior.

Oral levodopa caused no noticeable change in motor behavior of 2 Tumblers. Both of these pigeons were very active throughout the time that they received L-DOPA, and both seemed unusually aggressive. The only other effect observed was diarrhea, which was first noticed on the 7th day of L-DOPA administration.

Benztropine mesylate induced vomiting in 2 of 5 Homers and in 3 of 5 Tumblers. There were no noticeable changes in tumbling, but Homer and Tumbler pigeons appeared much more alert after benztropine. The alerting effect was expressed as increased motor activity, during which the pigeons seemed much more "investigative" than usual.

d. Decapitation. At the completion of the drug studies 14 Homer pigeons were sacrificed by decapitation. Four of these birds were placed gently on the floor after decapitation, and exhibited tremulous

movements of the limbs and body for the next several seconds. Five of the remaining pigeons were dropped from several feet above the floor after decapitation, and all of these animals somersaulted backwards for several seconds. The other five pigeons were placed on the floor after decapitation, but were then moved by lifting them from the floor by the wing tips. Four of these pigeons somersaulted backwards for several seconds after the wings had been passively extended.

4. Discussion. The most significant finding in this series of experiments is the apparent involvement of the CNS in both hereditary and induced "tumbling". The evidence for CNS involvement in induced "tumbling" is direct; that for hereditary tumbling is largely indirect.

The picrotoxin, pentylenetetrazol and decapitation experiments allow one to draw a number of conclusions regarding induced "tumbling". First, standard-flying (Homer) pigeons possess the neural and muscular components necessary for tumbling. Second, these elements are usually inhibited by some means, but result in "tumbling" under certain conditions. Third, "tumbling" after picrotoxin and pentylenetetrazol shows that abnormal brain function can result in "tumbling". Fourth, decapitation experiments show that the uninhibited spinal cord alone is sufficient for "tumbling". Fifth, the fact that decapitated pigeons "tumble" only after the wings are extended suggests that this form of "tumbling" is mediated by spinal reflexes.

Other drug experiments in Homer pigeons also support the possibility of a CNS basis for induced "tumbling". The convulsant actions of picrotoxin and pentylenetetrazol are supposedly limited to the brain, since

Table 13. Diphenylhydantoin in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
2 mg/Kg	1 injection, i.v.	3 Homers 5 Tumblers	None	None
4 mg/Kg	1 injection, i.v.	3 Homers 5 Tumblers	None	None
20 mg/Kg	1 injection, i/p.	3 Homers 5 Tumblers	None	One Homer and one Tumbler vomited.
40 mg/Kg	2 injections, i.p.	3 Homers 5 Tumblers	One Tumbler tumbled more slowly	Two Homers and 4 Tumblers vomited within 20 minutes after the 2nd injection. The pigeon that had decreased velocity of tumbling was lethargic.
80 mg/Kg	3 injections, i.p.	3 Homers 4 Tumblers	None	Three Homers and three Tumblers had writhing, side-side movements of the head within 15 minutes after the 3rd injection.

Table 14. DPH-Mephenytoin Combination in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
6 mg/Kg	DPH, orally, t.i.d., for 7 days			
plus				Day 5: all 4 pigeons were lethargic.
4.3 mg/Kg	Mephenytoin, orally, q.d., for 7 days			Day 9: 1 Homer and 1 Tumbler unusually defensive; both of these birds vomit within 30 minutes after ingestion of drug.
		2 Homers 2 Tumblers	None	
6 mg/Kg	DPH, orally, t.i.d., for 7 days			
plus				Day 11: all 4 birds are defensive; all vomit daily.
8.6 mg/Kg	Mephenytoin, orally, q.d., for 7 days			

Table 15. Phenobarbital in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
0.13 mg/Kg	b.i.d.,orally for 10 days	2 Homers 3 Tumblers	Day 7: decreased duration of tumbling and slower tumbling by one Tumbler	Day 7: decreased motor activity in the one Tumbler that is tumbling less.
0.26 mg/Kg	b.i.d.,orally for 10 days		Day 12: all 3 Tumblers tumble more slowly and for shorter distances	Day 12: all pigeons are lethargic; this is especially noticeable one to two hours after drug ingestion.

Table 16. Pentobarbital in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
5 mg/Kg	1 injection, i.p.	5 Homers 5 Tumblers	Increased severity of tumbling; increased ease of provocation and increased duration.	Homers stand quietly and appear lethargic. Tumblers are all incoordinated; walk with staggering gait; have opisthotonus at rest.
10 mg/Kg	2 injections, i.p.	5 Homers 5 Tumblers	Tumbling slowed and decreased in duration.	Homers are lethargic. Tumblers are now lethargic; stand in place with eyes closed.
20 mg/Kg	3 injections, i.p.	5 Homers 5 Tumblers	Very difficult to elicit tumbling; duration of tumbling decreased.	Homers and Tumblers asleep within 20 minutes after 3rd injection.
40 mg/Kg	4 injections, i.p.	5 Homers	-------	All 5 Homers asleep; 3 died within 20 minutes after 4th injection.
80 mg/Kg	5 injections, i.p.	2 Homers	-------	Both died within 15 minutes after 5th injection.

Table 17. Trimethadione in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
10 mg/Kg	t.i.d.,orally for 7 days	2 Homers 3 Tumblers	None	None
20 mg/Kg	t.i.d., orally for 7 days			
125 mg/Kg	1 injection, i.p.	2 Homers 5 Tumblers	Increased ease of provocation and duration of tumbling in one Tumbler	Homers: no change Tumblers: 4 unchanged; the one that has increased severity of tumbling has motor incoordination.
175 mg/Kg	2 injections, i.p.	2 Homers 5 Tumblers	Increased ease of provocation and duration of tumbling by all Tumblers	Homers: motor incoordination in one; other one is unchanged. All Tumblers are uncoordinated.
250 mg/Kg	3 injections, i.p.	2 Homers	--------	Motor incoordination in both Homers; walk with staggering gait; fly into stationary objects when forced to fly.

Table 18. Ethosuximide in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
20 mg/Kg	b.i.d.,orally for 7 days	1 Homer 3 Tumblers	Day 7: Increased ease of provocation and duration of tumbling	Day 3: all birds appear more alert than usual
40 mg/Kg	b.i.d.,orally for 7 days		Day 14: tumbling still more severe than before drug ingestion.	Day 7: Homer is very "nervous"; motor incoordination in Tumblers.
				Day 14: Motor incoordination in all 4 pigeons.
50 mg/Kg	1 injection, i.p.	2 Homers 3 Tumblers	None	None
100 mg/Kg	2 injections, i.p.	2 Homers 3 Tumblers	Tumbling more severe in all 3 Tumblers; ease of provocation and duration are both increased.	All pigeons have motor incoordination when walking; when standing in place all birds have peculiar "squatting" posture.
200 mg/Kg	3 injections, i.p.	2 Homers 3 Tumblers	Tumbling worse: increased ease of provocation is dramatic; spontaneous tumbling; duration increased.	Both Homers and Tumblers still have "squatting" posture; will not move unless forced.

Table 19. Phenacemide in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
7 mg/Kg	t.i.d.,orally for 5 days	1 Homer 2 Tumblers	Day 6: increased severity of tumbling; increased ease of provocation and increased duration of tumbling.	Day 6: Motor incoordination is evident in all three pigeons
14 mg/Kg	t.i.d.,orally for 5 days			
28 mg/Kg	t.i.d.,orally for 10 days		Day 11: increased severity of tumbling; increased duration and increased frequency of spontaneous tumbling.	Day 11: Motor incoordination in all three pigeons.

Table 20. Strychnine in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
0.5 mg/Kg	1 injection, i.p.	10 Homers 5 Tumblers	Duration of tumbling greatly decreased in 4 Tumblers.	Homers: no change Tumblers: four had tonic convulsions, during which tumbling did not occur. During these convulsions the legs were extended in abduction, the tail was in line with the body or vertically downward, and the wings were extended.
0.7 mg/Kg	2 injections, i.p.	10 Homers 1 Tumbler	Duration of tumbling greatly decreased; no tumbling during tonic convulsion.	One Homer had a tonic convulsion 10 minutes after the 2nd injection
1.0 mg/Kg	3 injections i.p.	9 Homers	---	Three Homers had tonic convulsion 10 minutes after 3rd injection.
1.4 mg/Kg	4 injections, i.p.	6 Homers	---	Four Homers had tonic convulsion 10 minutes after 4th injection.
2.0 mg/Kg	5 injections, i.p.	2 Homers	---	Both Homers had tonic convulsions 10 minutes after 5th injection.

Table 21. Picrotoxin in Pigeons.

Dose	Schedule, Route	No., Type of Pigeons	Effects on Tumbling	Other Effects
0.5 mg/Kg	1 injection, i.p.	10 Homers 5 Tumblers	Spontaneous tumbling by one Tumbler	Tumblers: all vomited; one tumbled spontaneously 20 minutes post-injection and died 25 minutes post-injection.
0.7 mg/Kg	1 injection, i.p.	15 Homers 4 Tumblers	All 4 Tumblers began tumbling spontaneously by 20 minutes post-injection.	Homers: 3 vomited 15 minutes post-injection; rapid, jerky head movements 25 minutes post-injection. Tumblers: all vomited; jerky head movements by 20 minutes post-injection; two died.
1.0 mg/Kg	2 injections, i.p.	15 Homers	------	Homers: 4 vomited; others lethargic.
1.4 mg/Kg	3 injections, i.p.	15 Homers	Three (20%) "tumbled."	All Homers vomited after 3rd injection; all had jerky head movements by 20 minutes after injection. Three that "tumbled" died.
2.0 mg/Kg	4 injections, i.p.	12 Homers	All "tumbled."	Nine of the 12 died.
4.0 mg/Kg	1 injection, i.p.	5 Homers	All "tumbled."	All died within 20 minutes after injection.

Table 22. Pentylenetetrazol in Pigeons.

Dose	Schedule, Route	No., Type of pigeons	Effects on Tumbling	Other Effects
30 mg/Kg	1 injection, i.p.	10 Homers, 5 Tumblers	Spontaneous tumbling by one Tumbler pigeon.	Homers: all vomited Tumblers: all vomited; one tumbled spontaneously then died.
42.5 mg/Kg	1 injection, i.p.	10 Homers, 4 Tumblers	Frequent spontaneous tumbling by all four Tumblers	Homers: all vomited; all had rapid, jerky head movements Tumblers: one died
60 mg/Kg	1 injection, i.p.	10 Homers	----------	All Homers vomited and had rapid, jerky head movements
85 mg/Kg	2 injections, i.p.	10 Homers	Two "tumbled"	Two Homers that "tumbled" died; other 8 vomited and had rapid, jerky head movements.
120 mg/Kg	3 injections, i.p.	8 Homers	All "tumbled" within 20 minutes after 3rd injection.	Six of the eight Homers died; the two that survived remained on their backs for about two hours before showing signs of recovery.

these agents do not produce convulsions in spinal chicks as they do in chicks with an intact CNS (Osuide, 1966). Pentobarbital, which is thought to depress neuronal activity in the mid-brain reticular formation (Sharpless, 1970), antagonized "tumbling" induced by picrotoxin and pentylenetetrazol, and trimethadione, which exerts anticonvulsant activity upon many parts of the CNS, but especially upon thalamic nuclei (Toman, 1970), antagonized picrotoxin-induced "tumbling". It has been shown previously that trimethadione antagonizes pentylenetetrazol-induced convulsions (Toman and Goodman, 1948). The failure of trimethadione to convincingly antagonize pentylenetetrazol-induced "tumbling" would seem to be related to too small a dose of the drug.

The other major convulsant drug of interest in Homer pigeons is strychnine. This drug produces tonic extension in most vertebrates, presumably by blocking post-synaptic inhibition within the CNS (Bradley, Easton and Eccles, 1953). Although this action is often attributed to the spinal cord alone, the brain also seems to be involved (Esplin and Esplin, 1970). The strychnine seizure pattern in Homer pigeons was similar to that induced by ACA, and provides further evidence that tumbling is not associated with tonic rigidity.

The unusually high sensitivity of Tumbler pigeons to the convulsant effects of picrotoxin, pentylenetetrazol and strychnine indicates that the CNS of these pigeons is abnormal. Whether this high sensitivity to convulsant drugs reflects increased excitatory activity, decreased inhibitory activity, or a combination of both is not clear.

The effects of anticonvulsant drugs upon hereditary and induced

"tumbling" indicates that hereditary tumbling is not a typical "epileptic" seizure. The major finding in this regard is that drug-induced "tumbling" is antagonized by classic anticonvulsant drugs and hereditary tumbling is not. The failure of anticonvulsant drugs to decrease the severity of hereditary tumbling was not totally unexpected due to the previous findings by Lange (1952). In fact, Lange's main conclusion that depression of the central nervous system decreases the severity of hereditary tumbling seems quite valid. This is supported by the finding in the present study that all drugs that decreased spontaneous motor activity also decreased the severity of hereditary tumbling. Unfortunately, the drugs that decreased the severity of tumbling have differences in mode of action, and, therefore, provide no specific information regarding the site of the abnormality in the CNS of Tumbler pigeons. As a whole, however, these findings provide an impressive amount of information in support of the CNS theory of hereditary tumbling.

CNS involvement in hereditary tumbling is further suggested by the increase in severity of tumbling by certain drugs. The common features of these drugs are: 1) a relatively high proportion of central to peripheral effects and; 2) production of motor incoordination at some dose. Motor incoordination alone is not sufficient to induce "tumbling" in standard-flying pigeons, but it definitely worsens hereditary tumbling. The relationship between motor incoordination and increased severity of tumbling is exemplified by the effects of low doses of pentobarbital. One possible explanation for this relationship is

the known EEG activation and overt excitement produced by sub-sedative doses of pentobarbital in man (Sharpless, 1970). Whether this explanation holds for pentobarbital, or for any other drug that increased the severity of tumbling, is not certain. One finding that does support this explanation is that all of these drugs increased spontaneous motor activity at doses that also increased the severity of tumbling.

The observation that the DPH-mephenytoin combination, d-amphetamine, L-DOPA, and benztropine did not affect hereditary tumbling is inconclusive. Since no consistent behavioral changes were noted after administration of these drugs, it is quite possible that the doses employed were too small.

Two drugs that merit special attention are amitriptyline and apomorphine. The main behavioral effect of both of these drugs was to decrease the severity of hereditary tumbling. The beneficial effect was not observed in all Tumbler pigeons, nor was the effect spectacular in all cases. Still, these were the most effective drugs for decreasing the severity of hereditary tumbling.

Amitriptyline is known to decrease spontaneous motor activity in some animals (Sulser and Brodie, 1961), but this effect was not observed in Homer or Tumbler pigeons. The mechanism of action of amitriptyline has not yet been determined, but it is probably similar to that of the chemically-related drug, imipramine, which alters the cholinergic-adrenergic balance within the CNS (Jarvik, 1970). Whether this action is responsible for the anti-tumbling effect of amitriptyline is unknown.

Apomorphine affects the CNS (Jaffe, 1970) and is known to decrease the signs of Parkinsonism in people (Cotzias et al., 1970; Schwab, Amador and Lettvin, 1951). The beneficial effects in Parkinsonism are attributed to a dopaminergic action, presumably upon the extrapyramidal system. This action might also apply to the anti-tumbling effect of apomorphine, but this possibility must be questioned on the basis that neither L-DOPA nor benztropine antagonized hereditary tumbling. It has been pointed out that the doses of these drugs may have been too low, so this problem is unresolved at present.

B. Neuroanatomical Studies

1. Introduction. This section describes anatomical studies of brains and spinal cords from Homer and Tumbler pigeons. There have been no previous studies of this type in Tumbler pigeons, but detailed descriptions and drawings of the central nervous system of normal pigeons (Karten and Dubbledam, 1973; Karten and Hodos, 1967) and chickens (Ariens Kappers, Huber and Crosby, 1960; Huber and Crosby, 1929; van Tienhoven and Juhasz, 1962) are available for comparison.

Neuroanatomical studies of a number of avian mutants have shown that good correlations between abnormal motor activity and lesions of the CNS do exist in some cases. As examples, gross cerebellar lesions have been described in chickens (Winterfield, 1953); Purkinje cell degeneration has been described in "shaker" (Scott et al., 1950) and "jittery" (Godfrey, Bohren and Jaap, 1953) chickens; an abnormality of the optic retina has been described in "clumsy" pigeons (Hollander, 1938); and marked reduction in size of the entire CNS has been described in "ataxic" pigeons (Hoshino, 1919; Koch and Riddle, 1918; Riddle and Hollander, 1943).

In other avian mutants with motor dysfunction no consistent neural lesions have been identified. Among these are: "congenital tremor" in chicks (Hutt and Child, 1934); "paroxysm" in chicks (Cole, 1961; Kuenzel and Rubenstein, 1974); "epileptiform seizures" in chickens (Crawford, 1970); "pirouette" in chickens (McGibbon, 1974); "con-

genital loco" in turkeys (Cole, 1957); "vibrator" in turkeys (Coleman et al., 1960); and "star-gazing" in quail (Savage and Collins, 1972).

Although no lesion has been identified in Tumbler pigeons, the effects of certain experimental lesions on the motor activity of normal pigeons have been studied. The thin layer of cerebral cortex in birds is virtually unresponsive to electrical stimulation (Rogers, 1922 a) and decerebration results in no locomotor disturbances other than difficulty in feeding (Langworthy, 1926; Martin and Rich, 1918; Rogers, 1922 b). Removal or ablation of one or both cerebral hemispheres, which in pigeons are composed mainly of the corpus striatum (Hunter, 1924; Langworthy, 1926; Rogers, 1922 a, 1922 b), causes slight increase in flexor muscle tone at rest, but these pigeons can walk and fly normally (Hunter, 1924; Langworthy, 1926). Ablation of the thalamus results in further increase in flexor muscle tone and forced flying motions but these are diminished if a cut is then made below the midbrain (Langworthy, 1926). Electrical stimulation of the cerebelli of chickens and pigeons results in tilting forward of the body, lowering of the tail, and head-turning, but no evidence of somersaulting in any plane (Raymond, 1958).

Experimental procedures that produce backward movements in birds usually involve rather specific areas of the cerebellum, archistriatum, or paleostriatum. Lesions in the medial cerebellar nuclei, in the commissura connecting these two nuclei, or in the paleostriatum (n. basalis, n. entopeduncularis in chickens; Kuhlenbeck, 1938) cause a

rearing backwards and sometimes somersaulting in pigeons (Muskens, 1929, 1930). Lesions in various areas of the cerebellum after bilateral labyrinthectomy are also reported to result in backward somersaulting in pigeons (Muskens, 1930). Similar behavior in chickens sometimes results from electrical stimulation of the nucleus intercalatus (zona incerta in mammals) or nucleus entopeduncularis (Putkonen, 1967).

2. Methods. Parlor Tumbler and Racing Homer pigeons weighing 0.3-0.5 Kg were anesthetized with 40-80 mg/Kg sodium pentobarbital (Nembutal, Abbott) or 2.5 cc/Kg Equithesin (Jensen-Salsbery). Each pigeon was then placed on its back, the feathers on the ventral surface moistened with 70% alcohol, and a transverse incision made through the abdominal wall immediately posterior to the apex of the sternum. The sternum was lifted to expose the heart, a 20 gauge needle was inserted into the left ventricle, and the vena cava cut close to the right atrium. The pigeon was perfused with 0.9% sodium chloride solution for 1-2 minutes, followed by 10% buffered formalin until vital organs showed signs of clearing.

Since the majority of perfusions were incomplete, as evidenced by the presence of blood in close proximity to the CNS after perfusion, the bone was quickly dissected from around the brain and spinal cord. Each intact CNS was then further fixed in 10% buffered formalin for 14-30 days.

At the end of the fixation period, each CNS preparation was examined in one of three ways. In one group, the intact CNS of five

Homer and five Tumbler pigeons was examined by unaided vision. The general size and shape of the forebrain, optic lobes, cerebellum, and spinal cord were compared in an attempt to demonstrate gross differences between the CNS of Homer and Tumbler pigeons. In the second group brains from two Homer and two Tumbler pigeons were sliced transversely into 6-8 gross sections, each of which was about 20 mm thick. All sections were then stained to allow differentiation of the grey and white matters (Barnard, Roberts and Brown, 1949), examined by light microscopy, and photographed. The third group consisted of brains and spinal cords from four Homer and six Tumbler pigeons. Each brain was sliced in half transversely, and a 1 cm length removed from each of the following areas of the spinal cord: upper cervical, cervical enlargement, and rhomboid sinus. These 5 pieces of tissue from each pigeon were dehydrated in a graded series of ethyl alcohol solutions, cleared in cedarwood oil, and embedded in Paraplast. Serial sections 8-10 μm thick were then made through each tissue block with a rotary microtome. At intervals of 15-20 sections, four consecutive tissue sections were removed from the ribbon of tissue and placed on a glass microslide. Tissue sections were fixed to the slide with a solution of Mayer's egg albumin (7 drops) in distilled water (15 cc) and air-dried for 5-10 days. A set of 12-16 slides from each pigeon was then stained with hematoxylin and eosin, or Holme's silver, or luxol fast blue-cresyl violet, and examined by light microscopy.

3. Results. Examination of brains and spinal cords revealed no differences between cytoarchitecture of Homer and Tumbler pigeons.

Figure 15 shows that the brains of Homer and Tumbler pigeons are similar in shape by gross section. In general the CNS of Tumbler pigeons was somewhat smaller than that of Homer pigeons, but no attempt was made to quantify this difference on the basis of size or weight. In spite of the difference in size of the Homer and Tumbler CNS, the normal size relationships between various areas of the CNS were evident in Tumbler pigeons.

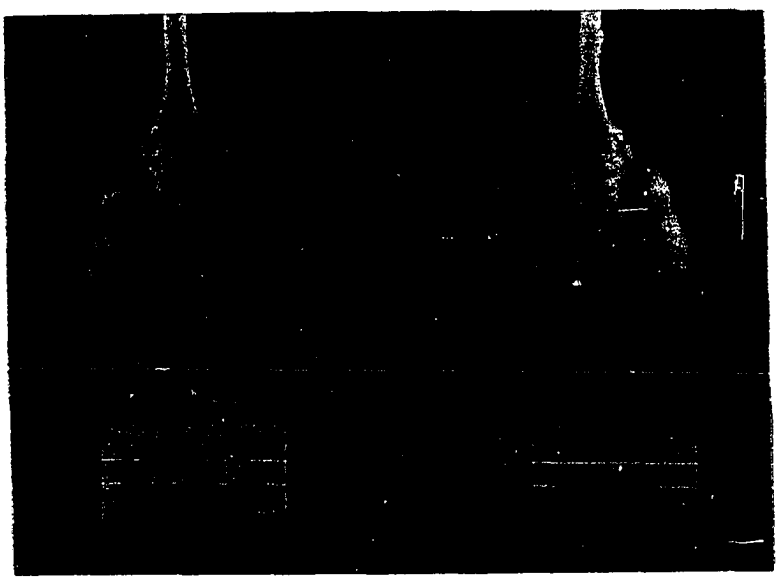

Fig. 15. Gross Brains of Homer and Tumbler Pigeons. Homer brain is on the left; Tumbler brain on the right. Magnification, 1.2 X.

Specific nuclear groups and nerve tracts in the forebrain were not identified. The most that was gained from examination of the forebrain was that the shape was similar in Homer and Tumbler pigeons. Figure 16

is a photograph of a gross section through the forebrain and optic lobes. The optic lobes stained well, but no differences between Homer and Tumbler pigeons could be detected by gross inspection or light microscopy.

Fig. 16. Photograph of Gross Section through the Forebrain and Optic Lobes of Homer and Tumbler Pigeons. Homer brain is on the left; Tumbler brain on the right. Magnification, 2.8 X.

The area examined in most detail was the cerebellum, but no differences between cerebelli of Homer and Tumbler pigeons could be detected by gross inspection or light microscopy. The lamination of the

cerebellar cortex was examined closely, and the molecular and granular layers were easily recognized. Special attention was paid to the appearance of the Purkinje cell layer, and Figure 17 shows that normally appearing Purkinje cells are present in the cerebellar cortex of Tumbler pigeons. The deep cerebellar nuclei were also examined in detail, but again no differences were observed between cytoarchitecture of Homer and Tumbler pigeons. Figure 18 shows gross sections through the cerebellar nuclei of Homer and Tumbler pigeons, and Figure 19 is a

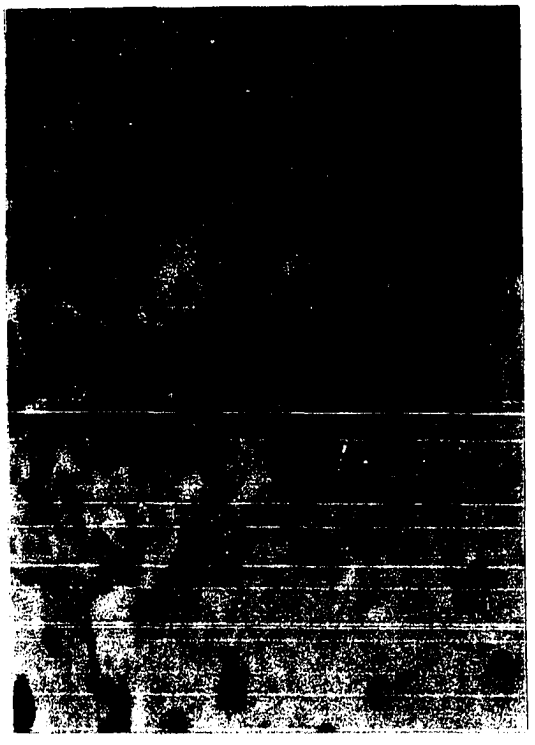

Fig. 17. Photograph through Purkinje Cell Layer of Tumbler Pigeon Cerebellum. Magnification, 500 X.

higher magnification of medial and lateral cerebellar nuclei of a Tumbler pigeon.

The three areas of the spinal cord examined were also similar in Homer and Tumbler pigeons. An attempt was made to count cell types, but the same nuclear groups and nerve tracts could be seen in sections from Homer and Tumbler pigeons.

Fig. 18. Photograph of Gross Sections through the Deep Cerebellar Nuclei of Homer and Tumbler Pigeons. Homer section is on the left side; Tumbler section is on the right. M = middle cerebellar nuclei; L = lateral cerebellar nuclei. Magnification, 4 X.

Fig. 19. Higher Magnification View through Medial and Lateral Cerebellar Nuclei of a Tumbler Pigeon. M=medial cerebellar nucleus; L = lateral cerebellar nucleus. Magnification, 40 X.

4. Discussion. The main conclusion from the morphological studies is that the CNS of Tumbler pigeons is not grossly abnormal. It is possible that at some higher level of resolution one could demonstrate some difference between the CNS of control and Tumbler pigeons, but the significance of such minor differences would be difficult to in-

terpret. The smaller size of the Tumbler pigeon CNS may simply be related to the generally smaller body size of Tumblers compared to Racing Homers.

The normal appearance of all areas examined supports the possibility that hereditary tumbling is related to a biochemical abnormality of the CNS. Morphological studies of Tumbler pigeons have to this point included the inner ear (Entrikin, 1971; Entrikin and Erway, 1972; Mowrer, 1940), skeletal muscle (Entrikin and Bryant, in press), brain and spinal cord, but no consistent abnormality has been observed.

The normal cytoarchitecture of the cerebellum in Tumbler pigeons has special significance since it has been demonstrated that certain experimental lesions of the cerebellum cause backward somersaulting in normal pigeons (Muskens, 1929, 1930).

It seems advisable that future studies of the CNS of Tumbler pigeons should employ more specific techniques. If tumbling is in fact due to a biochemical abnormality, histochemical methods might allow one to determine quite precisely the area(s) responsible for tumbling. From the earlier ablation studies in normal pigeons (Hunter, 1924; Muskens, 1929, 1930; Langworthy, 1926; Rogers, 1922 a, 1922 b), the midbrain would seem the most appropriate area upon which to concentrate such efforts.

V. GENERAL DISCUSSION

This section takes into account the significant findings of the preceding sections and proposes a hypothetical scheme to explain the physiological basis of the tumbling phenomenon. The major findings are summarized by section, and then discussed in relation to generally accepted concepts of neural physiology and pharmacology.

Section II, Description of Tumbling, shows that within milliseconds after a Tumbler pigeon is released from a height, an acute angle is formed between the body and tail of the pigeon.

Section III A, Isolated Biventer Cervicis Muscles, shows that these muscles are hypertrophied in Tumbler pigeons, but that they are not electrically abnormal (as in myotonia congenita) or abnormally sensitive to acetylcholine (as in denervation).

Section III B, In Vivo Administration of Drugs Known to Affect Skeletal Muscle Function, shows that drugs that decrease activity of skeletal muscle or peripheral nerve do not alter tumbling unless such high doses are used that there are also signs of CNS involvement. The myotonia-inducing agent, ACA, produces tonic rigidity in Homer and Tumbler pigeons. This rigidity greatly decreases the duration of tumbling and makes it impossible for Homer pigeons to fly of their own accord.

Section IV A, Central Nervous System Drug Experiments, shows that anticonvulsant drugs antagonize "tumbling" induced by picrotoxin or pentylenetetrazol, but do not antagonize the hereditary form of tumbling. Anticonvulsants and a group of drugs with diverse actions do

decrease the severity of hereditary tumbling, but only at doses that also decrease spontaneous motor activity. Drugs that produce motor incoordination will not induce "tumbling" in control pigeons, but will increase the severity of hereditary tumbling. Apomorphine and amitriptyline decrease the severity of hereditary tumbling at doses that do not affect other aspects of motor behavior. Decapitation causes control pigeons to "tumble", but extension of the wings must occur to initiate this form of "tumbling".

Section IV B, Neuroanatomical Studies, shows that no differences between control and Tumbler pigeons have been found in the gross appearance of the CNS or in the appearance of serial sections through the spinal cord, cerebellum, and optic tectum upon examination by light microscopy.

The first consideration in a model for the tumbling phenomenon is the initiation of tumbling. Extension of the wings is the first perceptible movement during "tail-sitting" in young Tumbler pigeons (p. 10), and in adult Parlor Tumbler pigeons that are released from a height. Decapitated control pigeons also do not "tumble" unless their wings are passively extended. These observations, and the simple fact that decapitated pigeons do "tumble", indicate that tumbling is a reflex movement initiated by extension of the wings and mediated by the spinal cord.

In adult Parlor Tumbler pigeons extension of the wings is followed by formation of an acute angle between the body and the tail. This movement also appears to occur in young Tumbler pigeons during "tail-

sitting", and during induced "tumbling". It has been shown that drugs such as ACA and strychnine, which prevent formation of the acute angle between the body and the tail, antagonize hereditary tumbling. It has not been determined whether elevation of the tail is the only movement responsible for formation of the angle between the body and the tail, and the possibility still exists that muscles of the back and neck may also be involved in this movement.

Whatever the muscles involved in tumbling, it is clear that they do not play a prominent role in normal motor activity of control pigeons under usual circumstances. This indicates that these muscles are somehow prevented from contracting, and suggests that removal of these inhibitory influences might cause control pigeons to "tumble". This seems to be the case in "tumbling" induced by picrotoxin, pentylenetetrazol, and decapitation. That convulsant actions of picrotoxin and pentylenetrazol are confined primarily to the brain, and that these actions are antagonized by classic anticonvulsant drugs, suggests that descending inhibitory influences are disturbed in drug-induced "tumbling". "Tumbling" after decapitation is further evidence that disturbances of higher influences upon the spinal cord can cause "tumbling". The main evidence that such a disturbance is involved in hereditary tumbling is the occurrence of spontaneous tumbling episodes in Tumbler pigeons after injections of picrotoxin or pentylenetetrazol.

As reported by Lange (1952), and verified by the present investigation, anticonvulsant drugs do not specifically antagonize hereditary tumbling. These drugs, as well as a number of drugs with diverse sites

and mechanisms of action, decrease the severity of hereditary tumbling, but only at doses that greatly decrease spontaneous motor activity. The common feature of these drugs is their ability to cause depression of the central nervous system.

A complete model of tumbling must account for a number of additional observations. Among these are: decreases in severity of hereditary tumbling by amitriptyline and apomorphine; "fatigue" of hereditary tumbling during forced, repeated tumbling; and the ability of Tumbler pigeons to exercise their wings without tumbling.

The decrease in severity of hereditary tumbling by amitriptyline suggests involvement of some neurotransmitter in tumbling. Amitriptyline has two main actions that could conceivably be related to its anti-tumbling effect: 1) it decreases reuptake of norepinephrine by nerve terminals (Glowinski and Axelrod, 1965) and; 2) it has anticholinergic properties (Hollister, 1972).

The current interest in the role of the so-called cholinergic-adrenergic balance within the CNS stems from the impressive evidence that a disturbance in this balance is the basis for the clinical signs of Parkinson's disease. Dopamine (Hornykiewicz, 1973; Yahr and Duvoisin, 1972) and acetylcholine (Duvoisin, 1967) are of most interest in this regard, but serotonin and norepinephrine have also been implicated (Munkvad et al., 1968).

Dopamine, norepinephrine, and serotonin have depressant effects when injected into chicks prior to development of the blood-brain barrier, and when injected directly into the cerebral ventricles of the adult

chicken (Bolton, 1971). It would appear that amitriptyline, as well as apomorphine, which stimulates central dopaminergic receptors and relieves signs of Parkinsonism in people (Anden et al., 1967; Cotzias et al., 1970; Cotzias et al., 1972; Schwab et al., 1951), might exert anti-tumbling effects by increasing the inhibitory influences of one or more of these biogenic amines. The place of amitriptyline and apomorphine in the proposed model of tumbling would then be to increase the inhibitory influence of the brain upon the spinal cord.

Reduction in the duration of tumbling during episodes of forced, repeated tumbling suggests fatigue of some system. It is difficult to imagine how an inhibitory substance would be produced by repeated tumbling, but it does seem reasonable that an excitatory substance could be depleted during repeated activity. Table 23 lists putative neurotransmitters that have been identified in the avian brain, their areas of distribution, and whether these substances have mainly excitatory or inhibitory effects upon motor behavior.

This Table shows that acetylcholine is the only endogenous excitatory substance thus far detected in the avian brain. Within the framework of the proposed model, the effects of acetylcholine, or some as yet unidentified excitatory substance, would have to be diminished during repeated tumbling episodes.

The only readily apparent explanation for the fact that some Tumbler pigeons can exercise their wings without tumbling is to suggest a similarity to the tremor of Parkinsonism. This type of tremor is considered the opposite of the so-called intention tremor that accompanies

Table 23. Putative Neurotransmitters in the Avian CNS

SUBSTANCE	DISTRIBUTION	PRIMARY ACTION
Norepinephrine	hypothalamus (Juori and Vogt, 1967) cerebellum (Pscheidt and Himwich, 1963)	Depressant (Dewhurst and Marley, 1965; Spooner and Winters, 1965, 1967)
Epinephrine	hypothalamus (Juorio and Vogt, 1967)	Depressant (Dewhurst and Marley, 1965)
Dopamine	n. basalis and striatal axons arising from the mesencephalon (Aprison and Takahashi, 1965; Bolton, 1971; Bowman and Osuide, 1967; Juorio and Vogt, 1967)	Depressant (Dewhurst and Marley, 1965)
Tyramine	spinal cord (Bowman et al., 1964)	Depressant (Dewhurst and Marley, 1965)
5-hydroxytryptamine	highest: n. basalis (Juorio and Vogt, 1967) lowest: cerebellum (Juorio and Vogt, 1967; Pscheidt and Himwich, 1963)	Depressant (Hehman et al., 1961; Spooner and Winters, 1965, 1967)
Gamma-aminobutyric acid	optic lobes and cerebral hemispheres (Bolton, 1971)	Depressant(Kramer and Seifter, 1966; Scholes, 1965)
Acetylcholine	highest: optic lobes and diencephalon lowest: cerebellum (Aprison and Takahashi, 1965)	Stimulant (Kramer and Seifter, 1966)

cerebellar lesions, and has been found to be somewhat diminished during voluntary activity. This is not to say that tumbling is a model for Parkinsonism, but only that one aspect of tumbling might be related in a mechanistic sense to one aspect of Parkinsonism. The main factor that appears to allow Tumbler pigeons to exercise their wings without tumbling is the relatively slow velocity of the controlled wing-beating. The "reflex" extension of the wings that occurs when a Tumbler pigeon is released from a height occurs very rapidly, and is possibly accompanied by an excess flow of excitatory impulses that the pigeon cannot inhibit voluntarily.

Figure 20 illustrates the proposed model for hereditary (left-hand side) and induced (right-hand side) tumbling based on the foregoing findings and discussion. For the most part the model is self-explanatory. A positive sign (+) indicates an agent or procedure that increases the severity of hereditary tumbling or induces "tumbling" in control pigeons.

The essential point in the model is the fact that both hereditary and induced tumbling can be modified by drugs or procedures that alter descending impulses to the spinal cord. The fact that no neuroanatomical lesions have been demonstrated in Tumbler pigeons, and the fact that drugs can alter the severity of this condition, support the possibility that tumbling is associated with abnormal chemical transmission within the brain. It appears that induced "tumbling" is caused by decreased descending inhibitory impulses. This is supported by the facts that: 1) excess spinal cord activity after cord transection is generally

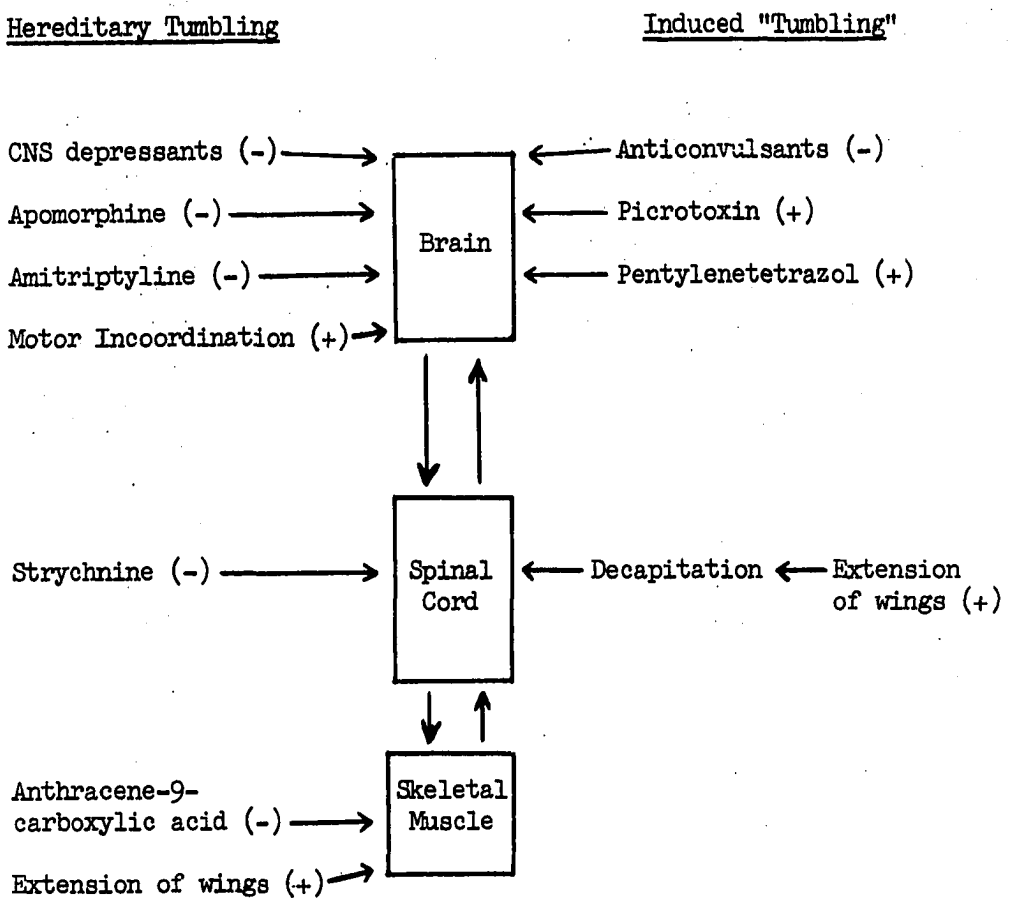

Fig. 20. Hypothetical Scheme to Account for Observations of Hereditary and Induced "Tumbling" in Pigeons. Positive (+) sign indicates agent or procedure that increases severity of hereditary tumbling or induces "tumbling" in control pigeons. Negative (-) sign indicates agent or procedure that decreases the severity of hereditary tumbling or that prevents induced "tumbling.

attributed to removal of the inhibitory influence of the midbrain reticular formation (Gatz, 1970); 2) picrotoxin is thought to antagonize the inhibitory neurotransmitter, gamma-aminobutyric acid (Esplin and Esplin, 1970) and; 3) the severity of pentylenetetrazol-induced convulsions has recently been shown to correlate well with the degree to which pentylenetetrazol decreases brain serotonin levels (Diaz, 1974).

It is not possible to state with certainty whether hereditary tumbling is related to excess excitatory influences, inadequate inhibitory influences, or a combination of both. The abnormally high sensitivity of Tumbler pigeons to the convulsant actions of picrotoxin and pentylenetetrazol shows that reduction of central inhibition causes spontaneous tumbling. If the level of inhibition were already reduced to an appreciable degree, one would not expect further decreases to result in such a profound alteration of behavior as seen after convulsant drugs. This indicates that there is excess excitatory activity in the brains of Tumbler pigeons, and could help to explain the "fatigue" of tumbling observed during episodes of forced, repeated tumbling.

Whatever the precise neurochemical abnormality in the CNS of Tumbler pigeons, these pigeons have great potential as models for the study of human neurological diseases. Their use in research should be of special interest to those persons interested in the interactions among drugs, endogenous neurochemicals, and behavior.

VI. SUMMARY

1. The hereditary trait of backward somersaulting in Tumbler pigeons was examined by a variety of methods.

2. High-speed cinematography (2000 frames per second) revealed that in addition to the actual tumbling motions the only abnormal movement in Tumbler pigeons after release from a height of 0.3 m was formation of an acute angle between the body and tail within 15 ms after release.

3. Biventer cervicis muscle fibers from Tumbler pigeons were larger than fibers from control pigeons of similar size and weight.

4. Cable properties and excitability characteristics of Tumbler pigeon biventer cervicis muscle fibers showed that the fibers were not myotonic. In general differences in electrical properties of the muscle fibers were as great between two strains of control pigeons as they were between either control strain and Tumbler pigeons.

5. Isolated biventer cervicis muscles of Tumbler pigeons were not abnormally sensitive to acetylcholine, but they did maintain tension to acetylcholine longer than did control muscles.

6. Procainamide, d-tubocurarine and dantrolene sodium were administered in an attempt to decrease the severity of tumbling by alteration of function of peripheral nerve and skeletal muscle. None

of these drugs greatly modified tumbling. At high doses procainamide and dantrolene produced signs of CNS depression and weakness, as well as slight decreases in the severity of tumbling

7. Having found no peripheral abnormality to account for tumbling, the CNS of Tumbler pigeons was then studied by means of drugs with prominent CNS effects and by neuroanatomical techniques.

8. Gross inspection and light microscopic examination revealed no differences in cytoarchitecture between brains and spinal cords of control and Tumbler pigeons. The cerebellum was examined in most detail; the forebrain in least detail.

9. A number of drugs, including the anticonvulsants diphenylhydantoin and phenobarbital, slightly decreased the severity of tumbling, but only at doses that also caused CNS depression. In general any drug that produced signs of CNS depression caused slight decrease in the severity of tumbling.

10. Drugs that produced motor incoordination, including the anticonvulsants trimethadione and ethosuximide, tended to increase the severity of tumbling.

11. Pentobarbital increased the severity of tumbling at low doses that were accompanied by motor incoordination, but decreased the severity of tumbling at high doses that produced signs of CNS depression.

12. Picrotoxin and pentylenetetrazol induced "tumbling" in control pigeons, and produced spontaneous tumbling in Tumbler pigeons. The drug-induced "tumbling" in control pigeons was antagonized by trimethadione and pentobarbital. Tumbler pigeons were more sensitive to the convulsant actions of picrotoxin and pentylenetetrazol than were control pigeons.

13. Strychnine and anthracene-9-carboxylic acid produced muscular rigidity in control and Tumbler pigeons. During periods of rigidity Tumbler pigeons could not tumble.

14. Hereditary tumbling was decreased by amitriptyline, apomorphine, and forced, repeated tumbling. These findings suggest involvement of some central neurotransmitter in tumbling.

15. Extension of the wings is the first discernible movement prior to tumbling, and is necessary to initiate "tumbling" in a decapitated control pigeons. This suggests that tumbling is a reflex mediated by the spinal cord.

16. It is proposed that hereditary tumbling is associated with a biochemical abnormality of the central nervous system.

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