OBSERVATIONS ON THE ELICITATION OF SECONDARY AND INVERTED PRIMARY NYSTAGMUS FROM THE CAT BY UNILATERAL CALORIC IRRIGATION

WILLIAM E. COLLINS, Ph.D

Sensory Psychology Section
Psychology Branch

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FEDERAL AVIATION AGENCY
AVIATION MEDICAL SERVICE
AEROMEDICAL RESEARCH DIVISION
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OBSERVATIONS ON THE ELICITATION OF SECONDARY AND INVERTED PRIMARY NYSTAGMUS FROM THE CAT BY UNILATERAL CALORIC IRRIGATION[1]

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ABSTRACT

Vestibular stimulation by repeated unilateral caloric irrigation of cats occasioned the appearance of secondary, tertiary, and inverted primary nystagmus in some animals. These inverse responses were recorded with stimulus temperatures of 5, 23.5, and 53.5 C, applied for durations ranging from 15-35 seconds. The inverse reaction most frequently obtained was the secondary nystagmus. Several possible explanations for the occurrence of the phenomena were examined. The findings appear related to "habituation" of the vestibular system, and thus have implications for vestibular adaptation in clinical situations and during air-vehicle maneuvers.

Secondary nystagmus occurs after, and is in an opposed direction to, a primary response to a vestibular stimulus. It appears in the absence of a change in vestibular stimulation, when the primary has begun to decline. The secondary is a commonly observed response to rotatory stimuli both in humans (1,2) and animals (3,4). Under conditions of caloric irrigation, Aschan and Bergstedt (5) have stated that a secondary appears in man only when both ears are simultaneously stimulated with warm water to one, and cold to the other, although unusually prolonged unilateral calorizations (20 min or more) have sometimes produced a weak, short-duration secondary nystagmus (6). More recently, Fluur and Mendel (7,8) have reported the occurrence of a secondary as a result of repeated unilateral stimulation under ordinary clinical conditions. Little information is available concerning such findings in animals (9).[2]

Kobrak (10) and Grahe (11) noted the appearance of an unusual response in normal humans – a reversed initial nystagmus (i.e., a primary response in which the direction of the fast and slow phases was reversed)—which was elicited with very minimal cold caloric stimulation. Thornval (12) reported a single similar occurrence under different stimulus conditions. Fischer (13), using "pulsion reflexes" as a measure and employing "double irrigations", related reversals of primary nystagmus in humans to repeated stimulation. Such inverted primary responses are almost never seen during rotation.[3]

In caloric studies of rabbits, Riskaer and Permin (9) observed various combinations of primary, reversed primary, and secondary nystagmus, although a marked inverse reaction could be demonstrated only with water of 15 C or less. Kristensen (14), however, using 10 rabbits and mild stimulation, reported that "within various categories of head positions the reactions are uniform from one animal to another", and "nystagmus was always reversed when the nose of the animal was lowered by 15-20° in relation to the normal position."

Riskaer and Permin (9) subsumed all forms of inverse response to cold calorizations, includ-

[1] Data collected at U. S. Army Medical Research Laboratory, Fort Knox, Kentucky. The technical assistance of Stanton Warburton, III, and Kenneth E. Swain is gratefully acknowledged.

[2] Dr. Joseph Meek (U. S. N. School of Aviation Medicine, Pensacola, Florida) has observed a secondary nystagmus in squirrel monkeys as a result of ice-water caloric stimulation (personal communication). In addition, recent experiments in this laboratory with a Western Ewe have indicated that a secondary reaction may be elicited by both cool (30 C) and warm (45 C) stimulation.

[3] Dr. F. E. Guedry (U. S. N. School of Aviation Medicine, Pensacola, Florida) has observed this unusual reaction in one human subject after repeated exposure to prolonged, constant, angular acceleration (personal communication).

Table 1

Outline of Caloric Conditions Employed

Cat	*Restraint Method*	*Stimulated Ear*	*Stimulus Condition*	*Recording Condition*	*Temp. (°C)*	*Duration (sec.)*	*Inter-trial Rest (min.)*	*Previous Stimulation*
A	Wire	Right	Dark	Dark	5.0	15	6-8	Rotation
P	Cast	Right	Dark	Dark	5.0	15	10-12	Rotation
Z	Wire	Left	Light	Dark	5.0	35	6-8	Rotation
W	Wire	Right	Dark	Dark	23.5	30	10-12	None
W	Wire	Right	Dark	Dark	5.0	15	10-12	Caloric (4 weeks prior)
S	Wire	Left	Dark	Dark	53.5	30	10-12	Right-Ear Caloric

ing the secondary, under the term "homolateral." More recently (15), this term was restricted, for descriptive purposes, to an anomalous initial nystagmus (reversed fast and slow phases) obtained under conditions of cold caloric irrigation. "Inverted primary nystagmus" is probably an equally descriptive term for this latter phenomenon, and one with more general applications.

The observations presented here were obtained from 5 cats selected from a larger group which had been used in a series of pilot studies. The stimulus situation and the number of trials differed in each of the preliminary studies and only these 5 animals demonstrated prominent inverse responses.

Methods

Recording Apparatus

An Offner Type-T Electroencephalograph, located in an adjoining room, was used to record horizontal eye movements. Leads from needle electrodes inserted into the skin at the outer canthus of each eye and on the crown at the mid-line of the skull were plugged into a patch-panel. Changes in potential were transmitted through slip-rings to the recorder. A 1.4 sec RC time constant was employed in amplification.

Restraint

With one animal (Cat P), a casting technique was used (16). Briefly, a plaster cast was fitted for the cat and was bisected lengthwise to provide 2 shells into which the animal could be placed. The method used with Cats A, Z, W, and S was similar to that reported by Henriksson, Fernandez, and Kohut (17). Several days prior to testing, cats were anesthetized and a tiny hole was drilled transversely through each of their canine teeth. For testing, the cat was wrapped snugly in a towel, placed in a restraint box, and a strand of piano wire was inserted through the holes in the teeth. The wire was tightened by means of a device attached to the front of the box, fixing the animal's head in a position elevated slightly from that of normal carriage.

Procedure

Data obtained from 5 animals are presented here. Three of these, cats A, P, and Z had received previous rotatory tests (12-15 rotations, 2-3 weeks earlier). For cats P, A, W, and S stimulation was applied in total darkness; for Cat Z, the room was illuminated during irrigation. For all animals, the room was in total darkness for the several minutes of recording immediately after cessation of stimulation and rest periods were in full-room illumination. A procedural outline appears in Table 1.

Results

Cat A

Cat A, tested in total darkness, received 50 trials and in no case exhibited inverted primary nystagmus. However, she demonstrated an occasional clear secondary reaction (see Fig. 1, trials 17 and 19).

Cat P

Cat P received stimuli of the same temperature and duration as Cat A and demonstrated an appropriate response with a strong secondary during the first 4 trials. On the fifth trial, a particularly vigorous secondary appeared. In trials 10-15, 17, 19, and 20, inverted primary responses were obtained. In addition, during these two latter trials, a secondary (which was in the appropriate direction for the primary) began to evidence itself (see Fig. 2).

Four days later, Cat P was re-tested under the same schedule and demonstrated the same type of reversals. During the first 6 trials, an appropriate and brisk response was elicited. Trials 7 and 8 yielded an appropriate reaction with a vigorous secondary. Trials 9, 10, 11, 16, and 18 showed an inverted primary response of long duration and high magnitude. A series of trials was then conducted with inter-trial rest intervals reduced to 4 min. Inverse primary reactions did not reappear.

Cat Z

Cat Z was the only animal tested in the left ear and stimulated in full-room illumination.

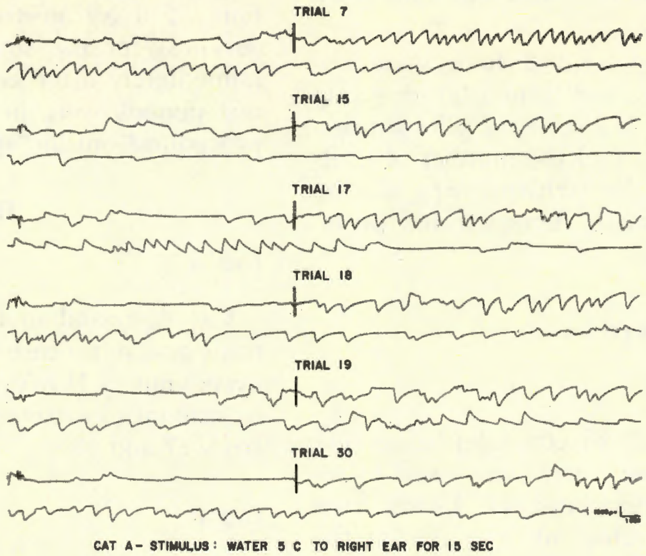

FIGURE 1. Nystagmus tracings obtained in total darkness from Cat A. Upward pen deflections indicate eye movements to the right; downward deflections, to the left. Each record begins with the onset of the stimulus. Vertical bars indicate termination of stimulation. In all cases, the primary response is in the appropriate direction (fast-phase left). Note changes in slow-phase slope with repeated testing, the brisk secondary nystagmus on Trial 17, and differences in the time of appearance of the secondary on later trials.

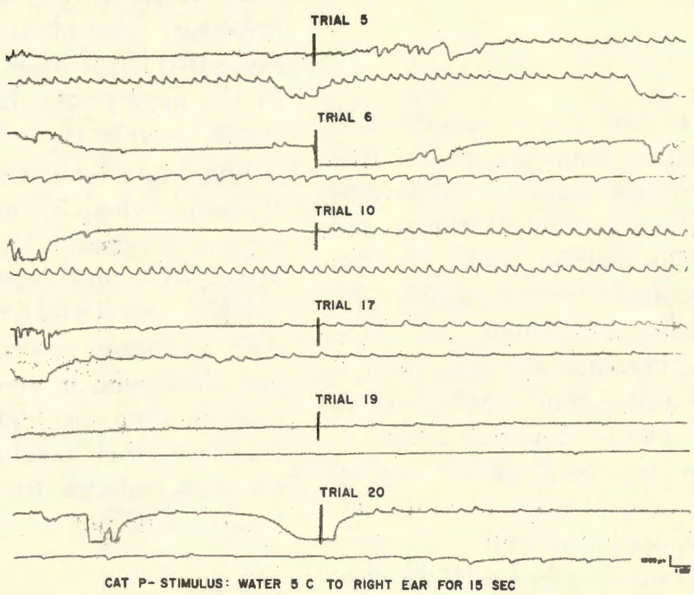

FIGURE 2. Nystagmus tracings from Cat P. Test procedure and figure markings are the same as for Cat A. An appropriate response was obtained during the first four trials. Note the early appearanrce of a vigorous secondary in Trial 5, the clear inverted primary response in the last 4 depicted trials, and on Trial 20, the brisk secondary in the direction expected for the primary.

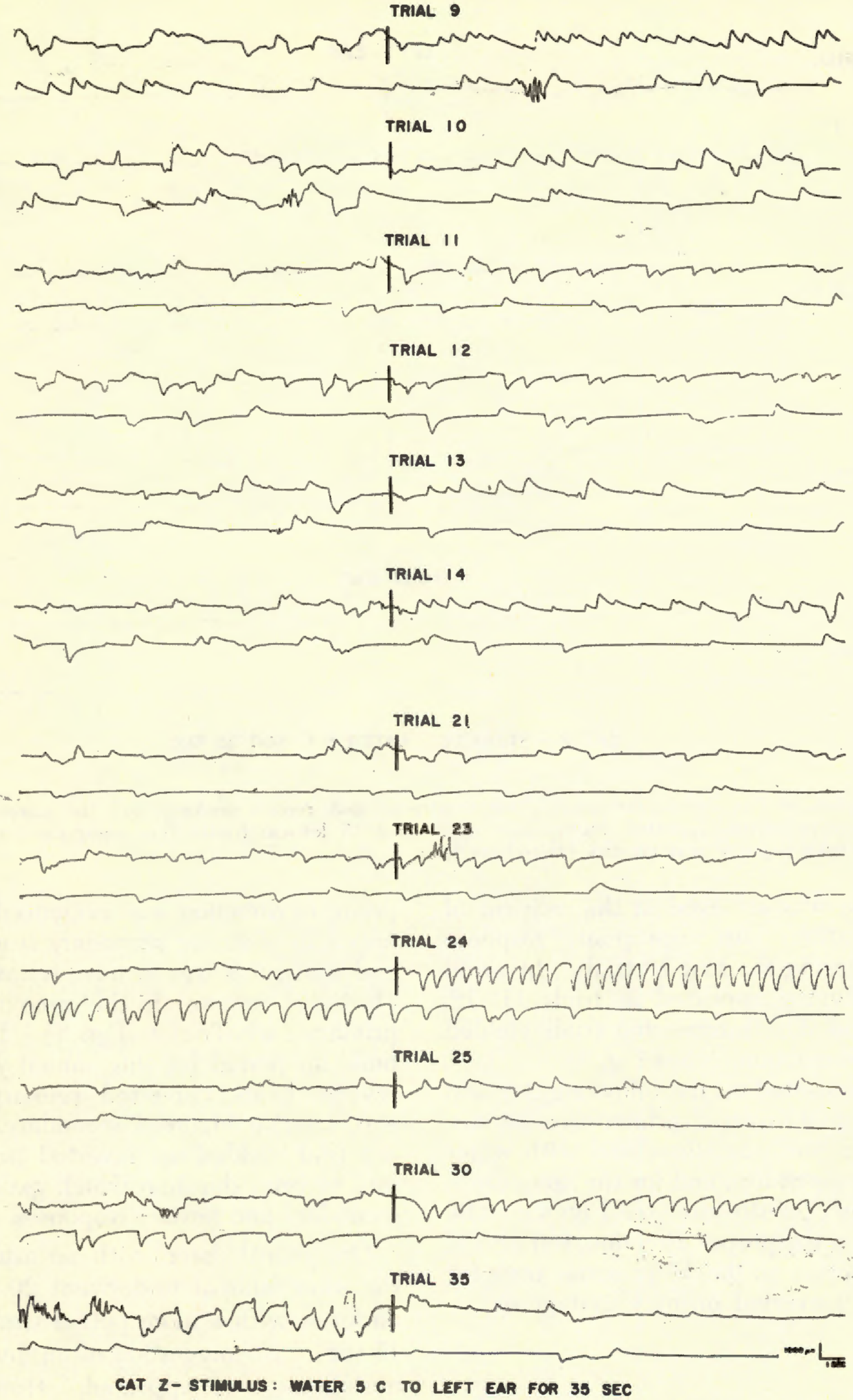

FIGURE 3. Nystagmic responses obtained from left-ear stimulation of Cat Z. The last 15 seconds of the 35-sec stimulus (applied in illumination) are depicted. Vertical bars indicate moment of stimulus-termination and onset of total darkness. Appropriate responses were obtained during the first 10 trials (fast-phase right). Note the particularly vigorous inverted primary responses on Trials 24 and 30.

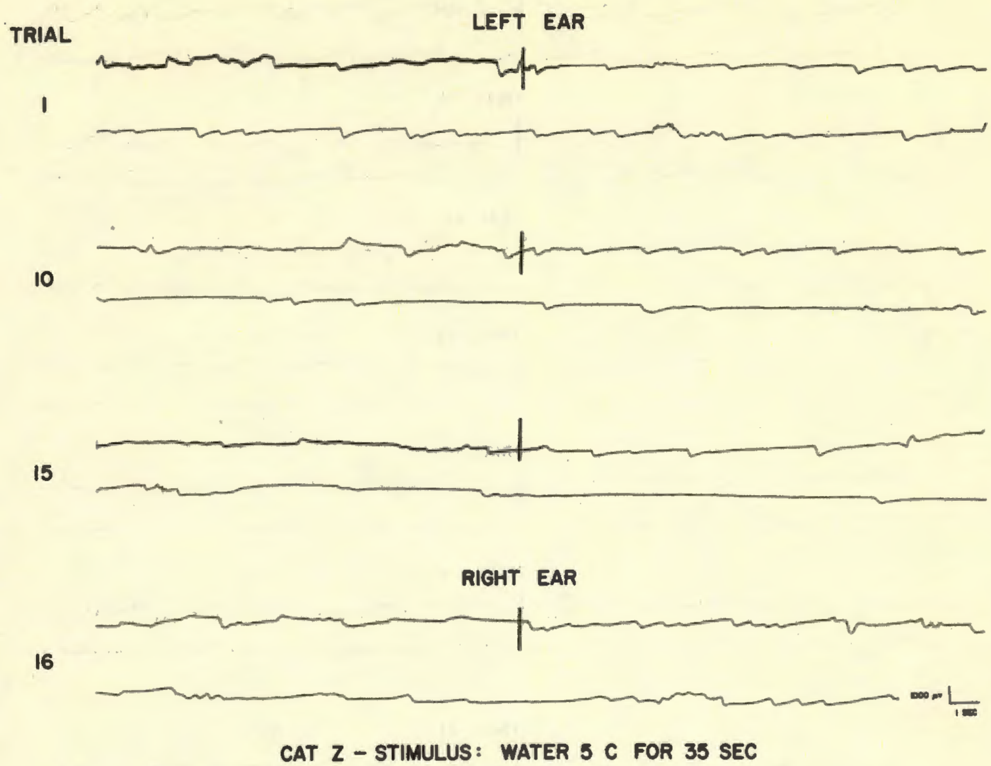

FIGURE 4. Re-test of Cat Z one day later. Test conditions and record markings are the same as in Figure 3. Inverted primary nystagmus appeared during each of the first 15 left-ear trials. The right ear was then stimulated and an appropriate response was elicited (fast-phase left).

Total darkness was achieved at the moment of stimulus cessation. An appropriate response was elicited during the first 10 trials. Inverted primary nystagmus appeared in trials 11, 12, 22, 23, 24, and 30. Intervening trials yielded an appropriate reaction. (See Fig. 3).

Cat Z was re-tested on the following day and continued to give inverted primary nystagmus. After 15 trials, she was stimulated with water of the same temperature and for the same duration but in the opposite ear (see Fig. 4). The response was in the proper direction, but also in the same direction as the 15 previous tests for the other ear (inverted primary nystagmus).

Cat W

Cat W received a stimulus milder than that administered to the aforementioned cats (23.5 C for 30 sec) and was tested in total darkness. In all cases, the nystagmic response took several seconds to build up after termination of stimulation. In early trials, a response appropriate in direction was evidenced, and was followed by a strong secondary reaction. In several trials, this was in turn, followed by a third (tertiary) response in the same direction as the primary (see Trial 8, Fig. 5). In trial 13, the build-up period for this animal yielded several reverse beats (inverted primary nystagmus) and, later, a vigorous secondary. The following trial yielded an inverted primary nystagmus of brief duration which gave way to brisk secondary and tertiary responses.

One month later, with no intervening tests, the same animal underwent 20 trials in total darkness with a more potent stimulus (5 C for 15 sec). No suggestion of an inverted primary nystagmus ever appeared. However, a clear secondary reaction was evidenced. (Fig. 6).

Cat S

Cat S was given 20 right-ear calorizations using water of 23.5 C temperature for irrigation

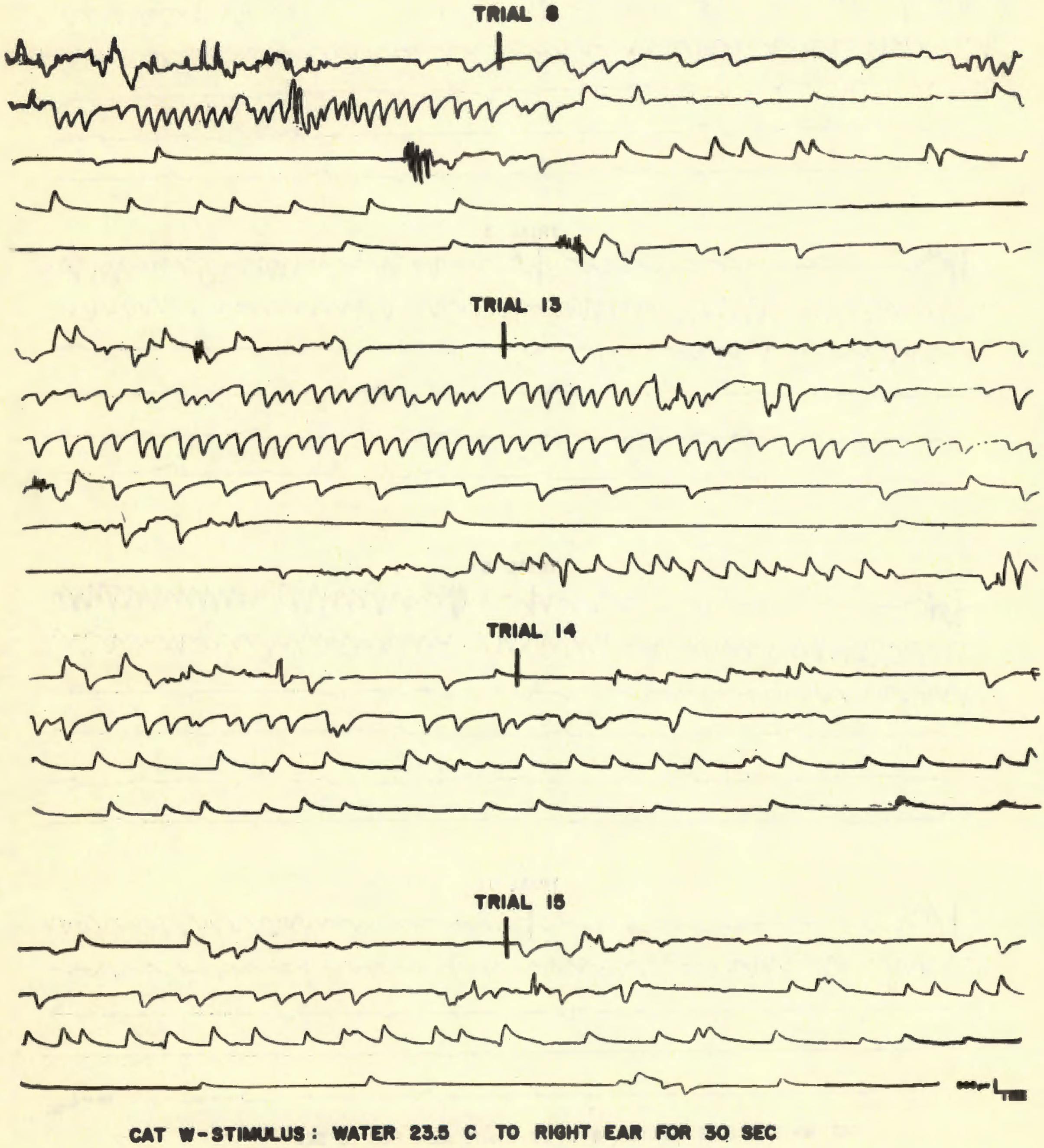

FIGURE 5. Recordings obtained from Cat W. The last 15 seconds of the 30-sec stimulus (applied in total darkness) are depicted. The secondary is brisk on all trials. Note the clear inverted primary nystagmus on Trial 14.

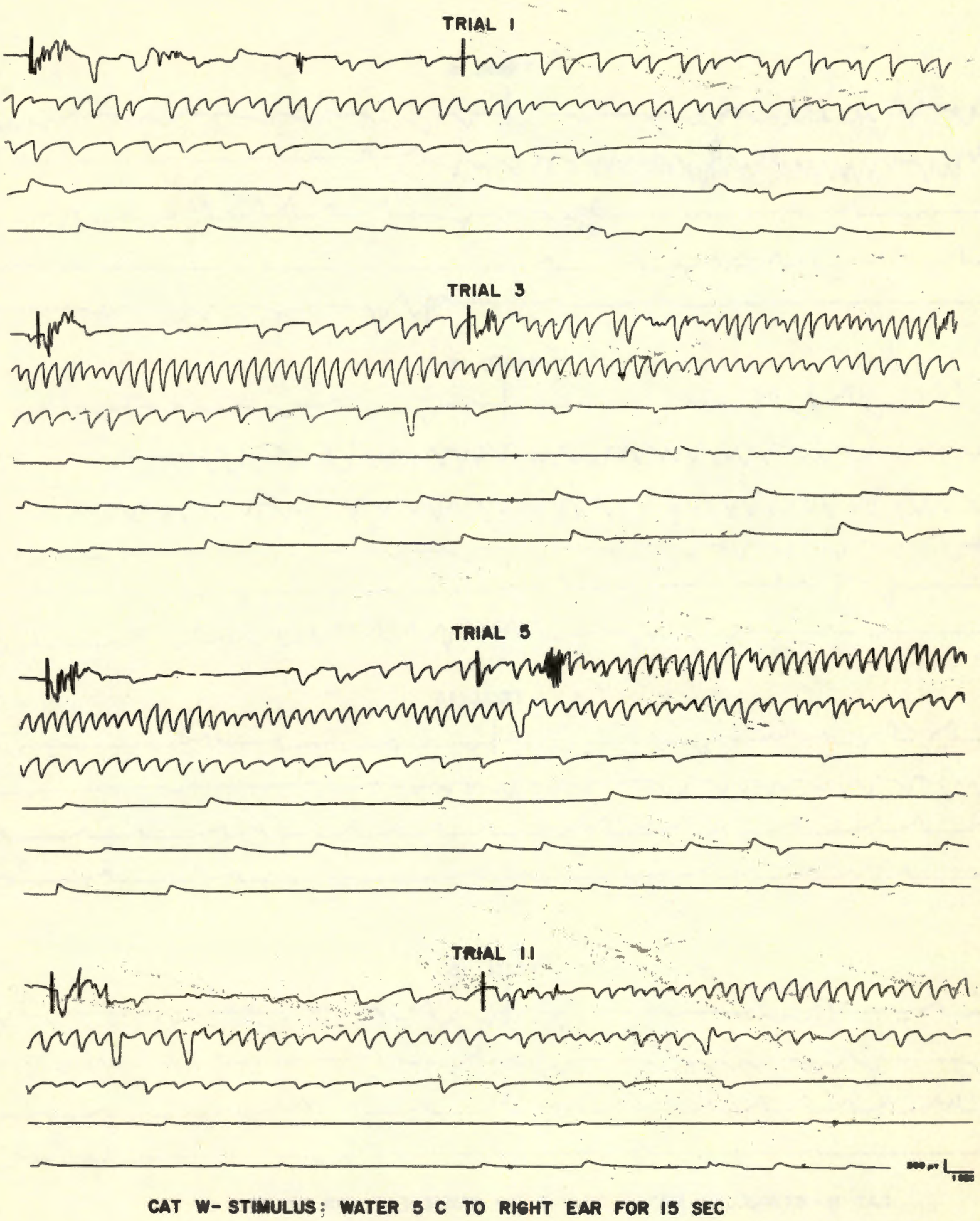

FIGURE 6. Re-test of Cat W one month later with a more potent stimulus. The entire stimulus period (total darkness) is presented. Secondary reactions are clearly evident but no inverted primary responses appeared.

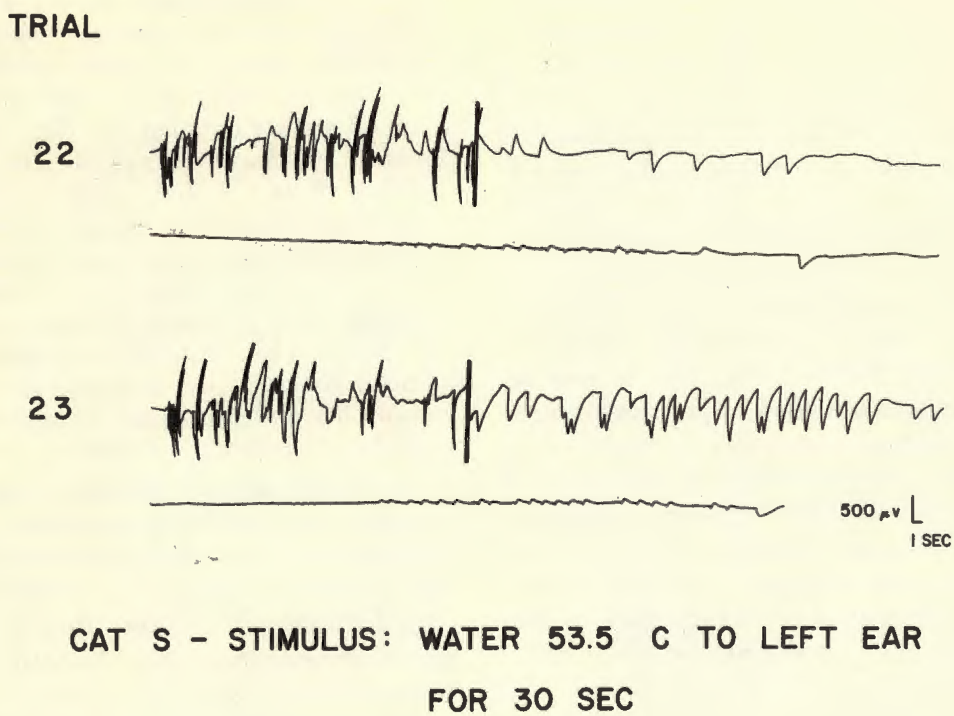

FIGURE 7. Nystagmus recordings obtained from Cat S. In previous trials, the right ear was stimulated with cool (23.5 C. for 20 trials) and warm (53.5 C. for 1 trial) irrigations. Note the inverted primary beats in the upper record.

periods of 30 sec. In the twenty-first trial, the stimulus temperature was raised to 53.5 C. In the following trial, the 53.5 C stimulus was applied to the opposite (left) ear, yielding an inverted primary, a secondary, and a tertiary response. An appropriate primary and a secondary appeared during the next trial under identical stimulus conditions (Fig. 7).

Discussion

The data presented here indicate that both secondary and inverted primary nystagmus may be elicited from cats by means of unilateral caloric stimulation applied under a variety of test conditions. The reaction has appeared after irrigation in light and in darkness, with stimulus temperatures of 23.5 and 53.5 C applied for 30 sec, and 5.0 C applied for 15, 30, and 35 sec. However, not all cats demonstrate an inverse response.

In agreement with studies of rabbits (9), the inverse caloric reaction most frequently noted is the secondary. It is, however, a labile response and differs in this regard from one produced by rotation. Under usual rotatory conditions with normal cats and humans, the secondary is a fairly common occurrence and is most often, if not invariably, present during the first trial (1, 2, 3, 4, 18). There appears to be a tendency for the reaction to remain relatively stable over several trials (2), or to decline in intensity with repeated testing (19) under controlled conditions of alertness, a factor extremely important for the maintenance of nystagmus in total darkness (20, 21). The caloric secondary does not seem to be regulated as systematically.

In summarizing their findings with rabbits, Riskaer and Permin (9) noted that, (a) with repeated irrigations, inverted nystagmus was more likely to occur, and (b) stimulus repetition did not yield a constant type of nystagmus, i.e., the inverse reaction did not always recur. Data obtained in the present study are in agreement with these two observations.

Several explanations for the occurrence of the inverse responses, obtained here and in the other cited reports, may be examined:

1) *Cooling effects.* Some explanations of inverse caloric responses involve the physical generalization of cooling effects, either within the labyrinthine structure or the cerebellum (9). In favor of this view are the facts that the response has been elicited most readily after repeated stimulation, with extreme temperatures, or with prolonged irrigation. The view appears weakened, however, by the following considerations: (a) the inverse responses appear unpredictable with respect to occurrence on successive trials, time of onset of the reaction, and vigor of the beats; (b) inverse responses have been obtained by pressure-induced endolymph currents and appear related to a changed state of contraction of the involved occular muscle (22); (c) follow-up data from one animal indicate retention of the inverted primary nystagmus for the "practiced" ear a day later (see Fig. 3); (d) another animal (Cat W) gave inverted primary nystagmus to the milder of two stimuli (23.5 C vs. 5 C). It should be noted, however, that the duration of stimulation was longer for the less extreme temperature.

2) *Peripheral events.* Thornval (23) produced inverted nystagmus experimentally by caloric stimulation of the exposed canals of pigeons. Depending upon the orientation of the canal and the point at which the stimulus was applied, responses in one direction or another, or a lack of response could be observed. Thornval (12) felt that certain endolymph movements (which he described in the pigeon study) caused the inverted primary response he observed in one normal human. In addition, he stated that the response probably occurred in every caloric test, but was usually too weak to be observed.[4]

Thornval (12) also differentiated between secondary (which he obtained with hot as well as cold irrigations) and inverted primary nystagmus. The secondary, he felt, had a central origin; the inverted primary response was peripherally caused. It would seem somewhat questionable, however, to attribute to the peripheral events detailed by Thornval (23) the inverted primary nystagmus observed in the present study. Initial, weak endolymph currents would appear to be an inadequate cause for the production of some of the more vigorous inverse reactions obtained. Neither do such currents seem sufficient to explain the findings of Fischer (13) nor the pressure-induced responses obtained by Szentagothai (22). The posssibility of peripheral causation, however, must be given careful evaluation.

3) *Central factors.* Several authors have expressed the view that secondary nystagmus responses are due to central rather than peripheral events (2, 5, 12, 18). Hauty and Wendt (2), for example, indicate that the secondary phase of nystagmus "may be attributed to the reciprocal after-effects of primary nystagmus which cause the discharge of opposable central components to become imbalanced." Fischer (13) has also ascribed a central process to the production of inverted primary responses.

There is the possibility that the inverse reaction is an active process which is built up mainly to inhibit the primary response. It may represent one of the means by which the organism responds to repeated vestibular stimulation (24, 25) and nystagmus becomes "habituated". However, the only clear direct evidence presently available to support this hypothesis is from recent studies of adaptation to Coriolis accelerations (26). As a result of living in a rotating room, human subjects developed an inverse nystagmus when tipping their heads in a static condition. That is, a compensatory nystagmus, in a direction opposite to that which the same head-tilt would produce during rotation, was present in a non-rotating environment after many hours of rotatory experience. Moreover, a similar reaction was evident for the oculogyral illusion (27).

Additional, though less direct, supportive evidence may be adduced from studies of subjective rotatory responses. Human data obtained

[4] Within a series of repeated irrigations, inverted responses were occasionally observed during the stimulus period, although an appropriate primary nystagmus was evidenced upon stimulus termination. Attempts to interrupt the stimulus at such times were unsuccessful in eliciting the inverse response, but, rather, a directionally appropriate nystagmus would appear, usually after a brief latency.

by Guedry, Cramer, and Koella (28) led them to conclude that the secondary subjective reaction (i.e., a sensed turning, without adequate stimulation, in a direction opposite to an initial rotatory sensation appropriate to a given stimulus) is best described as a process which develops to counteract the primary subjective reaction.

4) *Central and peripheral factors.* Recently, Fluur and Mendel (8, 9) obtained secondary and spontaneous nystagmus[5] from normal humans subjected to repeated unilateral caloric stimulation. They regard both kinds of response as a part of the habituation process and emphasize a relation to efferent activity. Repeated caloric stimulation of a given ear is regarded as either inhibiting or enhancing efferent activity (depending upon stimulus temperature), and results in a disturbance of the dynamic state of balance between the two labyrinths (8, 9). "Habituation could thus develop in any one of three ways: via the cerebellum from the contralateral labyrinth, via the recticular formation or, possibly, via direct communications between the two vestibular nuclei by secondary fibers" (9).

Data currently available appear too incomplete to allow a clear choice of the explanations for nystagmus reversals. It is possible that several causes may be operative, depending upon the stimulus situation, with only the end result (inversion of nystagmus) common to all conditions. The explanations presented point to a number of approaches for determining the cause and meaning of nystagmus reversals, and the cat appears to be an adequate subject for the examination of these problems.

[5] A clarification of some terms is probably in order. Hauty and Wendt (2) define a spontaneous nystagmus as "a sustained nystagmus with the slow phase in a particular direction and of a very low level of intensity or amplitude. It cannot be attributed to physical stimulation." Most authors would agree on such a definition. A second type of sustained nystagmus which persists in the absence of a physical stimulus is "nystagmus alternans." Here, however, the direction of the nystagmus changes periodically. If a similar response should occur as a result of vestibular stimulation (e.g., reversals of nystagmus exceeding a tertiary response), it is suggested that such a reaction be differentiated by the term "induced alternating nystagmus."

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