THE BIOELECTRIC PHENOMENA OF THE AUDITORY APPARATUS

by

Peter Edwin Kellaway

Submitted in Partial Fulfillment of

the Requirements for the degree of Ph. D.

in Physiology

McGill University

September 1946

TABLE of CONTENTS

SECTION I. INTRODUCTION

SECTION II - THE MECHANISM OF THE ELECTROPHONIC EFFECT

It is a pleasure to acknowledge the assistance given me by Mr. Parr Tate in the mathematical portion of Section II of this thesis, and to express appreciation for the advice, encouragement and help Professor H. E. Hoff has given me throughout the experimental researches which are reported herein.

PART I - INTRODUCTION

Historical Survey

In 1896 Beauregard and Dupy (1) succeeded in recording electrical potentials from the eighth cranial nerve in the guinea pig. Their report was the first published investigation concerned with the electrical phenomena of the auditory apparatus. Using an aperiodic d'Arsonval galvanometer with non-polarizable electrodes applied to the tympanum and to the cut surface of the nerve, they were able to demonstrate the presence of the demarkation potential. More important was their observation that a deflection of the galvanometer in the opposite direction to that of the demarkation potential occurred when the sound of a whistle or tuning fork was applied to the ear.

Ten years after the publication of Beauregard and Dupy's paper, Piper (2)(3) recorded with a galvanometer potential changes from the saccule and otolith in fish on stimulation with sounds of 100 and 260 vibrations per second. Buijtendijk (4), a few years later, was unable to verify Piper's observations but obtained what he believed to be action currents from the eighth nerve in the guinea pig and rabbit following stimulation of the ear with pistol reports and loud sounds from a flute.

Forbes, Miller and O'Connor (5) were the next investigators to apply electrical methods to the study of the ear. In an attempt to answer the problem of representation of frequency in the auditory tracts they placed electrodes on the medullae of decerebrate cats and registered the potentials arising therein in response to loud sounds. Impulses coincident with the stimuli were obtained when sharp sounds such as the clicks of a

watchman's rattle were used but only "imperfectly synchronized" responses could be initiated with tones of low frequency. Forbes et al. concluded from these experiments that tonal stimuli do not elicit synchronized potentials in the auditory tracts -- a conclusion which received apparent support from results obtained by Foa and Peroni (6) in the facial-auditory nerve of the giant sea turtle. The latter workers observed discharges of from 50 to 60 impulses per second during acoustic stimulation irrespective of the frequency or character of the stimulus.

All of the early work in this field suffered from severe limitations of technic. The galvanometers used were either too slow, or at high string tensions too insensitive for the purpose of investigating the electrical phenomena of the auditory apparatus. Indeed until the vacuum tube amplifier and later the oscillograph were adapted to the study of bioelectricity, recording methods were in most instances quite inadequate. The first definite evidence that synchronized potentials may be recorded from the auditory nerve was obtained in 1930 by Wever and Bray (7)(8). These workers found that when electrical currents picked up from the auditory nerve were amplified and led to a telephone receiver they faithfully reproduced in the receiver sounds impinging upon the ear of the animal. Wever and Bray took extensive precautions to exclude artefacts, and having shown by various means that the phenomena observed depended upon the physiological activity of the auditory system, attributed the effect to synchronized action currents produced in the nerve through excitation of the inner ear by the sounds employed.

At first, many investigators considered that the Wever and Bray

results were due to electrical and mechanical artifacts such as vibration of the pick-up electrodes, electrical interference due to insufficient shielding, etc. (9). Kreezer and Darge (10), for example, found that when they took precautions to avoid such artifacts they could obtain only negative results, and suggested that the effect, as originally observed, was due to electrical interference at the site of the operation. However, the criticisms advanced by these authors have been adequately answered through subsequent experimentation, and the effect has been verified in many different laboratories (e.g. Hughson and Crowe (11)(12)(13), Crowe (14), Adrian et al. (15), Rademaker and Bergansius (16), Elmquist and Sjöström (17), Davis and Saul (18)(19), Bast et al. (20), Hathaway and Rasmussen (21), Fromm et al. (22)(23), Hallpike and Rawdon-Smith(24)).

The Nature of the Wever and Bray Effect

The presence of action currents in the auditory nerve had been taken for granted long before it was first directly demonstrated by Beauregard and Dupy. However, the introduction by Rinne (25) and Voltolini (26) of the theory of central analysis of sound, and Rutherford's (27) subsequent development of the telephone or frequency theory of hearing, created new interest in the problem. Contrary to the then widely accepted resonance hypothesis of Helmholtz, Rutherford proposed that the discrimination of pitch depended upon the number of impulses travelling in the auditory nerve per second, and the loudness of the perceived sound upon the number of fibers activated. The responsibility of furnishing proof for one or the other of the two theories devolved upon the electrophysiologists; their

problem was to determine whether the discrimination of pitch depends upon the number of impulses travelling in the nerve as a whole, or upon the activation of a certain specific fiber or group of fibers.

As was mentioned in the historical introduction, Wever and Bray were the first to observe synchronized potentials in the auditory nerve. Their observations appeared to show that the nerve was capable of reproducing frequencies of stimulation up to at least 5,000 cycles per second. But transmission of impulses at a rate of 5,000 per second required the nerve to have a functional recovery period (refractory phase) of less than 0.2 milliseconds, which is approximately ten times shorter in duration than the recovery period in other sensory fibers of similar size and character.*

The briefness of this refractory phase cast some doubt on Wever and Bray's conclusion that the potentials recorded by them were nerve action currents and on the basis of certain tests, Adrian (28) suggested that the phenomenon depended upon microphonically generated potentials arising in the cochlea itself. He found, for instance, that cooling the bulla or narcotizing the nerve, measures which normally would abolish responses of nervous origin, had little or no effect upon the potentials which are picked up by electrodes placed on the nerve and round window in the manner of the original authors. Adrian subsequently reversed this judgment, because in later experiments carried out in collaboration with

* The functional refractory phase for the whole nerve must necessarily be imposed by that part in which its fibers have the smallest diameter: In the case of the auditory nerve the intra-cochlear endings of the fibers are unmyelinated and of very fine diameter. According to the schema developed by Gasser and Grundfest such fibers should have an absolutely refractory period of about 2 msec.

Bronk and Phillips (15) it was found that the phenomenon was no longer demonstrable after cocainization of the intra-cochlear nerve elements. His suggestion that the potentials were of physical rather than nervous origin was nevertheless taken up by several other laboratories. Rademaker and Bergansius (16) from experiments similar to those originally made by Adrian, decided in favor of what they termed an "electrical spread" from the cochlea as the basis of the effect. Similarly, Bast and associates (20), using the technic of amplifying the potentials and converting them to sound, found that not only were the potentials undiminished after the nerve had been immersed in chloroform, but that the reproduced sounds had an increased clarity. If the potentials thus amplified were entirely nervous in origin why should chloroform which would normally depress or obliterate them have in this case the type of action just described? Bast et al. did not, at the time, propose any solution to the problem but in another laboratory a series of experiments were gradually providing an answer to this apparent paradox by showing quite clearly that the Wever and Bray phenomenon had a dual nature.

Davis and his co-workers (29)(30)(31) presented the first complete evidence that the Wever-Bray effect actually had two electrical components: action currents from the nerve and a non-neural electrical spread from the cochlea. Their evidence depended mainly upon observations made with two different types of electrode system: one in which a co-axial electrode was placed in the auditory nerve or tracts, and another in which an unshielded 'active' electrode was placed on the round window of the cochlea, and an 'indifferent' electrode applied elsewhere on the animal. The rationale for

the use of the two different electrode systems was as follows: Because the 'pick-up' of a co-axial electrode is limited strictly to a small region within its immediate vicinity, the placing of such an electrode in the auditory nerve or tracts should permit observation of pure action currents uncontaminated by potentials of extraneous origin.* On the other hand, potentials generated within the cochlea itself, should be picked up by a recording system in which the active electrode is applied to the round window.

Differentiation of the two components of the Wever-Bray phenomenon was achieved on the basis of the following functional characteristics as determined by observation with the two types of electrode technic described above.

Vulnerability: Action-potentials are reversibly depressed by narcosis and by cold. They are also suppressed, especially in the higher auditory pathways, by deep surgical anesthesia. Cochlear potentials, on the contrary, are unaffected by cooling or by narcosis of the nerve and, although diminished in size, may persist for various periods after death (32).

Frequency Range: Synchronized potentials may be obtained from the cochlea in the cat in response to frequencies up to at least 12,000 cps. The upper frequency limit in the nerve, however, never exceeds about 3,000 cps., and in the auditory tracts the upper limit is still lower, probably not more than

* It must be pointed out that Wever and Bray and all other investigators up to this time had used unshielded wire electrodes insulated except at the tip where they made contact with the nerve.

1,000 cps. Above the limiting frequency impulses are, of course, still present in the nerve or tracts but they are disorganized and asynchronous with respect to the activating sound waves.

Refractoriness: The limit of frequency response in the nerve fibre, as defined above, is imposed by the period of refractoriness which inevitably follows each nerve impulse. The source of the cochlear potentials does not exhibit a phase of inexcitability and a continuous response is elicited with prolonged, repetitive stimulation.

Magnitude: The response magnitude from the cochlea is many times greater than that from the nerve for any given intensity of stimulation. Voltages as high as 800 microvolts (33) have been recorded from the cochlea, a potential which far exceeds the maximum which could be explained by summation of the action currents of the intra-cochlear fibers of the auditory nerve.

Stimulus-Response Relationships: The action of the stimulus in the excitation of a nerve fiber may be likened to the firing of a gun: When the trigger is pulled, the gun fires with all the energy it has. The force which is exerted on the trigger bears no relation to the resulting explosion once enough pressure has been applied to release the hammer. The single nerve fiber responds in a similar all-or-none fashion. The size of the action potential is not a function of the strength of the stimulus, but depends entirely upon the immediate condition of the tissue. In the case of a whole nerve trunk, however, the magnitude of the stimulus does bear a relation to the response size in the sense that, due to the fact that individual fibers differ from each other in excitability, the stimulus intensity will determine the number of fibers participating in the response -- the

increments therefore are quantal in character.

The magnitude of the cochlear potentials is a simple linear function of the intensity of the stimulus. There is neither evidence of step-like increments in their size as intensity of stimulation is increased, nor a suggestion of an all-or-none relationship between stimulus and response.

Latency: The action currents of the auditory nerve have a latency with respect to the cochlear potentials of from 0.55 milliseconds to as much as 2.0 milliseconds depending on the polarity and intensity of the stimulus (34) (35); such a latency is too long to be accounted for as the time taken for transmission of the impulse from the hair cells to the location of the recording electrode, a distance less than five millimeters. Nor can the presence of the ganglion cell in the path of the impulse be assumed to delay transmission enough to explain the latency (36).

Polarity: Nerve fibers always show negativity in the region of activity with respect to an indifferent electrode placed elsewhere on the animal. On the contrary, the electrical sign of the first oscillation of the cochlear response depends on whether the first sound wave impinging on the ear drum is one of negative or one of positive pressure (37)(38).

Masking: It is possible to cancel the nerve impulses elicited by one tone through simultaneous presentation of another, providing the frequency of the masking tone or one of its harmonics lies near the frequency of the masked tone, an effect which cannot be demonstrated in the electrical responses obtained from the cochlea.

Relation of cochlear potentials to the integrity of the auditory nerve.

The data outlined in the foregoing paragraphs clearly show that the functional characteristics of the potentials recorded from the intracranial portion of the auditory nerve differ in several significant aspects from those of the potentials obtained from the cochlea. Nevertheless, a few observations contradictory to the hypothesis that the Wever and Bray phenomenon involves a non-neural component must now be considered and explained.

From experiments in which it was found that cocainization of the cochlear elements abolished the electrical potentials from that structure, Adrian and his associates (15) concluded that the potential changes observed with the Wever-Bray technic have their origin in intra-cochlear nerve fibers. Apparent support for the hypothesis was forthcoming in results obtained in an investigation of the effect of eighth nerve section upon the electrical activity of the acoustic system. Contrary to the law of Wallerian degeneration, the spiral ganglion cells and their dentritic processes degenerate when the auditory nerve is severed at the entrance to the internal meatus. Hallpike and Rawdon-Smith (39)(40) took advantage of this anomaly in an attempt to determine if deterioration of the nervous elements within the cochlea is accompanied by irreversible loss of electrical responses from that organ. Because electrical responses could be elicited from one such preparation, in which all nerve tissue showed atrophic changes, but in which the other structures of the inner ear were apparently normal, first led these workers to ascribe a neural origin to cochlear potentials (40). Subsequent investigation (41)(42)(43)(44)(45) revealed, however, that when

care is taken to preserve the blood supply to the inner ear, section of the auditory nerve does not annul the electrical phenomena which are normally recorded from the round window. On the other hand, severance or blockage of the internal auditory artery which runs in close association with the nerve causes necrotic deterioration of all cellular elements of the cochlea and a concomitant loss of electrical responsiveness.

Adrian's results can be explained by the fact that the action of cocaine to abolish cochlear potentials is non-specific, for many diffusible substances including sodium chloride and glycerine have since been shown to have a similar action.*

Origin of Cochlear Potentials

Having established that electrical changes may be recorded from the cochlea after the neural structures therein have degenerated, it now becomes necessary to determine the precise origin of these potentials and to define the possible mechanisms by which they may be produced.

Soon after the discovery of the Wever-Bray effect, Howe and Guild (46)(47) showed that audioelectric phenomena are absent in congenitally deaf albinotic cats. Histological examination of the ears of these animals revealed that the hair cells and sometimes the supporting cells of Corti's organ were completely absent although the ganglion cells, their processes and the endolymphatic channels showed no abnormalities. Similar observations were later made by Davis and his associates (48)(49)(50) on both albino cats

* See section entitled "Data from the Application of Drugs" page 12.

and waltzing guinea pigs, and by Hughson, Thompson and Witting (51) on congenitally deaf Dalmation dogs. These studies of naturally occurring pathological conditions have served quite definitely to relate the electrical response to the cells of Corti's organ. The waltzing guinea pigs studied by Davis et al. are of special interest for the only abnormality detected in this instance was a slight but definite degeneration of the hair cells, yet one of these animals yielded no cochlear potentials and the other only a slight trace. The inference is that the hair cells are not only essential to the production of cochlear potentials, but that even slight deterioration in these cells is sufficient to abolish the effect.

Whatever the actual mechanism may be, whereby transformation of mechanical into electrical energy is accomplished in the cochlea, one factor has definitely been established, and that is that pure tone stimuli evoke electrical responses from discrete and localized regions of the end organ. The evidence for this statement stems from researches using several different types of technic, a description of which is given herewith:

Embryological Data: McCrady and his associates (52)(53)(54)(55) made a careful developmental study of the auditory apparatus of the opposum (Didelphys virginiana and Didelphys marsupialis), one of the few mammals in which the ear is immature at birth. They find that the nervous system is complete for about one week before hearing is possible and that this function seems to await not only the appearance of Corti's organ but the last subtle steps of its differentiation (52). The development of the sensory epithelium is not a simultaneous event throughout the length of the organ, but a progressive process about five-sixths of which occurs after birth. Cochlear responses

begin to appear on the fifteenth day and are at first limited to frequencies in the vicinity of 1,500 cps.; at this stage the organ of Corti has reached mature development in only the second half of the first turn of the cochlea. Differentiation of the organ begins in the distal portion of the basal coil, and then progresses in both directions. Likewise the range of the audio-electric response begins with tones of the lower middle frequencies then spreads to the upper and lower limits of the audible spectrum.

Data from the Application of Drugs: Many chemical substances including cocaine, quinine, calcium chloride and sodium chloride have been found to impair the electro-acoustic response when they are injected into the cochlea, or simply allowed to diffuse through the round window (57)(58). A systematic study of this effect has been carried out by Fowler and Forbes (59)(60)(61) who applied various crystalline substances to the round window. They found that the electrical responses to high tones were impaired sooner and to a greater extent than the responses to low tones. Microscopic sections of the cochlea subjected to these substances revealed that the hair cells nearest the round window were the structures most damaged. Fowler and Forbes' observations have been verified and extended by Wever and Bray (62) and by Walzl (63) who have also shown that when the diffusion gradient is reversed by placing the chemical substance in a hole drilled in the apex, instead of on the round window, low tone responses are the first to be impaired.

Surgical Data: The evidence obtained with various surgical procedures is not as definitive nor as conclusive as that obtained using other technics, for obviously the cochlea is not normal once it has been scorched, drilled or otherwise injured. Thus the failure of may investigators (64)(65)(66)

(67)(68) to obtain discrete losses with supposedly localized surgical lesions may be explained by the possibility that tissues other than those in the specific region of the operation may have been traumatized, with consequent changes in the hydrodynamic or mechanical characteristics of the acoustic system. Even when post mortem histological examination is made, it is often extremely difficult to evaluate the structural damage and to differentiate between functionally normal and abnormal cells. The success of some workers (69)(70)(71), on the other hand, in obtaining fairly discrete losses with localized lesions can be explained only on the basis that the technics employed successfully produced circumscribed regions of destruction in Corti's organ. The culminating study of this problem was made by Walzl and Bordley (72). They removed with a dental burr the bone over a selected area of the spiral ligament, and then with a blunt probe loosened the ligament by gentle pressure. This procedure caused a restricted area of the basilar membrane to bend and the portion of the sensory epithelium thereon to be crushed or dislodged; in this way Walzl and Bordley were able to destroy at will circumscribed regions of Corti's organ without traumatizing other areas and without causing an escape of endolymph. The results of many experiments made with this technic clearly demonstrate the fact that near threshold the electric response to any frequency is limited to a small portion of the organ of Corti.

Electrical Data: Hallpike and Rawdon-Smith (73) were the first workers to attempt to localize response areas within the cochlea by recording the electrical potentials from various loci on the surface of the cochlea. In one such experiment they made minute drill holes in the cochlear wall, filled

the holes with mercury and placed an electrode in contact with the metal in each of the holes successively. Their observations indicated that the electrical responses to low frequencies are transmitted with greater intensity when the electrode is near the apex than when it is near the base, and vice versa. Culler and co-workers (74)(75)(76) developed a similar technic using the guinea pig, an animal which is particularly suited to this type of experimental approach in that the cochlea is not imbedded in the petrous bone as it is in man but projects from it in such a way that nearly 70 per cent of the walls of its four and one-half turns are readily accessible. Culler et al. exposed the organ by cutting through the bulla from the ventral aspect and then applied short lengths of sharp tungsten wire to twenty-five carefully localized points on its bony surface. Using an amplifier and a wave analyser as a thermionic voltmeter, they measured the phono-electric response of each point to each of twenty tones ranging from 60 to 7,500 cps. In this way it was seen that each locus tested would respond maximally to a short range of frequencies, and that the electrical foci are so arranged that the organ is graduated in frequency response from base to apex. The cochlear map which Culler et al. constructed from this data coincides, within the range of experimental error, with a similar map drawn by other investigators employing similar methods (77).

Theories Concerning the Mechanism by Which Cochlear Potentials are Generated

The material in the foregoing paragraphs, which constitutes almost the entire empirical data on the nature and origin of the audio-electric

response, tends to elucidate but two aspects of the problem: First, it is evident that the process by which transduction of mechanical into electrical energy is accomplished in the cochlea is selective with respect to frequency, and, second, it is probable, though by no means certain, that the hair cells of Corti's organ are essential to the production of cochlear potentials. Beyond this very little is known and all other material regarding the mechanism of energy transduction by the cochlear elements is purely theoretical and based almost entirely upon analogical or deductive considerations.

"Streaming Potentials" Theory.

Eyster and his associates (78) demonstrated that the microphonic action of the cochlea may be simulated by a model in which the potentials arise as a result of flow (induced by the action of sound waves) of water through membrane pores. They pointed out that a system such as the internal ear, consisting as it does of aqueous phases separated by porous membranes, would inevitably generate potentials of this type, and on the meager evidence of this physical analogy concluded that streaming potentials across Reissner's membrane are the sole source of the audio-electric effect.

The theory does not account for the several instances where electrical activity was found to be depressed or absent in the presence of a normal membrane of Reissner and a normal endolymphatic system (72)(79). Nor does it seem possible that streaming potentials occurring at localized and restricted regions of Reissner's membrane could be of sufficient magnitude to account for the large cochlear potentials which arise in response to a single pure tone stimulus. For as pointed out elsewhere, a factor which has been definitely established is that a specific and circumscribed region of the

cochlea is responsible for the production of the electrical potentials arising in response to a single pure tone.

Leiri (80)(81)(82) has proposed a complicated variation of the streaming potentials theory which may be briefly stated as follows: Oscillation of the fluids in the inner ear initiates transverse vibrations in the tectorial membrane, causing the membrane to contact two hair cells situated at a mutual distance equal to the wavelength of the activating sound. As the vibrations of the tectorial membrane take place in the magnetic field set up by streaming potentials produced by blood movements in the vas spirale, induction-tensions are created whereby electrical fluctuations in the auditory nerve, "homorhythmical with the tones" are initiated in the same manner as voltage fluctuations in a dynamic microphone.

The same objections apply to Leiri's complex hypothesis as to the simple original. There are many other contradictory factors, the most important of which is the demonstration that latency of the action potentials in the auditory nerve bears a direct relation to the polarity and intensity of the stimulus (37).

Concentration Potentials Theory.

Hallpike and Rawdon-Smith (83)(84) postulate that cochlear potentials are developed across Reissner's membrane either as a result of a chemical difference between endolymph and perilymph or as a result of an electrical assymetry integral in the membrane itself. In association with Gatty, Rawdon-Smith has (85) demonstrated that audioelectric phenomena resembling the cochlear potentials may be observed in a model consisting of a frog's skin-membrane bounded by fluids.

While the latter experiment shows that the cochlear effect may be imitated by a model, it does not provide evidence per se that a polarized membrane is the source of the potentials generated in the inner ear. Indeed the membrane theory fails to account for many aspects of cochlear electrical activity including the essential factor that each stimulus frequency has a definite focus of response in the organ. Furthermore, Walzl (63) has shown that cochlear potentials are comparatively insensitive to changes in the ionic composition of the perilymph, and several authors have noted losses for specific frequencies when Reissner's membrane was normal throughout its length (49)(79).

ε and ζ Potentials Theory.

Kupfer and Voss (86)(87)(88)(89) maintained that the audioelectric potentials are produced by contact and electrokinetic effects at the marginal interfaces of solids and liquids in the cochlea. They draw attention to the fact that an electrical field is present at the boundary between a solid and a liquid such that the solid carries charges opposite in sign to the liquid which bounds it, and that alternating potentials are created when an applied oscillatory force displaces or separates these dipoles. Many factors tend to render the theory untenable, especially the circumstance that damage restricted to a small portion of the cochlea may almost completely abolish the response to a single specific frequency, when according to the theory the potentials represent the sum total of electrokinetic effects arising at all solid-liquid interfaces within the cochlea.

Piezoelectric Potentials Theory.

The several instances in the literature where the electrical

response from the cochlea was absent in the presence of but slight degenerative changes confined to the hair cells of Corti's organ led Davis and his associates (48) to conclude that these cells constitute the sole agency involved in the production of microphonic potentials in the inner ear. They postulated that the physical process by which the electrical potentials are generated depends upon a piezoelectric effect due to distortion of cells containing oriented organized molecules.

That cells of solid or semisolid nature having a special form of molecular structure could be responsible for the production of the audioelectric potentials is quite conceivable. It is well known that when pressure is applied to certain crystals characterized by a particular type of lattice structure, a dipole moment is produced, this being due to a separation of the centers of gravity of the loci of the positive and negative charges in each molecule. The potential, thus created, is essentially proportional to the distorting force, the dipole moment being a product of the multiplication of the values of the charges by their separation.

Unfortunately for the theory, there has not been any experimental data forthcoming to support the contention that the hair cells contain the necessary molecular lattice, but this is the only positive criticism that can be made at the present time*, and in general the characteristics of the cochlear response are typical of a piezoelectric mechanism.

* The objections which have been raised by Hallpike, Hartridge and Rawdon-Smith (90) depend upon certain basic assumptions which do not appear to be valid and they will be discussed in detail in the experimental section of this thesis.

The Physiological Function of Cochlear Potentials

Once the identity of the audio-electric phenomenon had been defined, the question immediately arose as to what function, if any, the potentials subserve in the mechanism of hearing. Davis (91) pointed out that the magnitude of the cochlear response is sufficient to make reasonable the supposition that the electrical disturbance is responsible for the excitation of the auditory nerve endings. The hypothesis is supported by evidence that nerve impulses are never present in the absence of the electro-acoustic response, and that the curve relating the threshold for the latter to frequency follows the "audibility" curve almost exactly. On the other hand several other factors are difficult to explain by the electrical hypothesis, as for instance, the observation that the bases of the hair cells become electrically positive at the time at which stimulation of the nerve occurs (92).

If cochlear potentials are not responsible for excitation of the neural elements of the inner ear, then it is difficult to see what function they do serve. It is possible, of course, that they are without functional significance and are merely an epiphenomenon -- a by-product of the processes responsible for the conversion of sound-waves into nerve impulses. Whatever the answer to the problem may be, it seems inevitable that the activity of the auditory nerve must be influenced to a certain extent by the large alternating currents which are generated in the cochlea.

The Electrophonic Response

Volta as long ago as 1800 recorded that he heard a bubbling sound "like the boiling of thick soup" when he passed a direct current through his ears. Later, Brenner (93) employed this effect of galvanic current on the ear as a device to evaluate the physiological state of the auditory nerve. Diagnosis was made according to certain principles formulated by Brenner as follows: "... the auditory nerve in health reacts to galvanic current in a regular manner by distinct sounds at and during closure of the negative and at the opening of the positive pole; that these sounds may be whistling, ringing, hissing, singing, humming and rumbling; that they vary in different individuals and are modified by the strength and duration of the current; that the most frequent is whistling, which is clear agreeable and musical, and that any departure from these reactions indicates disease."

Physiologists and otologists alike were apparently so certain that the effect depended upon direct stimulation of the nerve by the applied current, that no further investigation into the mechanism of the phenomenon was made. It also seems to have lost favor as a diagnostic device after some twenty years of use for mention of it disappears from the literature after about 1900. Recently, interest in Brenner's observations was revived by the discovery that when alternating currents are applied to the ear the subject hears a tone corresponding in pitch to the frequency of the stimulus (94). It is obvious that this action of alternating current to produce tonal sensations carries with it many implications for auditory theory. The immediate inference is that the effect is due to

a direct stimulation of the cochlear nerve endings, thus affording new evidence for Rutherford's (27) now discredited "telephone" theory of pitch analysis. This possibility is strongly contra-indicated however, by the physiological properties of nerve fibers in general and by the results of the electrical excitation studies which have been made on the eighth nerve in particular. The latter have not revealed that the auditory nerve possesses any special characteristics rendering its fibers capable of conducting the wide range of frequencies (100 - 14,000 cps) that can be heard with this form of stimulation (95)(96)(97).

The close resemblance between the sensations evoked by A.C. and by sound stimulation led Kahler and Ruf (98) to investigate the possibility that the electrophonic effect might be due to mechanical oscillations generated in some part of the external circuit. Their conclusion that vibrations of the boundary surface between electrode and the adjacent skin are responsible for the auditory sensations has not been confirmed by more rigorous studies. Indeed, in a series of conclusive experiments Gersuni and Volakhov (99)(100) and Perwitzschky (101) have excluded the following possible mechanisms as responsible for the electrophonic effect: (i) vibratory or mechanical forces arising at the electrodes or in any other part of the external circuit; (ii) volume changes in the fluid forming part of the electrode in the external auditory meatus; (iii) mechanical forces acting on the tympanum or ossicles of the middle ear.

The further demonstration that A.C. stimuli cease to be effective when the current is prevented from reaching the inner ear (100) indicates that the electrophonic phenomenon has its origin in some cochlear process.

But while there does not appear to be a reasonable doubt that the tonal sensations elicited by electrical stimuli are a result of the action of the current on certain cochlear structures, there is still considerable controversy regarding the nature of the mechanisms involved.

Zotterman (23) has suggested that the alternating currents exert a direct effect on the receptor (i.e. cellular) elements of Corti's organ, and that the discrimination of frequency is dependent upon the selective responses of electrically tuned elements within the cochlea. It seems improbable that the inner ear could contain a set of electrical resonators -- certainly there is no physical evidence to substantiate the contention. Nevertheless, Arapova and co-workers (97) in support of the hypothesis cite their data showing that the intensity of an alternating current stimulus necessary to produce a tone whose sensation level corresponds to a certain sound pressure, has a magnitude approximately equal to that of the microphonic potential generated in response to such a sound pressure. The logic of the argument is not apparent for it appears that these data equally support the alternative hypothesis originally suggested by Perwitzschky (101) that the electrical energy in some manner sets into vibration those structures of the inner ear which are normally activated by sound waves. The dynamics of the supposed conversion of electrical into mechanical energy has not been adequately defined, but Stevens and others have proposed that the elements responsible for the production of the audio-electric potentials may, like other electro-mechanical transducers, be capable of the reverse process. The problem as to how alternating currents of audio-frequency induce sensations of tone when applied to the ear is the subject of the first experimental section of this thesis.

SECTION II - THE MECHANISM OF THE ELECTROPHONIC EFFECT

I. THE ELECTROPHONIC RESPONSE TO PHASE REVERSAL

Introduction

Because most of the literature directly concerned with the electrophonic phenomenon was briefly discussed in the foregoing introduction, it will be necessary to review in this section only the material which is pertinent to the immediate problem, namely, the nature of the mechanism underlying the electrophonic response.

The first report that stimulation of the ear with alternating currents of audio frequency causes the subject to hear a tone corresponding in pitch to the frequency of the stimulus was made in 1930 by Jellinek and Schreiber (94). Their findings have since been confirmed by Perwitzschky (101), Kupfer (88), Fromm et al. (22)(23), Gersuni et al. (102) and by Stevens (96). Five mechanisms have been suggested as possible causes of the phenomenon: (i) Mechanical vibrations are set up somewhere in the external circuit, e.g., at the aural electrode; (ii) the conducting system of the middle ear is set into vibration and hence activates the cochlear fluid in the usual manner; (iii) the electrical stimulus activates specific cells of Corti's organ, their location depending upon the frequency of the applied current; (iv) the electrical stimulus activates the auditory nerve as a whole, the number of impulses elicited being a function of the A.C. frequency; (v) the electrical energy of the stimulus is transformed into mechanical oscillations by some element or elements within the cochlea.

All but two of the postulated mechanisms have been disqualified by experimental studies. Thus Perwitzschky (101) and Gersuni and his associates (99)(100) have shown that the cause does not lie in any mechanical artefact occurring in the external circuit, such as vibration of the aural electrode or of the liquid which surrounds it. A direct effect of the current on the nerve as a whole cannot be the mechanism responsible, for stimulation of the auditory nerve in the absence of the cochlea produces a sensation of noise irrespective of the stimulus frequency employed (103) (104). Similarly in the normal ear a sensation of noise is perceived when the intensity of the electrical stimulus is increased beyond a certain level and the current presumably escapes to and excites the auditory nerve (96). That the middle ear is not essential to the electrophonic process is evident from the demonstration that sensations of tone may still be elicited in the same way when the apparatus of the middle ear has been lost through disease, immobilized or by-passed by leading the current directly to the round window.

These data dispose of all but two of the original five possible mechanisms by which alternating current stimuli could induce sensations of sound when applied to the ear: Thus the alternating current must either excite a selective region of the neuroepithelium directly or it must be converted into mechanical energy and thence activate the sensory cells in the same manner as do sound waves. The experiment now to be described was designed in an attempt to determine which of these two mechanisms is the one responsible for the electrophonic phenomenon; but before proceeding with a description of this experiment, a digression should be made to clarify one factor which otherwise would cause confusion. Evidence has been obtained

by Stevens and his co-workers (105)(106) that at certain frequencies the tympanic membrane in some subjects is capable of acting as an electro-mechanical transducer. The mechanism in this case is an electrostatic effect occurring between the eardrum and the promontorium of the opposite wall of the tympanic cavity. This type of mechanism does not reproduce the frequency of the stimulus cycle for cycle, but obeys a 'square law'; hence, the subject hears a tone whose pitch is an octave higher than the frequency of the applied current (105)(107). Since this process has little or no significance for auditory dynamics as a whole, the writer proposes that the name electrophonic effect be limited to that mechanism only, whereby tonal sensations are produced by the action of the alternating current on the auditory end organ. That this mechanism was the one, and the only one, under investigation in the following experiments is illustrated by these factors: (i) The subjects at the frequencies tested always reported an exact correspondence between stimulus frequency and the pitch of the perceived tone -- a second or higher harmonic was either absent or of small magnitude; (ii) application of a polarizing current to the ear failed to alter the character of the response*; (iii) increasing the pressure on the eardrum through application to it of a high column of fluid did not diminish the loudness of the sound; (iv) subjects in whom the eardrum was unilaterally destroyed reported that the stimulus evoked the same type of tonal sensations whether applied to the normal or to the affected ear.

* When the tonal sensations arise as a result of electro-mechanical transduction at the eardrum, application of a polarizing current to the ear causes the subject to hear the fundamental rather than the second harmonic of the stimulating frequency (107).

Experimental Rationale: The audible effect of an abrupt reversal in the phase of a pure musical tone has been described by Hartridge (108) (109) and by Hartshorn (110) as a sudden discontinuity in the sound similar to the beat produced by two tones slightly out of unison. This effect Hartridge (111) believed to be due to a silent period produced in the auditory nerve and tracts by the action of the phase reversal upon the responding structures within the cochlea. He assumed that the basilar membrane behaves as a sharply tuned resonator and that as a result the abrupt phase reversal causes the vibrations of that element to die down to zero before building up in the new phase. The hypothesis is an attractive one, but its basic assumption that the basilar membrane is undamped is questionable in the light of the considerable evidence to the contrary. Moreover, an alternative and equally satisfactory explanation of the effect is possible: To reverse the phase of an applied harmonic force abruptly without introducing transients into the system activated is a physical impossibility -- thus the brief discontinuity hear in the sound may be a "line busy" effect brough about through a refractoriness of the auditory nerve fibers initiated by the action of such transients.

The question as to which of these mechanisms is the true one, although of interest for auditory theory, is irrelevant to the rationale of the experiment to be described. The important factor is that in either case the subjective phenomenon is dependent upon the mechanical events taking place in the inner ear. It is argued that if the electrophonic effect is a result of electro-mechanical transduction in the cochlea, then the audible effect of suddenly reversing the phase of an alternating

current stimulus should be essentially similar to that produced by a phase reversal in a tone activating the ear in the usual manner. Conversely, if mechanical forces are not involved in the process whereby alternating currents elicit sensations of sound, then a rapid phase change of 180° should be followed with considerable fidelity, for a direct action of the electrical current on the hair cells, whether it be to release a chemical mediator or to initiate some physical change within the cells themselves, will not be accompanied by transients nor characterized by anything analagous to mechanical resonance.

Experimental

Apparatus: Alternating current from a sine wave audio-oscillator (112) was fed through the simple bridge type phase changing device shown in Fig. 1A.

The variable resistance R_1 is large with respect to r_1 and r_2. Thus the input voltage V_1 is practically independent of the impedance changes due to variation of the value of R_1. The impedance of the grid input amplifier can be considered as infinite when compared with the resistances of the network. A vector analysis of the circuit is shown in Fig. 1B.

The input current I_2 flowing through C and R_1 gives rise to the voltage drops I_2X_c and I_2R_1 which are at right angles to one another. The output voltage V_2 is then the vector voltage appearing between the junction of I_2R_1 and I_2X_c and the junction of I_1r_1 and I_1r_2.

If the variable resistance R_2 is adjusted so that $r_1 = r_2$ then V_2 will be equal to $V_1/2$.

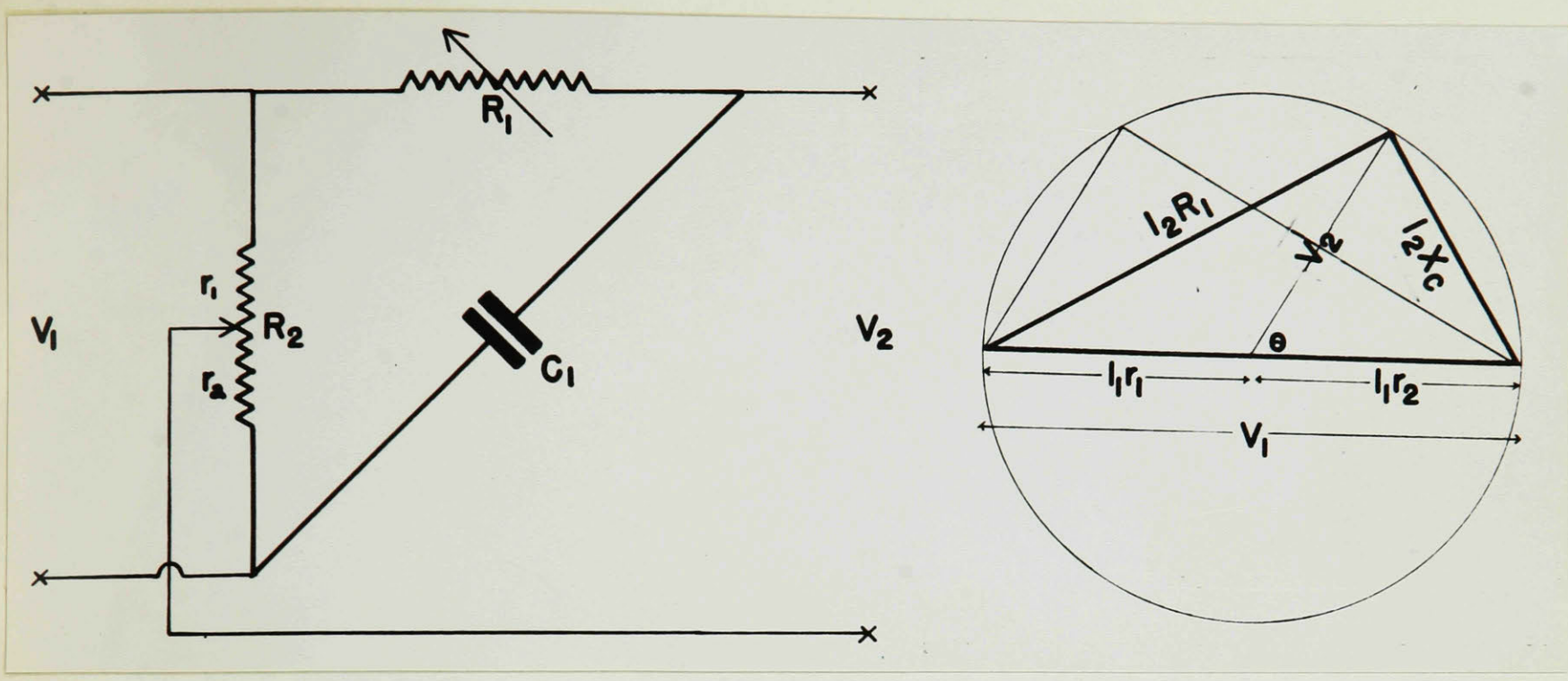

Figure 1A. Circuit diagram and vector analysis of the phase-changing bridge.

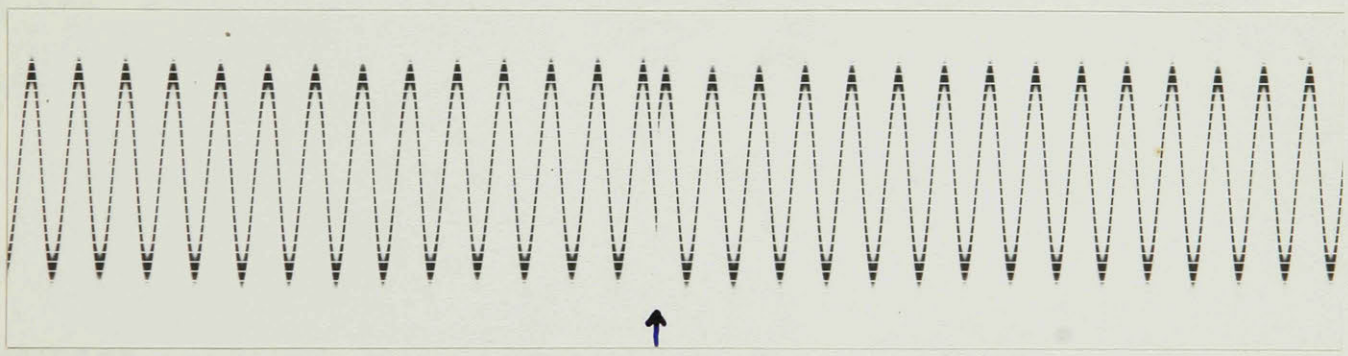

Figure 1B. Electrical output of the bridge recorded with a critically damped loop-type galvanometer. An instantaneous phase reversal was effected at the point marked by the arrow.

When R_1 = 0 the input impedance is R_2 shunted by the capacitive reactance X_c, and when R_1 is maximum the input impedance is very nearly R_2 shunted by R_1. As C is constant the point P will describe a semi-circle having the radius $V_1/2$ as the value of R_1 is varied from zero to its maximum.

The output of the bridge was led to the grid input of a resistance-capacity coupled amplifer and the high impedance output of the latter applied to the subject by means of electrodes placed in the external auditory meatus and neck muscles.

Procedure: Three human subjects were employed. The external auditory canal was cleared of wax and filled with a normal salt solution. Into the fluid was placed a short brass electrode which projected from a plaster mould fitting tightly into the opening of the meatus. An indifferent electrode, a hypodermic needle, was inserted subcutaneously into the neck or forearm of the subject.

When the subject reported that he heard the tone, a short period was allowed to elapse so as to familiarize him with the sound; the the phase was quickly reversed without his knowledge. Each subject was tested separately and each was instructed to report exactly what he heard; no indication of what he might expect to hear was given. Four frequencies, 600, 800, 1,000 and 1,200 cps were presented to each subject and a change of phase produced at each frequency -- several trials were made for each tone.

Results

At all frequencies, and at each trial, the subjects experienced

the same phenomenon; typical of their reactions to the phase change are the statements which follow:

S_1 reported that he heard a sudden brief period of silence followed by a "surge" of the sound as it returned.

S_2 said that he heard "a sudden stop in the sound and then it rushed back."

S_3 reported "a sudden break in the tone and then it came back louder."

In order to verify these impressions, each subject was asked to compare what he had heard with an abrupt phase change produced in a headphone. All three reported that the effect was essentially the same except for the presence of a click which is always heard with the headphone and which is due to transients arising at the diaphram.

Discussion

The rationale upon which this experiment is based is by no means unassailable. If the action of the electrical stimulus to produce tonal sensations depended upon a direct effect of the current upon localized cells of Corti's organ it would be necessary for the inner ear to contain a series of tuned impedance networks to direct the alternating current according to its frequency to corresponding regions of the neuroepithelium. Now if these hypothetical networks were sharply tuned, then applying Hartridge's theory of the phase-beat, it may be claimed that the discontinuity heard when the phase of an electrical stimulus is abruptly reversed is a result of a momentary arrest of current flow brought about by the

opposition of the persisting counter-force in the circuit to the new out-of-phase applied force. The conditions then would be analagous to those of a lightly damped mechanical system at resonance, but there is no morphological evidence for the presence of electrically tuned elements within the cochlea, and furthermore, the experiments which are next to be described when considered in relation to the data discussed here provide final evidence that such a mechanism is not involved in hearing by electrical stimulation.

II. THE INTERACTION OF ELECTRICAL AND MECHANICAL STIMULI

Introduction

Beats produced by the interaction of an electrical stimulus and an air-borne sound have been observed by Barany (113), Gersuni and Volakhov (95), and by Jones et al. (106). Each one of these authors commented on the possibility that such an interaction could be construed as evidence favoring the movement hypothesis of the electrophonic effect, but none of them made a special study of the phenomenon and all fail to point out that the interference of two harmonic motions as illustrated by the pattern of cancellation and reinforcement known as beats, cannot occur unless these motions involve the same process and the same system. If the two applied forces activated separate and distinct receptor elements, a pattern of interference could not arise; nor could two different forms of energy interact in this manner. It is inconceivable, for example, that the observed beats could arise as a result of a reciprocal action of mechanical and electrical energy; either two mechanical or two electrical forces must be responsible.

The simple demonstration that beats may be heard when an electrical and an air-borne stimulus are applied to the ear is not in itself proof that the alternating current is transformed into mechanical oscillations in the cochlea, for it is contingent that an interaction between the applied current and the cochlear microphonic potentials generated by the sound could result in the production of beats. In this event, however, it would be necessary for cochlear microphonics to be essential to the process whereby

impulses in the auditory nerve are initiated, and for a transient interference with their action to cause a momentary remission of nerve impulse formation.

The first experiment described hereunder was undertaken in the hope that further study of the beats observed with coincident A.C. and sound stimulation would provide some clue as to their nature.

Experimental

Apparatus: Twin oscillators of the resistance-capacity type used in the first experiment were employed. The electrodes originally used were found to be unsatisfactory and a new and better system was adopted. The aural electrode consisted of a length of heavy silver wire enclosed in rubber tubing which projected about two millimeters beyond the end of the metal, thus preventing the latter from making contact with the skin of the meatus. The external auditory meatus was filled with warm Ringer solution and the aural electrode placed therein. An indifferent electrode, a small silver plate, was attached to the forearm, the skin having been previously prepared with electrode jelly of the type usually employed in electrocardiography.

Electrical stimuli were applied to the ear from one oscillator by means of the electrodes just described. In addition, the output of the second oscillator was coupled through an amplifier to the voice coil of an eight-inch permanent magnet dynamic speaker. The latter was attached to the end of a flexible steel shaft in such a manner that it could be adjusted to hang directly over the subject's head about one inch above the pinna.

The hearing loss for air-borne stimuli resulting from the presence of the fluid mass in the auditory meatus was found to be between 30 and 40 db at 500 cps. Because it was necessary to employ therefore, sounds of relatively high intensity, there was a constant possibility that stimulation of the contralateral ear would occur. To avoid this a masking sound from a vacuum tube noise generator was conducted to this ear through a rubber-cushioned headphone held tightly over the meatus. The masking sound had a noise level with respect to the threshold of the opposite ear of approximately 10 db and was of the random or thermal noise type employed as standard practise in clinical audiometry.

Procedure and Results: When a test was to be made the oscillator supplying the electrical stimulus was adjusted to a given frequency and the subject allowed time to accustom himself to the sound. An air-borne tone differing in frequency from the A.C. stimulus by several cycles was then conducted to the same ear.

In response to this dual stimulation, all subjects reported that they heard beats, the frequency of which corresponded with the difference in frequency of the two sources.

The phenomenon known as negative masking was also reproducable with this type of dual stimulation. Thus two stimuli of slightly different frequency, each of which was below threshold when applied singly, produced audible beats when sounded together.

Finally the two oscillators supplying the stimuli were adjusted so that their outputs were of identical frequency, phase and loudness.*

* Sensation level.

The frequency of one of the two stimuli was then either decreased or increased slowly. As the difference between the two frequencies was gradually increased from zero, three successive changes in the resultant sensation were observed. First, the sensation was of slow rhythmic surges in the loudness of the perceived sound, then this gradually changed to a series of rapid beats, and finally to a rough but seemingly continuous tone.

Each of these stages may similarly be distinguished when the stimuli are both mechanical. Thus the classical description (114) of the succession of psychological qualities which are experienced when the beats are produced by the interaction of two air-borne sounds equally applies to the case where the beats arise through the interaction of an electrical and a mechanical stimulus.

Discussion

It will be recalled that in the first experiment of this series it was found that the electrophonic response to a phase reversal is characterized by an apparent discontinuity in the sound. It was pointed out that this silent period could be explained by assuming that the ear contained a set of electrically tuned resonators whose damping factor is so low that they are incapable of following an abrupt phase reversal faithfully. Now in order for the beats heard with dual sound and A.C. stimulation to arise through the interaction of the electrical stimulus with the microphonic potentials generated by the sound, the current would necessarily have to be the agent responsible for the initiation of impulses in the

auditory nerve.* For this to be so, the ear must contain a series of electrical impedance networks to direct the applied current to the zone of the neuroepithelium where the nerve fibers responsible for the mediation of the particular frequency of the stimulus are located. But as the first experiment demonstrated, such networks, if they exist at all, must be so sharply tuned as to be incapable of following a rapid phase change of 180°. Such a highly resonant system would tend to obey Ohm's acoustical law and therefore analyse an impinging wave into its component frequencies regardless of their phase relations. But beats are heard when two tones of nearly the same frequency are delivered to the ear because the two frequencies force into vibration overlapping areas of the basilar membrane.

If the basilar membrane were sharply tuned, a pattern of interference and the resultant alternating periods of cancellation and reinforcement could not eventuate, for as mentioned elsewhere, interaction of two harmonic motions cannot occur unless both forces actuate the same system. When an element is sharply tuned, forced activation by off-resonant vibrations can take place but only at relatively high intensities. Therefore, the fact that the succession of psychological qualities distinguished in the perceived sound when the difference between the frequencies of an electrical and a mechanical stimulus is gradually increased from zero

* Otherwise interference with their action would not be accompanied by a resulting psychological event. Evidence that the microphonic potentials are not the physiological agent of stimulation of the auditory nerve will be presented in a subsequent section of this thesis.

is similar to that distinguished when this procedure is carried out with two mechanical stimuli seems to indicate that the same mechanism is responsible for the production of the sensations in both instances. Furthermore, apart from the negatory data which these experiments afford, there is also a very great practical contradiction to the tuned circuit theory of the electrophonic effect. In order to achieve a resonant circuit at frequencies as low as 150 cps, the capacitive and inductive elements or their equivalents must of necessity be of very large physical magnitude. Thus, unless the cellular analogues of capacitive and inductive reactance have characteristics which are not found in any other known type of physical system, it is impossible that the required series of electrical resonators could exist within the narrow confines of the inner ear.

III. MUTUAL CANCELLATION OF ELECTRICAL AND MECHANICAL STIMULI

Introduction

Taking into consideration the fact that beats may sometimes be heard when two air-borne tones of slightly different frequency are applied to, and restricted to contralateral ears, it may be suggested that the interference of electrical and mechanical stimuli may arise in nervous centers after both have been converted into nerve impulses. In reply to this possible suggestion it is pertinent to cite the facts that synchronization of impulses in the auditory pathways, a circumstance essential to the phenomenon of nervous interference, never exceeds 1,200 cps, and that binaural beats cannot be heard when the stimulating frequencies are higher than 800 cps. The possibility then that the beats are of central origin is quite remote and the experiment to be described clearly contraindicates such a process and provides further evidence for the movement theory of the electrophonic effect.

Experimental

The apparatus was arranged in the manner indicated in Fig. 2. The oscillators, amplifiers and phase bridge have already been described.

The Lissajous figure produced on the screen of the oscilloscope by the interaction of the voltages applied to the horizontal and vertical plates provided a direct means of determining the phase relations of the two stimuli.

A sinusoidal current of fixed frequency was first applied to the

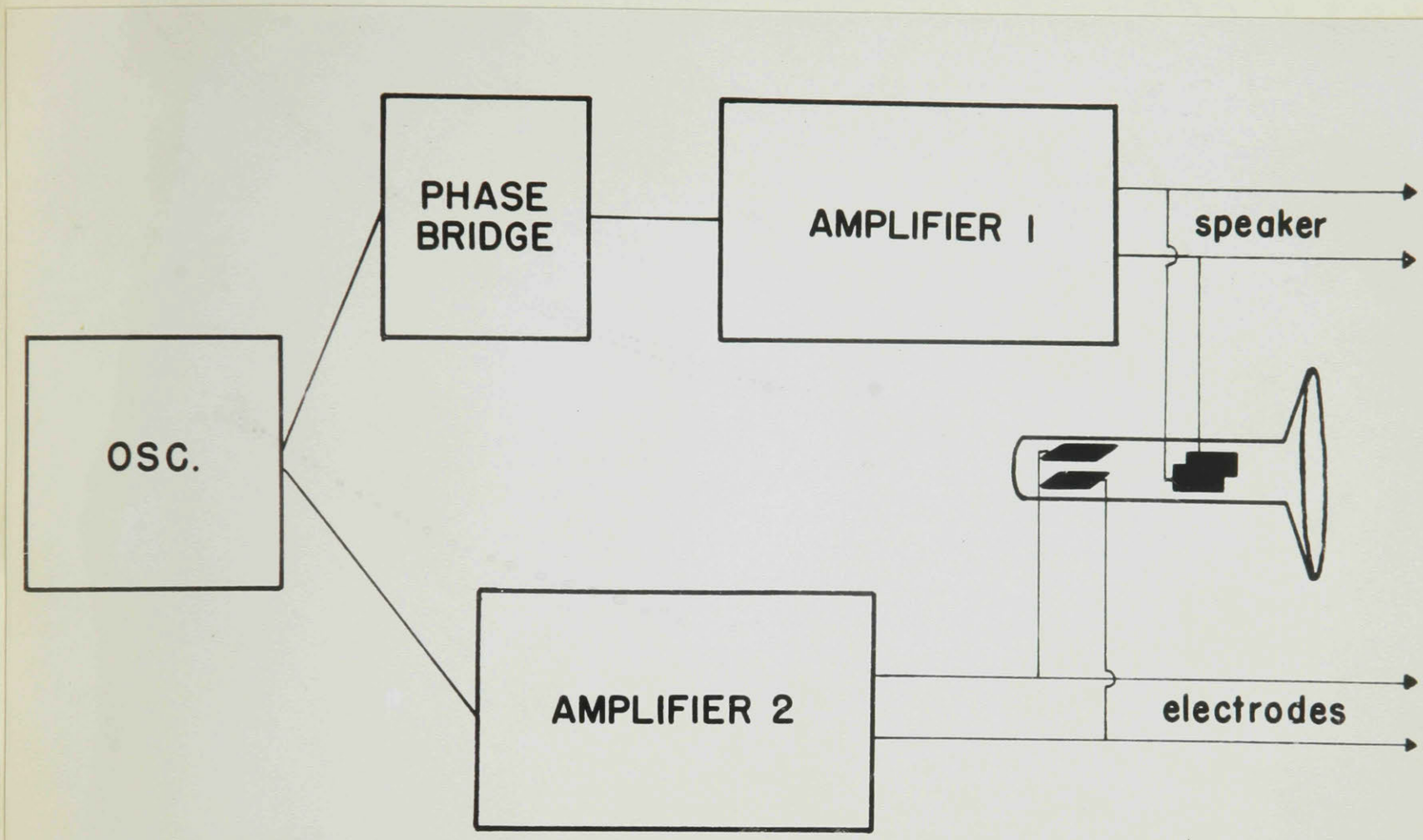

Figure 2. The apparatus arrangement for Experiment 3. The Lissajous figure produced on the screen of the oscilloscope by the interaction of the voltages applied to the horizontal and vertical plates provided a direct means of determining the phase relations of the two stimuli.

ear by way of the electrodes arranged for the purpose. After a short period during which the subject was given time to accustom himself to the tone so produced, an air-borne sound of similar frequency and loudness and in phase with the electrical stimulus was applied to the ipsilateral ear via the loud speaker.

An increase in the intensity of the sensation was observed by all subjects on presentation of the second stimulus. When, however, the two stimuli were of identical frequency and loudness but differed in phase by 180^{o}, each subject reported that he no longer heard any sound. Increase or decrease in the intensity of either stimulus, however, resulted in the return of the tone.

Discussion

When two harmonic motions of similar frequency and moving in the same direction set up travelling waves in a system, the resultant wave is simply the sum of the amplitudes of the separate waves. If these waves are in phase then the resultant wave will be greater than that of either of the activating waves. On the other hand, if there is any difference in phase then the resultant wave will be smaller than the larger of the two applied waves.

It follows that two harmonic forces of similar frequency, direction and magnitude will completely cancel one another if they differ in phase by 180^{o}. Such a pattern of interference cannot however be produced unless the alternating forces actuate the same system.

As the observed variations in the degree of cancellation with

changes in phase or intensity cannot be explained on a neural basis, it must be concluded that the electrophonic effect involves a transduction of electrical into mechanical energy, and that this energy activates the basilar membrane in the usual manner.

IV. RELATION OF THE ELECTROPHONIC EFFECT TO COCHLEAR MICROPHONIC POTENTIALS

Introduction

Reference to the review of the literature at the beginning of this thesis will reveal that the experimental evidence strongly favors the view that the cochlear microphonic potentials are generated by the hair cells of Corti's organ. Of the possible mechanisms by which such potentials could be generated by these cells, the piezoelectric effect seems to fit the facts best. The demonstration that the auditory sensations elicited by alternating current depend upon a transformation of the electrical stimulus into mechanical oscillations in the cochlea accords well with the latter hypothesis, for a characteristic of the piezoelectric phenomenon is its reversibility. Thus a quartz crystal or any other piezoelectric element when subjected to mechanical torsion develops a difference of potential along its structural axes, and conversely will undergo mechanical torsion when placed in an electric field. There is, however, one set of experimental data which seems to spoil this theoretical picture by contradicting the association of aural microphonics and the hair cells of Corti's organ. Hallpike and his associates (90)(115)(116) have found that whereas the response of the auditory tracts to an abrupt phase reversal in a continuous tone is a "well-marked silent period. the cochlear response follows the phase change with considerable fidelity. Because the potentials recorded from the cochlea follow the phase change and those recorded from the nerve pathways do not, the authors conclude

that the element responsible for the initiation of auditory nerve impulses (i.e. the basilar membrane and its associated neuroepithelium) cannot be the same structure as that responsible for the generation of the microphonic potentials.

The question is, does this difference, as Hallpike and his associates claim, prove incontrovertably that the structure from which the cochlear potentials arise is not the same as that from which the nerve impulses are initiated, or is it merely an expression of the fact that the two types of potential differ markedly from each other in character and in the mechanism by which they are generated. Obviously either possibility could be correct.

An abrupt phase change of 180° in a continuous tone is mathematically equivalent to initiating in the opposite direction a train of waves of similar frequency but twice the amplitude of the original tone.* Hence, Hallpike et al. argue, the silent period observed in the auditory tracts results from a transient arrest of the resonant structures of the inner ear brought about by the opposition of the new force to the after-swings due to resonance. The aural microphonics on the other hand must, they calim, be produced by an element which is critically damped, for they follow the phase change without evidence of any break in their continuity.

In discussing the results of the first experiment of this section it was remarked that a reasonable interpretation of the phase change beat can be made without postulating the presence of a sharply resonant element

* The theoretical basis for this statement will be discussed at the close of this section.

within the inner ear. An experiment was devised therefore to test the validity of the assumption of Hallpike and his associates that the phase change beat is a consequence of the resonant properties of the basilar membrane.

Experimental*

Procedure and Results: Two tones, A and B, approximately equal in frequency were presented simultaneously to the same ear. The oscillators supplying the tones were then adjusted so that the frequency difference was either (i) so great that their interference pattern produced a sensation of roughness in the perceived sound or (ii) so small that the periodic fluctuations could not possibly be confused with the phase change beat. The phase of one of the two stimuli, e.g. A, was then abruptly reversed.

Now if the basilar membrane is a highly resonant structure, that part of the membrane which is resonating in response to A should undergo a temporary arrest and the sensation of this tone should mementarily cease. Conversely, the vibration of the adjacent areas of the membrane which are just off resonance with respect to tone A should be facilitated by the phase reversal and hence tone B should actually increase in loudness. Apparently this does not occur for not one of the subjects tested reported such an experience and all agreed they were still able to distinguish the phase change beat; this in spite of the fact that they were being subjected to two distinct and simultaneously presented sounds.

* The theory of this experiment will be presented in a mathematical analysis at the conclusion of this section.

Discussion

The mathematical and theoretical considerations on which this experiment is based are quite complex, but they can be illustrated adequately by a simple practical demonstration: If two vibration galvanometers are tuned so that one is resonant and the other just off resonance to an applied alternating current of fixed frequency, a sharp phase reversal causes the oscillations of the string of the resonant instrument to diminish almost to zero and then build up to normal size in the opposite phase; the oscillations of the non-resonant string, on the contrary, do not diminish but are temporarily incremented by the change.

If the basilar membrane were a highly tuned element as Hallpike et al. claim to show, then it should be subject to analogous processes: thus the vibrations of that part of the membrane resonant to the phase-reversed tone should momentarily die down to zero while the vibrations of the adjacent parts of the membrane which are off resonance should be increased in magnitude. This in turn should result in a decrease in the loudness of one tone and a corresponding increase in the loudness of the other.

Theoretical Analysis

Hartridge (108) was the first investigator to conceive the ingenious idea of employing the subjective response to a phase change of 180° in a continuous musical tone as a measure of the resonant properties of the responding structures of the inner ear. His premise was that if the basilar membrane is sharply tuned as demanded by classical theory, an abrupt

phase reversal should be heard as a momentary discontinuity in the sound due to a transient interruption in the vibrations of that element brought about as a result of the opposition of the force in the new phase to the after-swings due to resonance. But this argument fails to take into consideration the fact that the basilar membrane is not a single resonator but a series of resonators, and that the off-tune areas of the membrane on either side of the zone resonant to the stimulating frequency must also be affected by the phase change. It can be shown that the oscillations of these areas will be augmented at the time of the phase reversal and that this augmentation is greatest when tuning is sharpest (damping factor small), and least when tuning is dull. Accordingly, a silent period would not be a necessary consequence of a sudden reversal of phase in a continuous tone even if the responding elements were completely undamped, for while it is true that the vibrations of the 'in tune' area of the basilar would undergo a transient diminution, a concomitant and almost proportional increase in the vibrations of the adjacent off-resonant areas would also occur. Thus the subjective result of the phase change should be that the sensation of the stimulating tone would be replaced momentarily by the sensation produced by the augmentation of the vibrations of the adjacent zones of the neuroepithelium. The explanation of the apparent transient interruption which is often heard when the phase of a continuous musical tone is suddenly changed by π must therefore be sought elsewhere, perhaps in some nervous process.

The objection to Hartridge's premise does not lie in the fact that he considers the basilar membrane a resonant structure -- some form of tuning is necessary in order for the now accepted place theory of pitch

analysis to be valid - but with his insistence that the subjective phase change beat is proof that the membrane is only very lightly damped. This point may be illustrated by an appropriate set of differential equations which describe the events which must take place in a structure composed of an 'infinite' series of resonators when it is subjected to a sudden reversal of phase in a continuous sinusoidal force of fixed frequency.

Let the external sinusoidal force acting on the system be represented by $F\cos pt$ where F is the maximum value of the force of frequency $p/2\pi$. The equation of motion of the responding element of mass m is given by:

$$m\frac{d^2x}{dt^2} + r\frac{dx}{dt} + sx = F\cos pt \qquad (1)$$

where r is the resistance per unit velocity and s the restoring force per unit displacement. Writing $s/m = n^2$, $F/m = f$ and $r/2m = k$ equation (1) becomes:

$$\frac{d^2x}{dt^2} + 2k\frac{dx}{dt} + n^2x = f\cos pt \qquad (2)$$

Assuming $x = \cos(pt-\varepsilon)$ and writing $\cos pt = \cos\{\varepsilon+(pt-\varepsilon)\}$, substitution in (2) yields: $a(n^2-p^2)\cos(pt-\varepsilon) - 2kpa\sin(pt-\varepsilon) = f\cos\varepsilon.\cos(pt-\varepsilon) - f\sin\varepsilon.\sin(pt-\varepsilon)$ (3)

As equation (3) must be true for all values of t , the coefficients of $\sin(pt-\varepsilon)$ and of $\cos(pt-\varepsilon)$ may be equated to obtain:

$$a(n^2-p^2) = f\cos\varepsilon$$

$$\text{and } 2kpa = f\sin\varepsilon \tag{4}$$

whence

$$a = \frac{f\sin\varepsilon}{2kp}$$

$$\text{and } \tan\varepsilon = \frac{2kp}{n^2-p^2} \tag{5}*$$

The displacement x is therefore given by

$$x = \frac{f\sin\varepsilon}{2kp}\cos(pt-\varepsilon) \tag{6}$$

and the amplitude a as given in equation (5) may be written

$$a = \frac{f}{\{(n^2-p^2)^2+4k^2-p^2\}^{\frac{1}{2}}} \tag{7}$$

* It should be noted that equation (4) and (5) reveal that $\sin\varepsilon$ is always positive but that $\cos\varepsilon$ may be either positive or megative depending upon whether n is greater or less than p . Therefore the angle lies between 0 and $\pi/2$ when the frequency of the force p is less than the natural frequency n and between $\pi/2$ and π when the forced frequency is greater than n . If the damping is small the lag ε will be nearly equal to 0 or π whichever the case may be. At resonance when $\tan\varepsilon$ becomes infinite $\varepsilon = \pi/2$ the force and the displacement differ in phase by 90° and the force and the velocity are in phase. Thus with no damping, as the frequency of the force passes through resonance, the phase suddenly reverses from 0 to π . When there is damping however, this phase change is less abrupt.

Equation (6) represents the steady state. The transient state will be given by the solution of

$$\frac{d^2x}{dt^2} + 2n\frac{dx}{dt} + n^2x = 0 \qquad (8)$$

The equation of indices is $m^2 + 2km + n^2 = 0$ (9)

$$\therefore m_1 = -k + \sqrt{k^2 - n} \qquad m_2 = -k - \sqrt{k^2 - n^2}$$

which yields

$$x = Ae^{m_1 t} + Be^{m_2 t}$$
$$= Ae^{(-k+\sqrt{k^2-n^2})t} + Be^{(-k-\sqrt{k^2-n^2})t}$$
$$= e^{-kt}(Ae^{\sqrt{k^2-n^2}\,t} + Be^{-\sqrt{n^2-n^2}\,t})$$

If $k < n$ then $\sqrt{k^2 - n^2}$ is imaginary

$\therefore$ Let $\sqrt{k^2 - n} = i\omega$ where ω is real (10)

$$x = e^{-kt}(Ae^{i\omega t} + Be^{i\omega t})$$
$$= e^{-kt}[A(\cos\omega t + i\sin\omega t) + B(\cos\omega t - \sin\omega t)]$$
$$= e^{-kt}[C_1\cos\omega t + C_2\sin\omega t]$$
$$C_1 = A + B \qquad C_2 = i(A - B)$$

Equation (11) may also be put in the form

$$x = \sqrt{C_1^2 + C_2^2}\, e^{-kt}\left[\frac{C_1}{\sqrt{C_1^2+C_2^2}}\cos\omega t + \frac{C_2}{\sqrt{C_1^2+C_2^2}}\sin\omega t\right]$$

Let $\sqrt{C_1^2 + C_2^2} = Y$ and $C_2/C_1 = \tan\gamma$

$$x = Ye^{-kt}[\cos\gamma\cos\omega t + \sin\gamma\sin\omega t]$$
$$= Ye^{-kt}\cos(\omega t - \gamma)$$

Thus the complete solution of the fundamental equation (2) is the sum

of (6) and (11)

$$x = a\cos(pt-\varepsilon) + e^{-kt}[C_1\cos\omega t + C_2\sin\omega t] \qquad (13)$$

At resonance $n = p$, $\varepsilon = \pi/2$ and $\tan\varepsilon = \infty$

$$a = \frac{f}{4kp}$$

$$x = \frac{f}{2kp}\sin kt + e^{-kt}[C_1\cos\omega t + C_2\sin\omega t] \qquad (14)$$

If the resonator start from rest i.e. at $t=0$, $x=0$ and $\frac{dx}{dt}=0$ we may evaluate $C_1 + C_2$

$$0 = \frac{f}{2kp}\sin p0 + e^{-kt}[C_1\cos\omega_0 + C_2\sin\omega_0]$$

$$0 = 0+1\,[C_1+0]$$

$$\therefore C_1 = 0$$

differentiating equation (14)

$$\frac{dx}{dt} = \frac{f}{2k}\cos pt - ke^{-kt}[C_1\cos\omega t + C_2\sin\omega t] + e^{-kt}[-\omega C_1\sin\omega t + \omega C_2\cos\omega t]$$

$$0 = \frac{f}{2k} - k[C_1+0] + \omega C_2$$

$$0 = \frac{f}{2k} + \omega C_2 \qquad C_2 = \frac{-f}{2k\omega}$$

$$x = \frac{f}{2kp}\sin pt - e^{-kt}\left[\frac{-f}{2k\omega}\sin\omega t\right] \qquad (15)$$

$$= \frac{f}{2kp}\left[\frac{\sin kt}{p} - e^{-kt}\frac{\sin\omega t}{\omega}\right]$$

If damping is small

$$k \ll p,\ \omega^2 = n^2 - k^2 \doteq n^2$$

since $n^2 = p^2 \therefore \omega^2 \doteq p^2$

$$x \doteq \frac{f}{2kp}\left[1-e^{-kt}\right]\sin pt. \qquad (16)$$

To determine the response of a resonant mechanical system when the phase of the forcing frequency is changed instantaneously by 180° let it be assumed that the change takes place t_o seconds after the displacement x reaches its maximum. It will also be assumed that the steady state has been reached and the resonator is vibrating in a manner described by the equation: $x = a \cos(pt - \varepsilon)$

The new force will then = $f \cos(pt + pt_o + \pi)$ where t is measured from the time of the phase change.

The new differential equation then will be

$$\frac{d^2x}{dt^2} + 2k\frac{dx}{dt} + n^2 = -f\cos(pt - pt_o) \qquad (17)$$

But now the initial conditions (i.e. at t_o) are those which may be found from the equations

$$x = a\cos(pt_o - \varepsilon) \quad \text{at} \quad t = t_o \qquad (18)$$

and

$$\frac{dx}{dt} = ap\sin(pt_o - \varepsilon) \quad \text{at } t = t_o \qquad (19)$$

From substitution in (13) the solution to (17) is

$$x = -a\cos(pt + pt_o - \varepsilon) + e^{-kt}(C_1\cos\omega t + C_2\sin\omega t) \qquad (20)$$

at t_o (20) becomes equal to (18)

$$x_o = -a\cos(pt_o - \varepsilon) + C_1 = a\cos(pt_o - \varepsilon)$$

$$\therefore C_1 = 2a\cos(pt_o - \varepsilon)$$

* The "t" which appears in equation (17) is not the same as that which appears in (18) and (19) because in (17) t is measured from the instant of the phase change.

Differentiating (18) and putting $t=0$

$$\left(\frac{dx}{dt}\right)_0 = pa\sin(pt_0-\varepsilon) - kC_1 + \omega C_2 = -ap\sin(pt_0-\varepsilon)$$

$$\omega C_2 = -2ap\sin(pt_0-\varepsilon) + kC_1$$

$$\therefore C_2 = \frac{2a}{\omega}\left[k\cos(pt_0-\varepsilon) - p\sin(pt_0-\varepsilon)\right]$$

Substituting for $C_1 + C_2$ in (20)

$$x = -a\cos(pt + pt_0 - \varepsilon) + 2ae^{-kt}\left[\cos(pt_0-\varepsilon)\cos\omega t + \frac{1}{\omega}\left\{k\cos(pt_0-\varepsilon) - p\sin(pt_0-\varepsilon)\right\}\sin\omega t\right] \qquad (21)$$

This expression gives the general form of a wave produced by a damped mechanical system when the phase of the driving force is changed instantaneously by 180°, providing that the system was vibrating before the change with a constant amplitude a, and that the damping was less than critical.

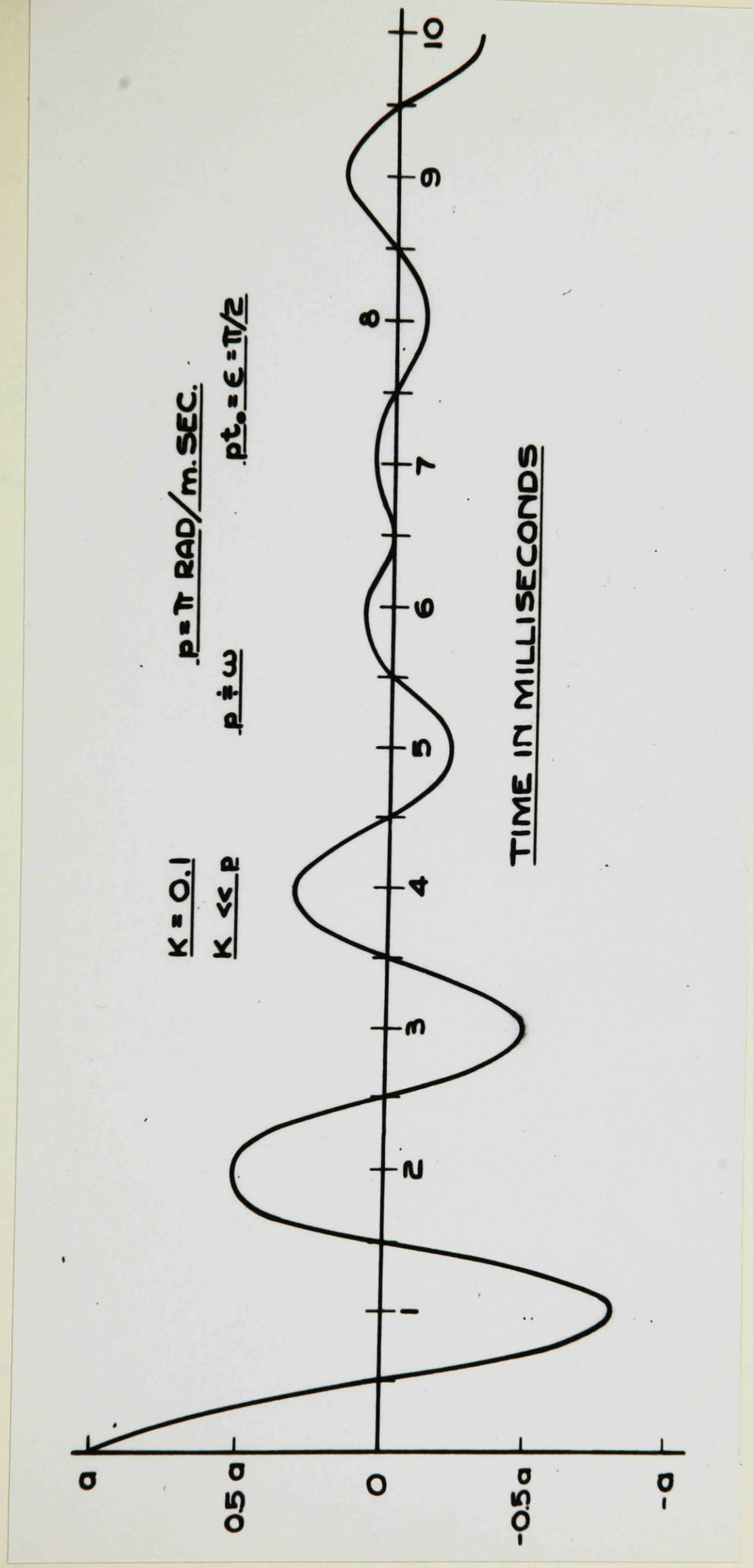

Figure 3. Response at resonance, negligible damping.
(Compare with Figures 4 & 5)

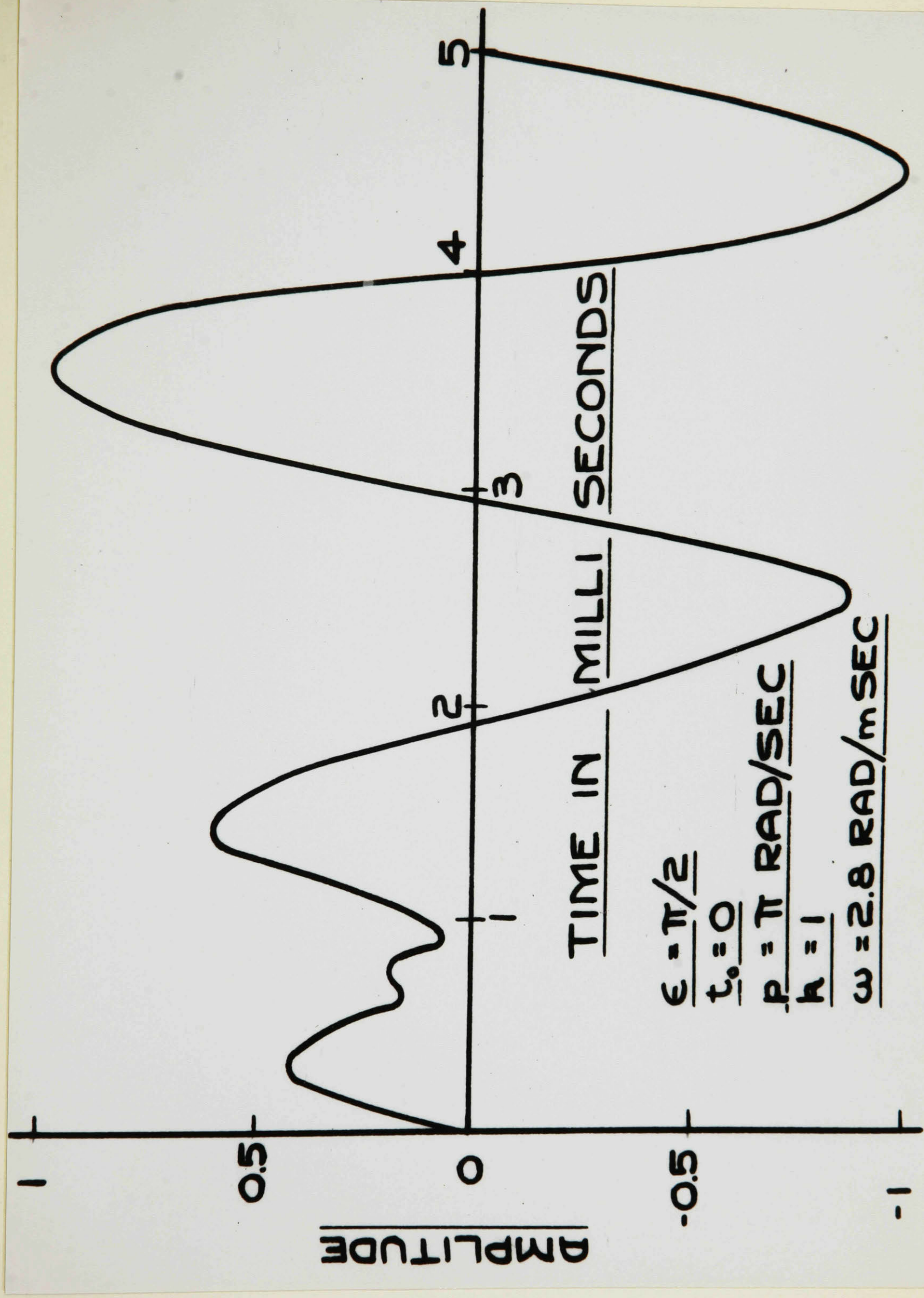

Figure 4. Response at resonance, appreciable damping.

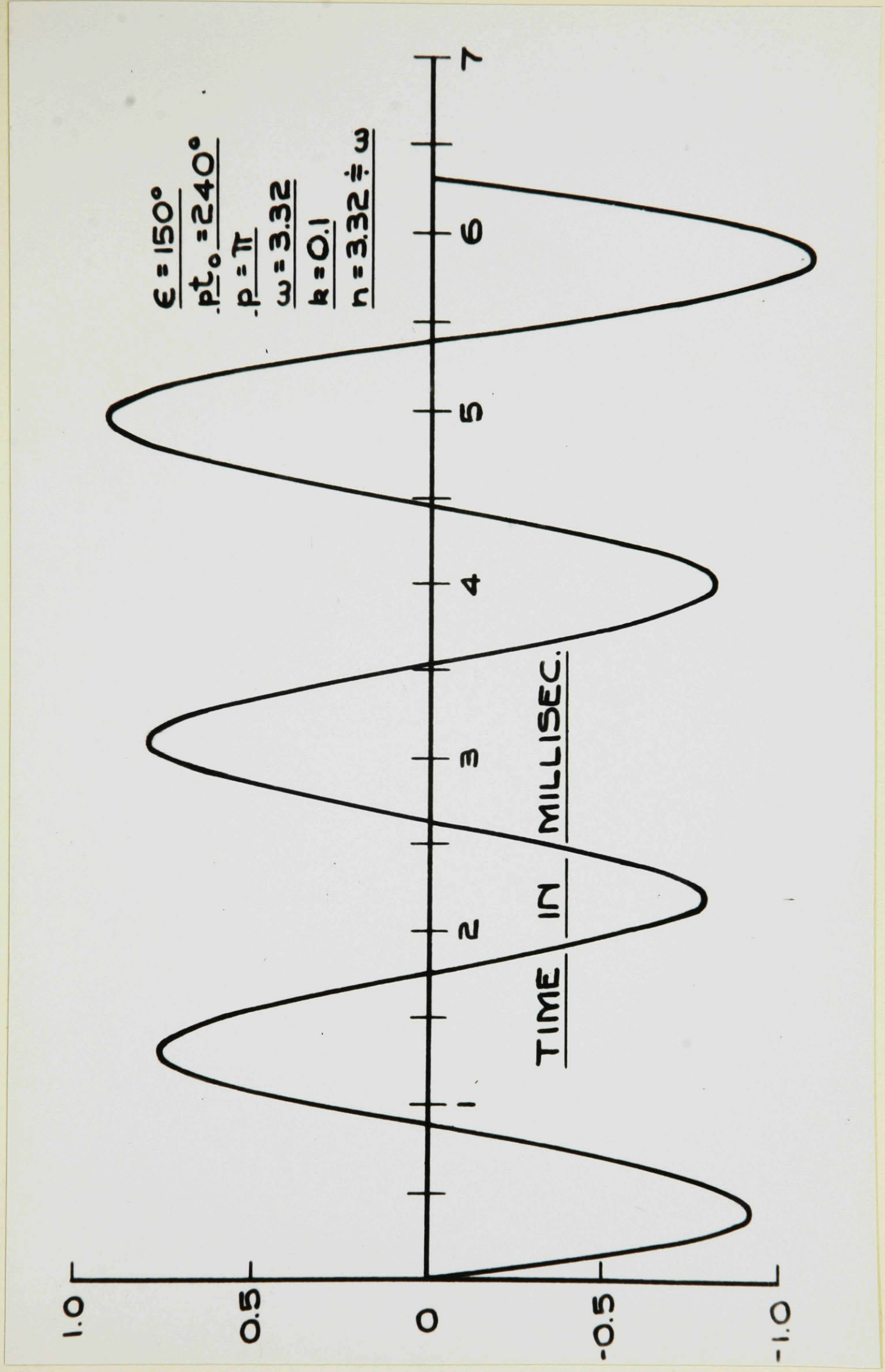

Figure 5. Resonant frequency less than driving frequency, small damping, and phase reversal occurring at point of minimum displacement (x=o).

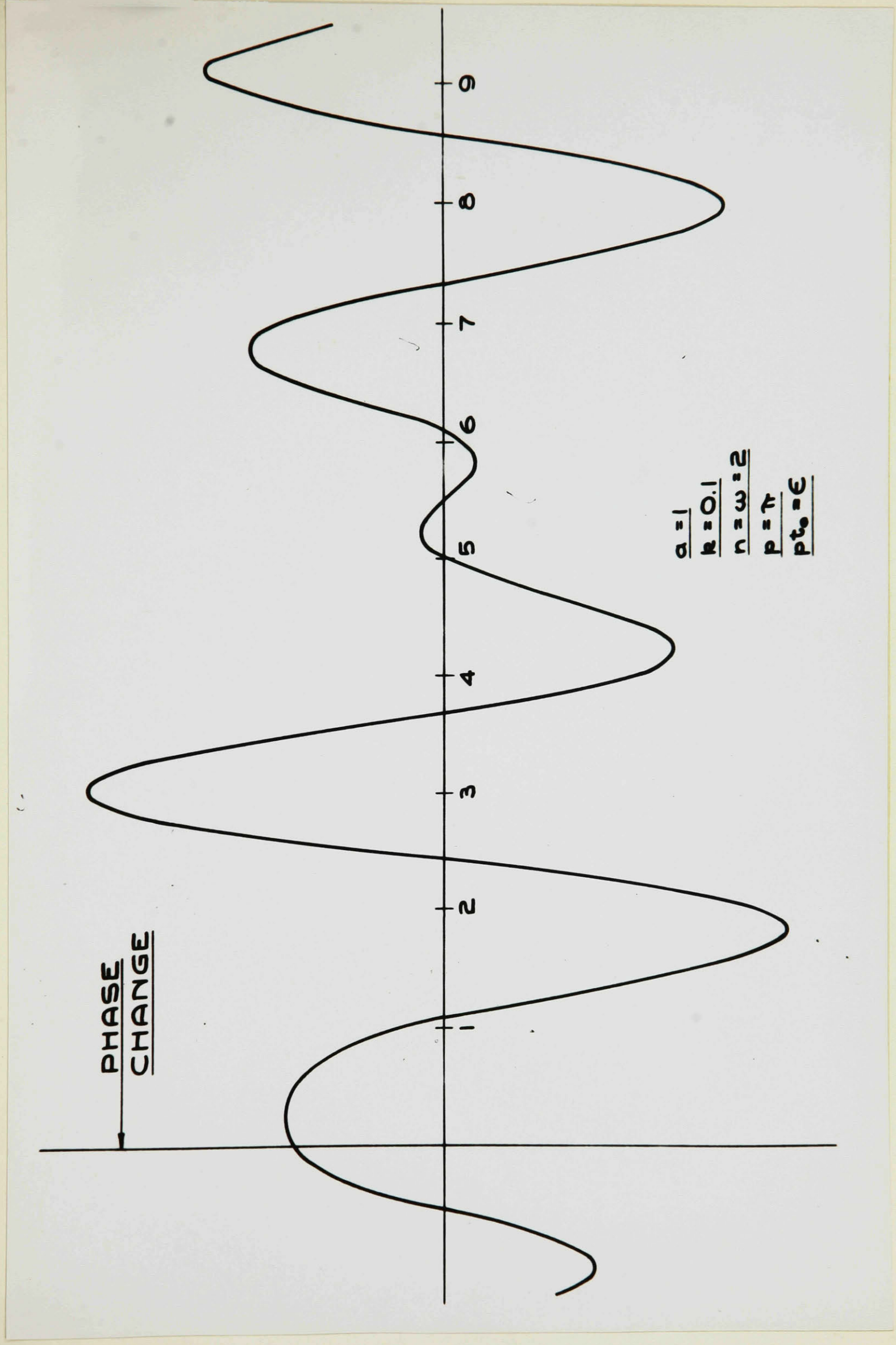

Figure 6. Resonant frequency less than driving frequency, damping small and phase reversal occurring at point of maximal displacement. Case where ω is comparable to p.

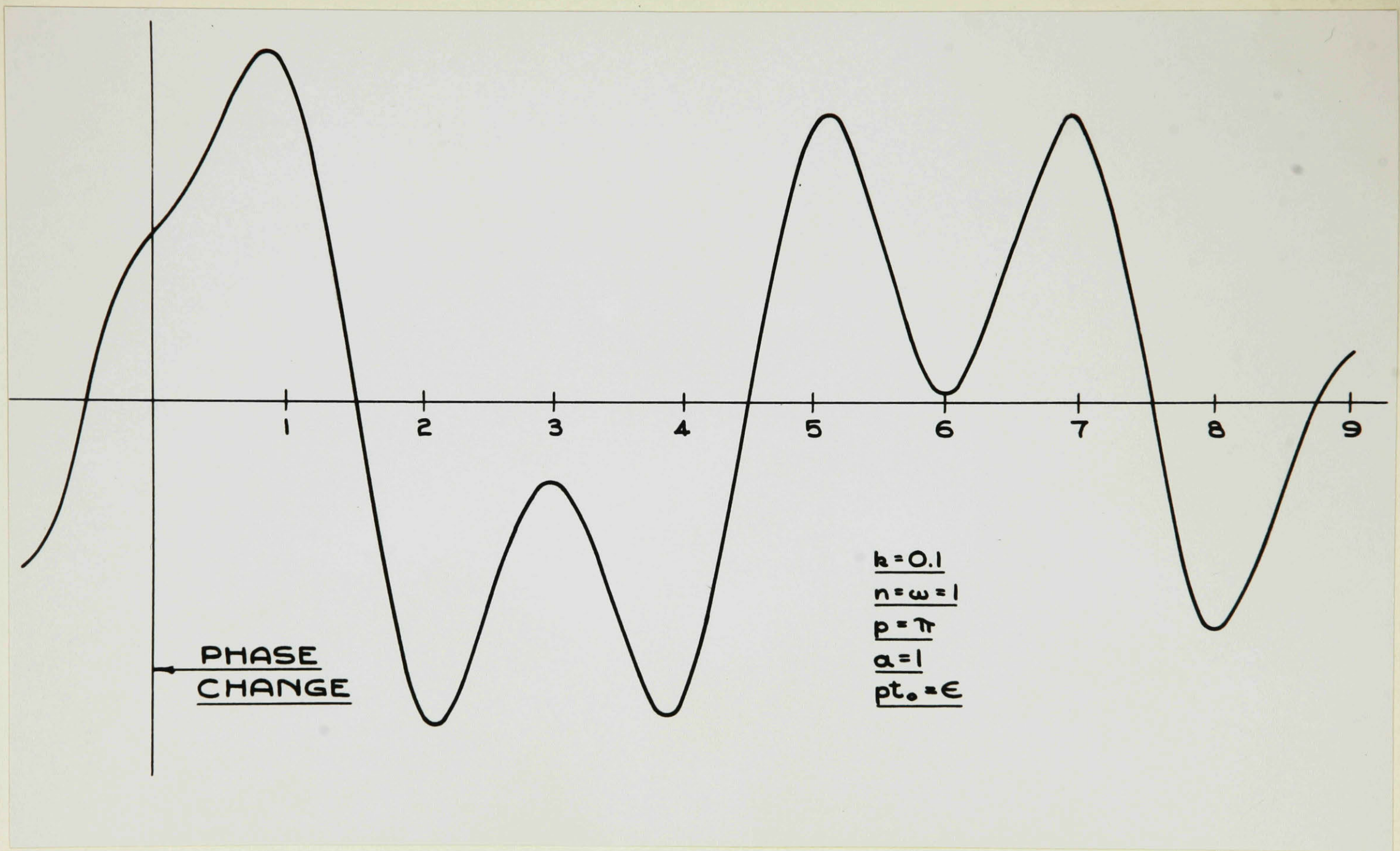

Figure 7. Resonant frequency less than driving frequency, damping small and phase reversal occurring at point of maximal displacement (x=a). Case where ω is much less than p. (Compare with Figure 6)

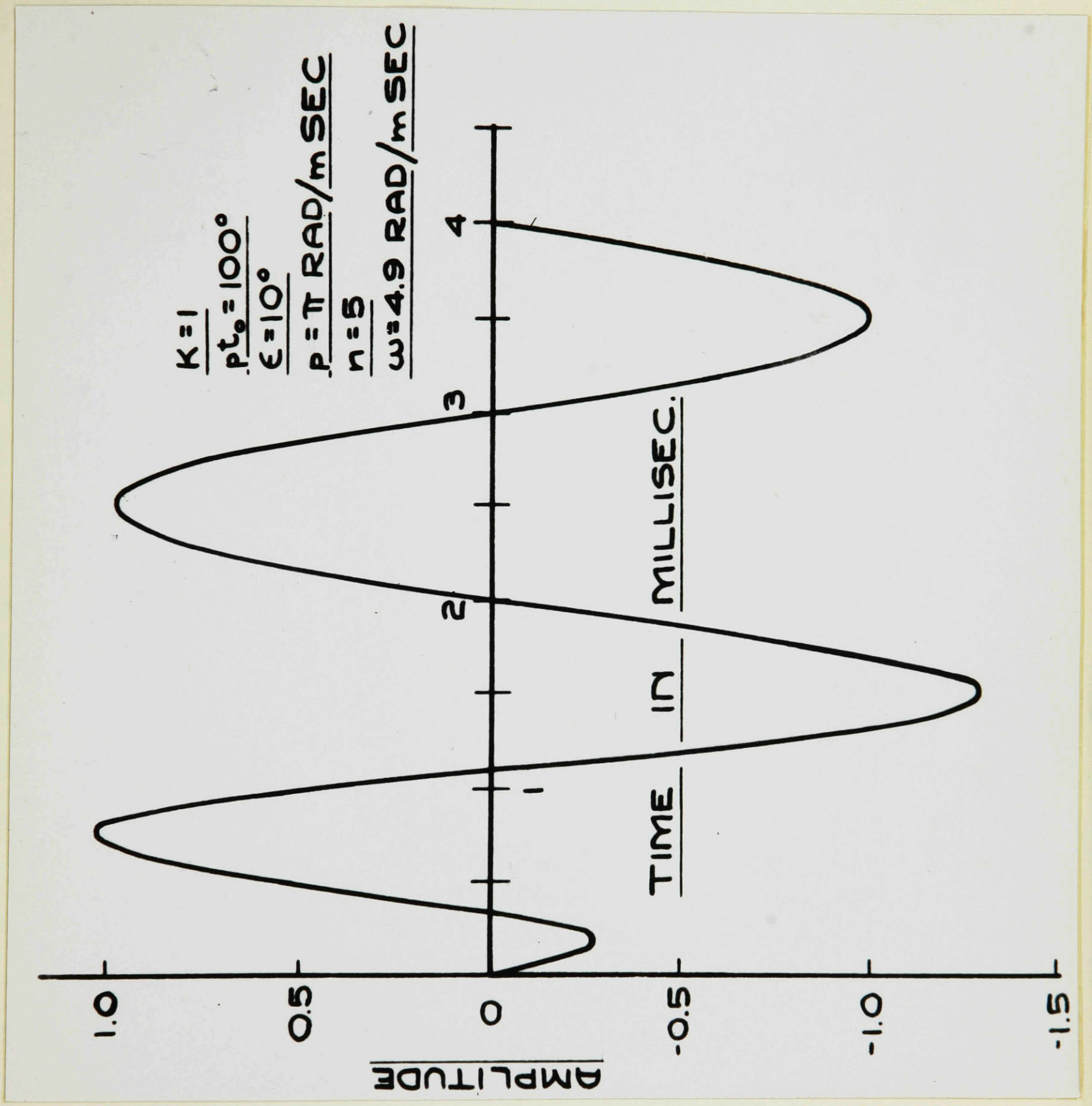

Figure 8. Resonant frequency above driving frequency, appreciable damping. (Compare with Figure 4)

SECTION III - OBSERVATIONS ON CERTAIN PHENOMENA ASSOCIATED WITH THE ELECTRICAL ACTIVITY OF THE COCHLEA, AND OF THE AUDITORY NERVE

I. INTRODUCTION AND PROCEDURE

After the discovery of the Wever-Bray effect in 1930, considerable interest was aroused in the electrical phenomena of the acoustic system, and in succeeding years many papers concerning this subject were published. Apart from the investigations related to the problem of origin and production of the electrical currents (discussed in Section I), the work which has been carried out in the field may be divided into three broad classifications:- (i) Phylogenetic studies; insects (117) (118) (119) (120) (121), amphibia (122) (123) (124) (125), reptiles (125) (126), birds (127), mammals (128) (129) (see also studies on cat, dog, guinea pig, opossum and rat listed in introductory section), and man (130); (ii) Studies concerned with the functional characteristics of the auditory apparatus: eardrum (131) (132), ossicular and bone conduction (131) (133) (134) (135), tympanic muscles (136) (137) (138) (139), and inner ear pressure (145) (146);* (iii) Studies directly concerned with the characteristics of the electrical manifestations themselves (19) (37) (48).

* All of this work has been critically reviewed in three papers by the author of this thesis (147) (148) (149), and only the data pertinent to the problems with which this report is concerned will be rediscussed here.

It is the latter aspect of the problem which has received the least attention, being the object of direct study in only three reports. Because of this, and because all of the work concerned with the fundamental characteristics of the potentials generated by the auditory apparatus has originated in the same laboratory, it was thought that an extensive re-investigation of this particular aspect of auditory physiology would be profitable.

Operative Technic

In order to record simultaneously the potentials arising in the cochlea and in the auditory nerve it was necessary to devise an operation whereby both of these structures could be exposed adequately for the placement of recording electrodes. Dissections of the field showed that the most satisfactory approach would be from the side of the head, and after several different operative procedures had been tried, it was found that the structures in question could be exposed with the least loss of blood when the operation was carried out in the following manner: After the head and neck had been shaved the animals were anesthetized with nembutal, 0.6 c.c. per kilogram of body weight, or in most instances with 3 c.c. per kilogram of chloralose-urethane solution.*

* Two decerebrate preparations were tried but the extra operative procedure appeared to counterbalance any advantage gained by lack of anesthesia, and it was decided to continue the use of either nembutal or chloralose-urethane. The latter agent seemed to give the best results and was used in eighteen of the thirty-two experiments performed. Cats were used throughout.

A tracheal cannula was inserted and the carotids tied bilaterally approximately at the level of the thyroid cartilage. The animal was then turned onto its ventral side, and the head placed in a holder. A long incision following the central suture of the skull was made from the bridge of the nose to the level of the spine of the second cervical vertebra. The skin on the side of the face nearest the operator was loosened from the underlying fascia and a skin incision made in a wide semicircle beginning at the second cervical vertebra passing about one-quarter of an inch below the pinna and ending at the beginning of the first incision. The pinna with the attached skin and platysma was then cut away leaving a short tube of the cartilaginous portion of the external auditory meatus projecting from the temporal bone. With blunt dissection the temporal muscle was freed from its insertion at the cranium and pushed back from the zygomatic arch. The neck muscles which insert into the lamboidal ridge were freed from the bone on the side of the operation and blunt dissection continued laterally following the ridge until the bulla was completely exposed. Freeing the muscles at the point of their insertion in this manner permitted the necessary bony areas to be cleared without cutting through fleshy tissue, and it was possible therefore to keep bleeding at a minimum.

The round window of the cochlea was exposed by cutting away the ventral wall of the tympanic bulla as far as the intratympanic septum. The auditory nerve was approached by making an opening in the skull about one centimeter wide by one and one-half centimeters long, having for its approximate center the point where the squamous-temporal,

parietal and occipital bones converge. Bleeding from the cut edges of the opening was checked by quickly packing wax between the inner and outer bone-tables and by gently squeezing the latter together. A cross-cut was made in the dura mater and the flaps laid back and excised. The portion of the cerebellum overlying the auditory nerve was then carefully sucked away with the aid of a suction pump extension, and finally thin strips of synthetic fibrin-foam soaked in thrombin* applied to the cut surface of the brain.

Apparatus

Following the operation the animal's head was placed in a specially designed holder which maintained the head in a suitable position for recording and at the same time did not obstruct the auditory meatus, the round window, or the opening in the skull. The tonal stimuli were conducted to the ear by means of a length of three-quarter inch rubber hose, the opening of which was placed approximately one-quarter of an inch from the external auditory canal. The stimuli were generated by a dynamic diaphragm type speaker actuated by a Hewlett-Packard 205AG resistance-capacity oscillator. In some experiments in which click stimuli were also employed, a thyratron stimulator was used to deliver brief square-wave impulses to a second dynamic speaker. In these experiments the rubber tubes carrying the sound outputs of the two speakers were connected

* Fibrin foam and thrombin (Human) Eli Lilly & Co.

by means of a Y-tube to a third length of tubing which carried the sounds into the shielded room where the animal preparation was kept.

Recording Electrodes: A simple metal clip or a silver plate attached to the neck muscles, and a hook of silver wire fixed into the lip of the round window niche served to pick up potentials of cochlear origin.

The nerve potentials were picked up by a new type of co-axial electrode especially designed for the purpose. A photograph of the complete electrode is shown in Figure 9 . The method of its construction is as follows: Thin walled Pyrex glass tubing of small bore was pulled into a very fine capillary and No. 44 gauge silver wire threaded through it under a dissection microscope or magnifying glass. The capillary was then threaded through a No. 26 gauge hypodermic needle, the hub of which had been previously made round and threaded to take a brass holder (2 in. diagram).

The hub and barrel of the needle were then filled with melted beeswax and when the wax had hardened the part of the capillary and its contained wire projecting from the tip of the needle were ground down flush with the needle orifice by applying it to a rapidly rotating rubberized-emery wheel. As a result of this procedure the end of the central electrode was cut at a slightly oblique angle and consequently the diameter of its exposed surface was a little greater than that of the cross section of the wire (approximately 80 microns).

The component parts of the co-axial electrode are illustrated in the photograph of Figure 10 and in the drawing of Figure 11, ar

explanation of which is given herewith:

(1) Hypodermic needle, 26 gauge, lugs turned off and the hub threaded No.1 B.A.

(2) Holder: Made from 3/8" solid brass turned down 1/4" O.D. for a length of 1". The remaining unturned quarter-inch of the holder barrel is threaded 3/8" x 24 T.P.I. to receive the cap (4). The barrel is drilled right through its length with a No. 16 drill and the smaller end tapped No. 1 B.A. to receive the threaded hub of the hypodermic needle (1). The larger 3/8" diameter end of the holder is recessed and tapped to receive an ebonite plug. Through the center of the ebonite plug a No.8 B.A. brass screw is tightly screwed with the head turned off flush with the ebonite. A small hole No.75 B.S. is drilled through the length of the screw to receive the central electrode-wire which is finally soldered to the screw head.

(3) A recessed brass plug, drilled through and tapped at the recessed end No.3 B.A. to hold in place a tightly fitting ebonite plug which completely fills the recess. Through the center of this ebonite plug a No.8 B.A. screw is inserted so that the screw-head is flush with the ebonite. The screw is drilled through to receive the central wire of the shielded cable which serves to connect the electrode with the amplifier. The braided wire shield of the cable is used as the ground lead to the amplifier and is attached to the electrode by soldering it into the tubular shaft of the brass plug.

(4) Brass knurled cap threaded internally 3/8" x 24 T.P.I. The cap is screwed to the holder and clamps together the central contacts of the two ebonite plugs. This system makes it possible to change the electrode lead without moving the needle from its position in the nerve.

The head-holder employed, permitted adjustment in three planes, and it was therefore possible to place the animal's head in any position necessary to facilitate an unobstructed approach to nerve and cochlea. The co-axial electrode was guided by means of a micromanipulator, and as the latter was attached to the same base as the head-holder, any movement of the electrode relative to the nerve was prevented once the final setting had been made.

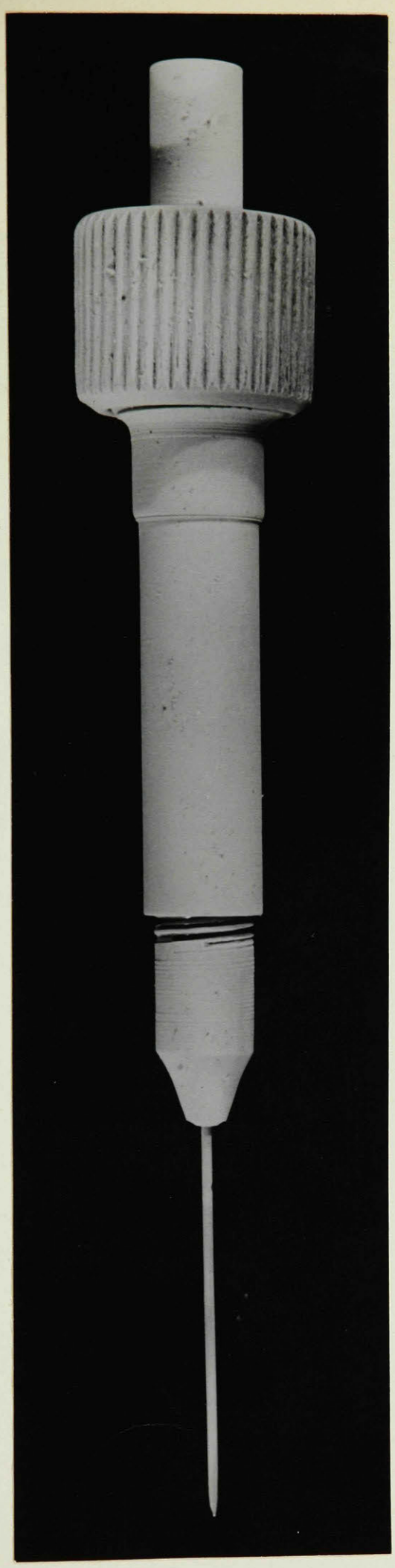

Figure 9. Photograph of coaxial needle electrode.
Magnification approx. 2-1/2 x.

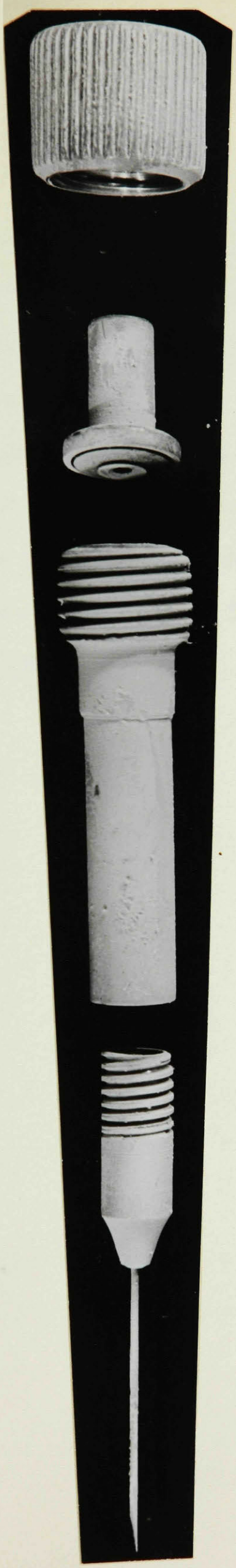

Figure 11. Photograph of the component parts of coaxial needle electrode. Magnification approx. 2x.

The electrical responses of nerve and cochlea were amplified by means of a four stage capacity-coupled preamplifier, and observered on the screen of a cathode-ray oscilloscope (Dumont). For purposes of recording, a second two stage power amplifier was employed in order to obtain sufficient output to drive a loop-type galvanometer (General Electric). The excursions of the galvanometer mirror were photographed with a variable speed camera (Hindle) on moving bromide paper. The galvanometer used had a natural frequency of 5000 cps and a damping factor approximately 65 per cent critical.

II. EQUILIBRATION IN THE AUDITORY NERVE

Introduction

In all the experiments carried out with the technics described in the foregoing section, it was observed that the auditory nerve action potentials do not maintain a constant amplitude at maximal intensities of stimulation, but diminish during the first few seconds to a much smaller size. The photographic record of Figure 12 shows a typical response of the auditory nerve to a tone of 600 cps. Note that, while the potentials were relatively large at the onset of the tone, a rapid decrease to approximately 25 per cent of the initial amplitude took place during the first two seconds of stimulation, almost 65 per cent of this diminution being complete within the first second. Following this rapid decline the action potentials usually continue to shrink in size for a period of from four to five minutes before a constant or equilibrium level is reached, but this shrinkage is of relatively small degree and amounts to a 10 to 15 per cent further reduction of response height.

This phenomenon*, a rapid then a slow decline in the amplitude of successive impulses in a continuous sensory nerve discharge, had been described before by Derbyshire and Davis (37) in the

* Hereafter referred to as equilibration, a name which was first applied to this phenomenon by Derbyshire and his associates because of its theoretical significance (see above).

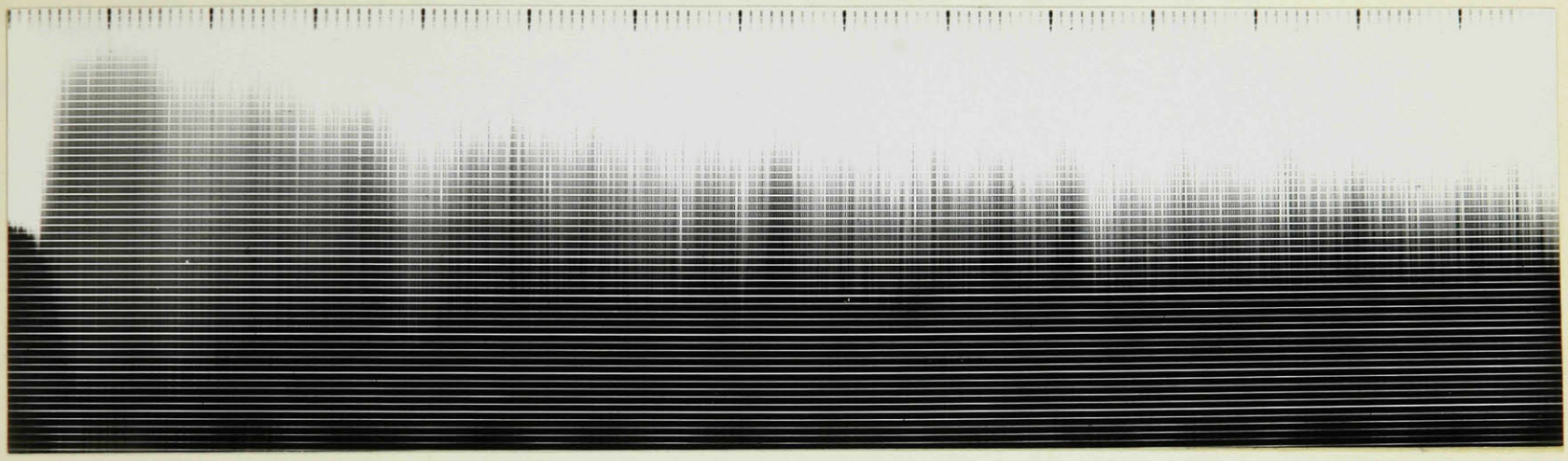

Figure 12. Equilibration of the auditory nerve action potentials elicited by an intense tone of 600 cps. The stimulus did not reach full intensity for several cycles, and for this reason the initial potentials are not as large as they would otherwise have been.

auditory nerve of the cat and by Pumphrey and Rawdon-Smith(120) in the cercal nerve of the cockroach. Davis and his co-workers attributed the effect to a fatigue brought about by failure of the nerve fibers to recover fully after each impulse. They pointed out that each individual sound wave in a wave train must constitute a separate and discrete stimulus, and that tonal stimulation at frequencies above 250 cps must therefore cause the fibers to respond at such a rapid rate that the period between successive impulses is insufficient for full recovery to occur.

Theoretical Development of Derbyshire and Davis' Hypothesis

As long ago as 1891 Pflüger (150) presented evidence that the responsiveness of a nerve may be markedly influencedby previous activity, and it is now well established that following a period of prolonged high frequency tetanization, the action potential of the nerve is reduced in size (151) (152) (153) (154), the conduction rate slowed (155) (156) (157) (158) (159) (160), the refractory period prolonged (161) (162) and the excitability depressed (163) (164) (165) (166). However, most of the experiments in which these effects were observed involved frequencies of stimulation far in excess of the fastest rate at which single fibers are known to fire under physiological conditions, and durations of stimulation much greater than are required for equilibration to become manifest in the auditory nerve, where the reduction in response size begins immediately after the first impulse and progresses with each succeeding impulse until a final equilibrium level is reached and main-

tained. In order then to validate the theory that auditory nerve equilibration is brought about as a result of a progressive failure of the nerve to recover fully after each impulse, it is necessary to show that the action of a high frequency stimulus to produce the effects described above begins to take effect immediately after the commencement of stimulation.

The explanation for the diminished size of the second impulse in a high frequency discharge is not difficult to find. The fact that a nerve exhibits first an absolute then a relative refractoriness to further stimultion following a unitary response indicates that the source of immediate energy in nerve is completely exhausted by the passage of a single impulse, and that the restoration process requires a certain finite time for completion. An impulse elicited during the recovery period must as a consequence of the energy depletion be of reduced amplitude.

In order to explain why the impulses continue to become smaller in size after this initial decrease, it is necessary to assume that the time course of recovery is progressively retarded with each successive response. Justification for the assumption is to be found in the work of Brücke and his associates (167) who observed that a nerve stimulated during its relatively refractory period recovers from the second impulse

considerably more slowly than from the first*. That the process of recovery is further retarded with each successive impulse until an equilibrium level is reached, is indicated by the results of experiments carried out by Forbes and Rice (168) and Gasser and Grundfest (169) in which it was found that the action potentials of artifically stimulated nerves always undergo equilibration when the stimuli are spaced at intervals shorter than a certain critical time period.

Having developed Derbyshire and Davis' original suggestion into a workable hypothesis**, it now becomes necessary to provide experimental

* Kato and his associates (170) have claimed that a nerve stimulated during the refractory phase of a previous impulse recovers from the resultant response along exactly the same curve as if there had been no preceding activity. They based the claim on results of nerve-muscle preparation experiments in which they measured the length of the least interval of time after an impulse elicited during the refractory phase of a preceding response at which a third stimulus would give a summated muscle contraction. There is no doubt that this method is subject to greater error than the more refined and direct method employed by Brücke and his co-workers. Furthermore it seems that Kato's technic may have revealed merely the stage of recovery at which the subnormal nerve impulse could excite across the neuro-muscular junction.

** When Davis and Derbyshire originally suggested that equilibration in the auditory nerve was a manifestation of a progressive failure on the part of the nerve to recover fully after each impulse, most of the data then available tendered to contradict a hypothesis which required the nerve to recover from a second of two rapidly repeated responses more slowly than from the first, and so on: There were Kato's observations which have already been cited and also the evidence that the heart, usually considered a model for excitable tissue, recovers more rapidly after an extrasystole than it does during the normal cycle (171) (172) (173). The Harvard workers made the suggestion solely on the basis of indirect evidence, namely, that the action potentials of a nerve electrically stimulated at high frequencies show a progressive decline in amplitude (170), and that refractoriness is prolonged following a long period of fatiguing stimulation (161).

evidence to substantiate it as fact. However, before the matter is discussed further it would be wise to consider any other mechanisms which could be responsible for the gradual decline in the size of the auditory nerve action potentials which immediately follows the onset of stimulation.

It is interesting to note that Derbyshire and Davis do not discuss in any of their papers the possibility that this effect could be brought about by a true sensory adaptation. The phenomenon has been observed in the responses of all other known mechanoreceptors and it appears to be the only other possible mechanism by which auditory nerve equilibration could be logically explained. Originally, sensory cells were thought to adapt only when subjected to a constant stimulus, but it is now known that certain mechanoreceptors show adaptation to iterative as well as non-iterative stimuli (174) (175) (176). Thus there is a priori no reason to believe that the auditory end-organ would not be subject to adaptation, and therefore, in the absence of any experimental evidence, no good reason to favor the mechanism of equilibration suggested by Derbyshire and Davis rather than this more obvious mechanism. The experiments which will now be described were carried out in an attempt to clarify this problem.

Experimental

If it could be shown that agents which tend to hinder the process of recovery in nerve magnified the equilibration effect when

applied to the auditory apparatus, definite evidence in favor of the nerve fatigue theory of equilibration would thus be obtained. If also these agents were known to exert the opposite effect on sensory adaptation, then the latter would automatically be excluded as a possible cause.

For many years it has been known that the recovery process in nerve is retarded at low temperatures* (177) (178) (179) (180) (181). If auditory nerve equilibration is brought about through a progressive failure of the tissue to recover fully after each response, then cooling the nerve endings should cause the phenomenon to be exaggerated. This is exactly the effect which is obtained when shaved ice is placed in the auditory bulla. Figure 13 shows a series of photographic records of the action potentials recorded from the eighth nerve: A before cooling; B after cooling; C during rewarming; D after return to normal temperature. Since Matthews (182) and others have found that adaptation is markedly decreased in sense organs which have been cooled, it seems improbable that the equilibration of auditory nerve impulses could be due to this cause. Moreover, asphyxia, which according to Bronk (183) has little or no effect on adaptation, greatly accelerates

* This is shown by the prolongation of the refractory period which takes place when a nerve is cooled. Both the absolute and the relative phase of the refractory period are lengthened. Because the temperature coefficient of the absolute is the same as that of the relative phase, and the coefficient of the rate of recovery of excitability is the same for all degrees of excitability, it is probable that a single process accounts for all the phenomena of the refractory state.

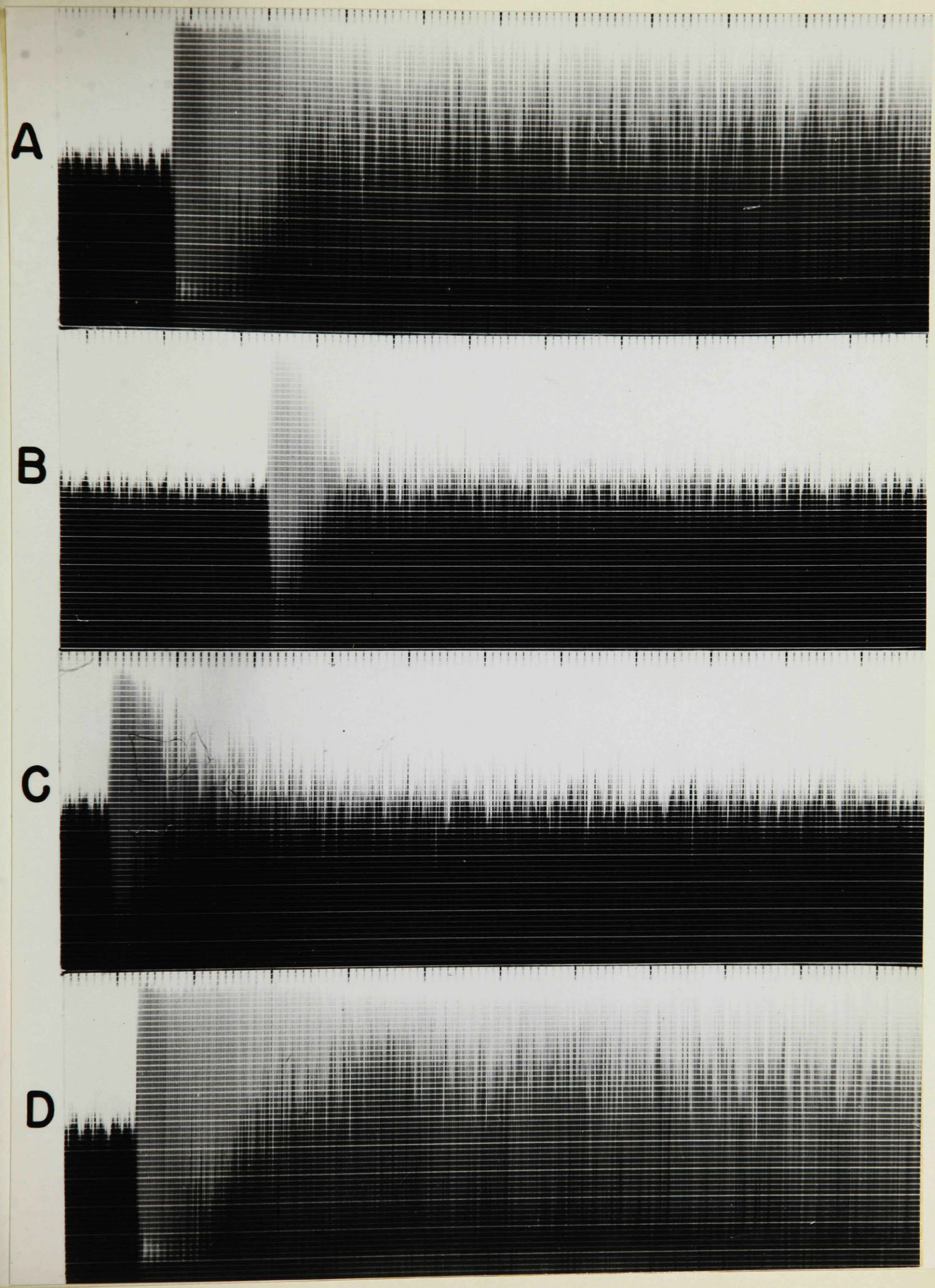

Figure 13. Equilibration in the auditory nerve: A before cooling; B after cooling; C during rewarming; D after the return to normal temperature.

equilibration in the auditory nerve and deepens it almost to the point of extinction. The curves shown in Figure 14 represent the course of equilibration before and after clamping of the trachea. The stimulus in this case was an intense 150 cps tone. At this frequency under normal conditions very little equilibration takes place* as can be seen from the higher of the two curves in the figure. A few minutes after the trachea has been clamped the curve changes its form completely and becomes a steeply sloping, almost straight line.

Here again, supporting evidence is afforded the fatigue theory of equilibration for there is no doubt that oxygen is essential to the processes responsible for restoration in nerve (184).

Conclusion

In conclusion it is interesting to note that equilibration has been observed in single auditory nerve fibers (185). Here the effect is seen as a decrease in both height of response and in rate of discharge. The diminution in the size of the action potentials is relatively slight, and after the first few impulses a constant height is maintained. The rate of firing, on the other hand, is reduced within the first second as much as 75 per cent, the reduction taking place rapidly at first and then more slowly until a final, fairly constant equilibrium level is reached after a period of about two seconds.

*This fact will be discussed in detail at the end of this section.

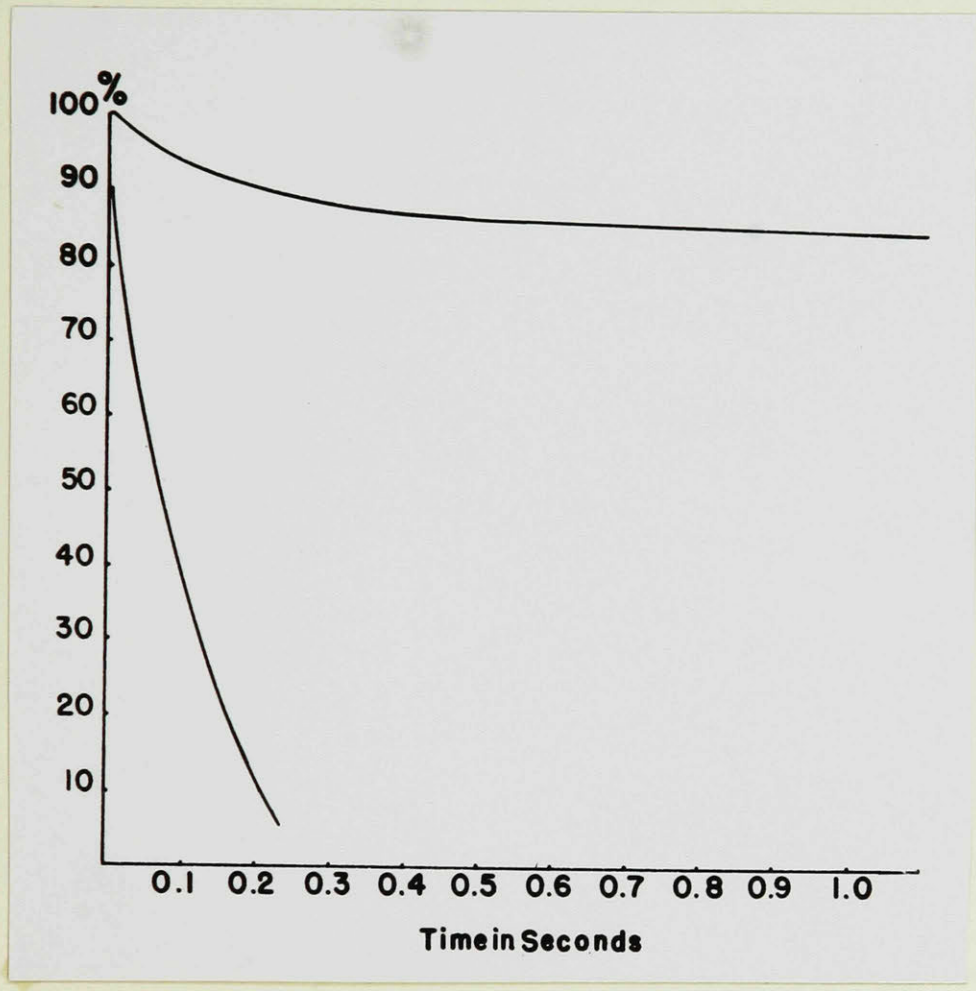

Figure 14. Equilibration before and after (lower curve) asphyxiation. Ordinate values represent the size of the action potentials expressed as a percentage of the amplitude of the first response of the discharge.

The observation is of special interest because it fits the predictions of the fatigue theory of auditory nerve equilibration so well: According to the data obtained by Brücke and his co-workers (167) and by Graham and Lorente de Nó (160) the restoration of responsiveness after tetanization takes place much more rapidly than does the restoration of excitability, and its time-course is retarded by fatiguing stimulation to a far greater extent than is the time-course of the latter. Hence the small initial decrease in amplitude and the large reduction in the rate of firing which constitute equilibration in single auditory fibers can easily be explained as follows: The decrease in the height of the action potential does not progress beyond the first few impulses because of the increasing divergence between the two curves of recovery with continuing stimulation. In other words, recovery of responsiveness will be almost complete after each impulse before the restoration of threshold is attained and another response elicited.

Explanation of the reduction in the rate of firing may be obtained by consideration of the events leading up to the elicitation of each individual response: After the first impulse at the onset of the stimulus, restoration of threshold may be completed so rapidly that, if the frequency is not too high, the second cycle of the wave train may also excite. Recovery from this second response will, however, be slower than from the preceding one, and threshold may not be attained until two further cycles of the wave train have been completed. Thus while initially it may require but one cycle to cause excitation,

eventually several cycles may be required.

There is but one other point left to be clarified: How does it happen that the frequency of discharge is kept at the low level which it finally reaches, when, according to theory, it is the rapid rate of firing which brings about the conditions responsible for retarded recovery? The answer is to be found in the work of Erlanger and Blair (186) who have demonstrated that stimuli which are ineffective because they occur during a period of depressed excitability, nevertheless further delay recovery. Thus those cycles of the wave train which fail to excite, extend the period required for restoration of threshold in the same manner that they would have if they had been effective.

eventually several cycles may be required.

There is but one other point left to be clarified: How does it happen that the frequency of discharge is kept at the low level which it finally reaches, when, according to theory, it is the rapid rate of firing which brings about the conditions responsible for retarded recovery? The answer is to be found in the work of Erlanger and Blair (186) who have demonstrated that stimuli which are ineffective because they occur during a period of depressed excitability, nevertheless further delay recovery. Thus those cycles of the wave train which fail to excite, extend the period required for restoration of threshold in the same manner that they would have if they had been effective.

III. PERIPHERAL INHIBITION IN THE AUDITORY SYSTEM

During an investigation of the neural basis of the auditory phenomenon known as masking, the writer observed that if a low tone is immediately preceded by an intense high* tone, the potentials evoked in the auditory nerve by the low tone are for a short time markedly reduced in size. This effect is illustrated in the photographic record reproduced in Figure 15: The sequence of events in the record is as follows: A to B are the nerve potentials elicited by a tone of 70 cps; at B this tone was switched off and a tone of 750 cps instantaneously switched on; at C the 750 cycle tone was switched off and the 70 cycle tone immediately switched on again. It can be seen that the potentials elicited by the 70 cycle stimulus were greatly diminished in size immediately following cessation of the higher tone, and that recovery was not completed until after a period of approximately two-fifths of a second.

A low tone does not exert a similar inhibitory effect upon the response to a high tone as can be seen from the record in Figure 15: Note that the potentials elicited by the 750 cycle stimulus are initially large rather than small, and that they undergo equilibration in the normal manner.

The inhibition phenomenon also is seen when after a period of stimulation with both a high and a low tone presented coincidentally,

* The term is used here in a relative sense -- all tones above 450 cps being considered "high" tones for the purpose of comparison.

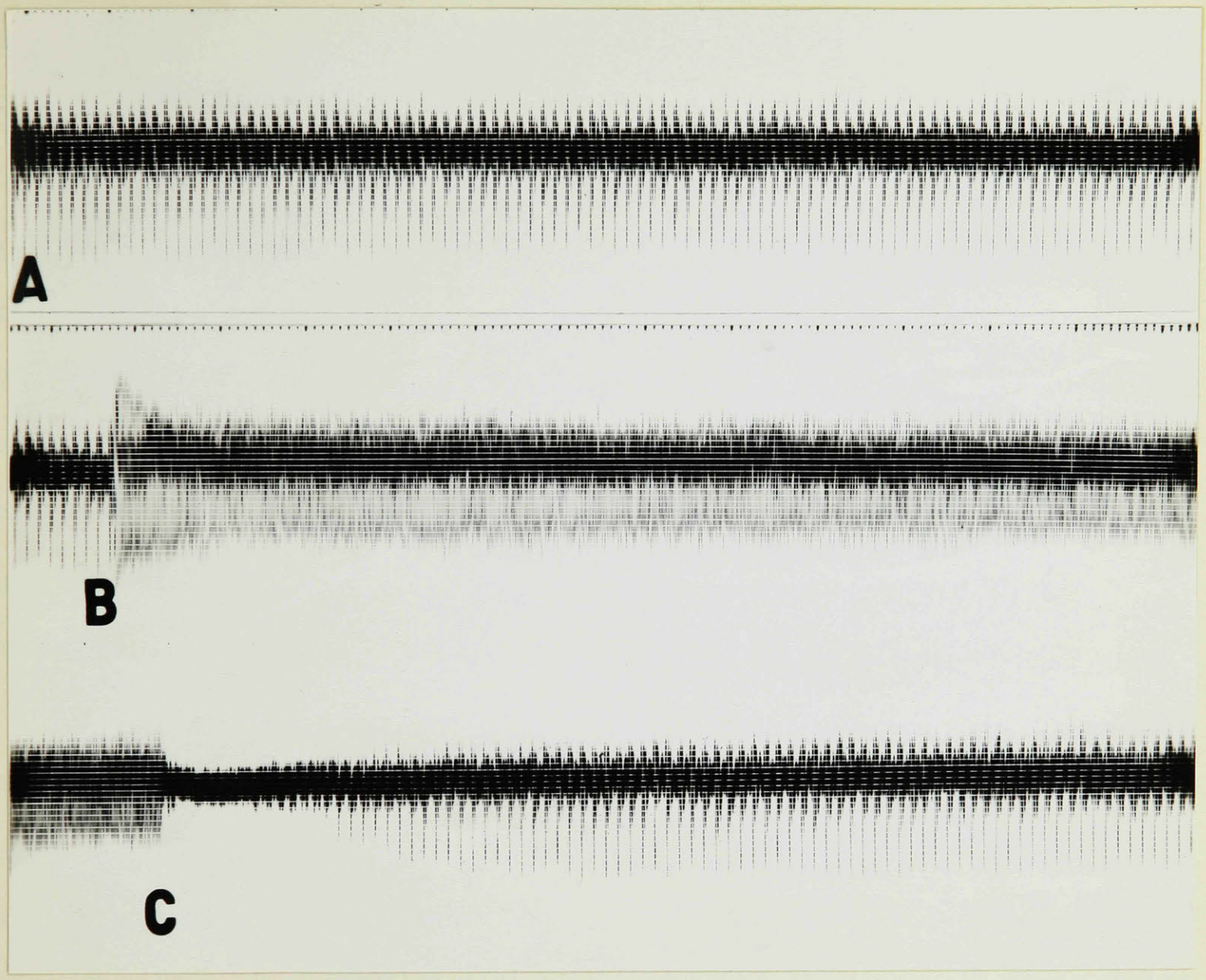

Figure 15. Inhibition of the action potentials evoked in response to a 70 cycle tone by an intense tone of 750 cps. Time marker 0.1 and 0.01 sec.

the high tone is switched off. Figure 16 illustrates this effect. The potentials from A to B in the record are those produced by an 85 cycle tone sounded alone; at B a 900 cycle tone was also switched on, then at C it was switched off again. This record is particularly interesting because it appears to show that during the time when the stimuli were sounded together there were rhythmic periods of inhibition and facilitation, the periods of facilitation being more pronounced at the beginning than towards the end of stimulation. A record taken of the cochlear microphonic potentials evoked by the same pattern of stimulation (Figure 17) does not show similar periods of depression and reinforcement, nor is the low tone response diminished in size following cessation of the high tone.

The fact that the cochlear microphonic potentials evoked by low tones are not subject to inhibition by high tones (Figure 17 and 18) provides incontrovertible evidence that the nerve phenomena are not merely stimulus artefacts, and furthermore, localizes them in some process occurring beyond the point of origin of the audio-electric effect. Thus also, the possible explanation, that the inhibition is due to a reflex contraction of the intra-aural muscles arising in response to the higher tone and outlasting it, is rendered untenable.

Impulsive as well as sinusoidal stimuli may be inhibited. The record in Figure 19 shows the effect of a 1000 cycle tone on the nerve responses to clicks. In this, a typical case, there was a complete inhibition of the click potentials during the time the tone was sounded and a lesser but still marked depression after it was switched

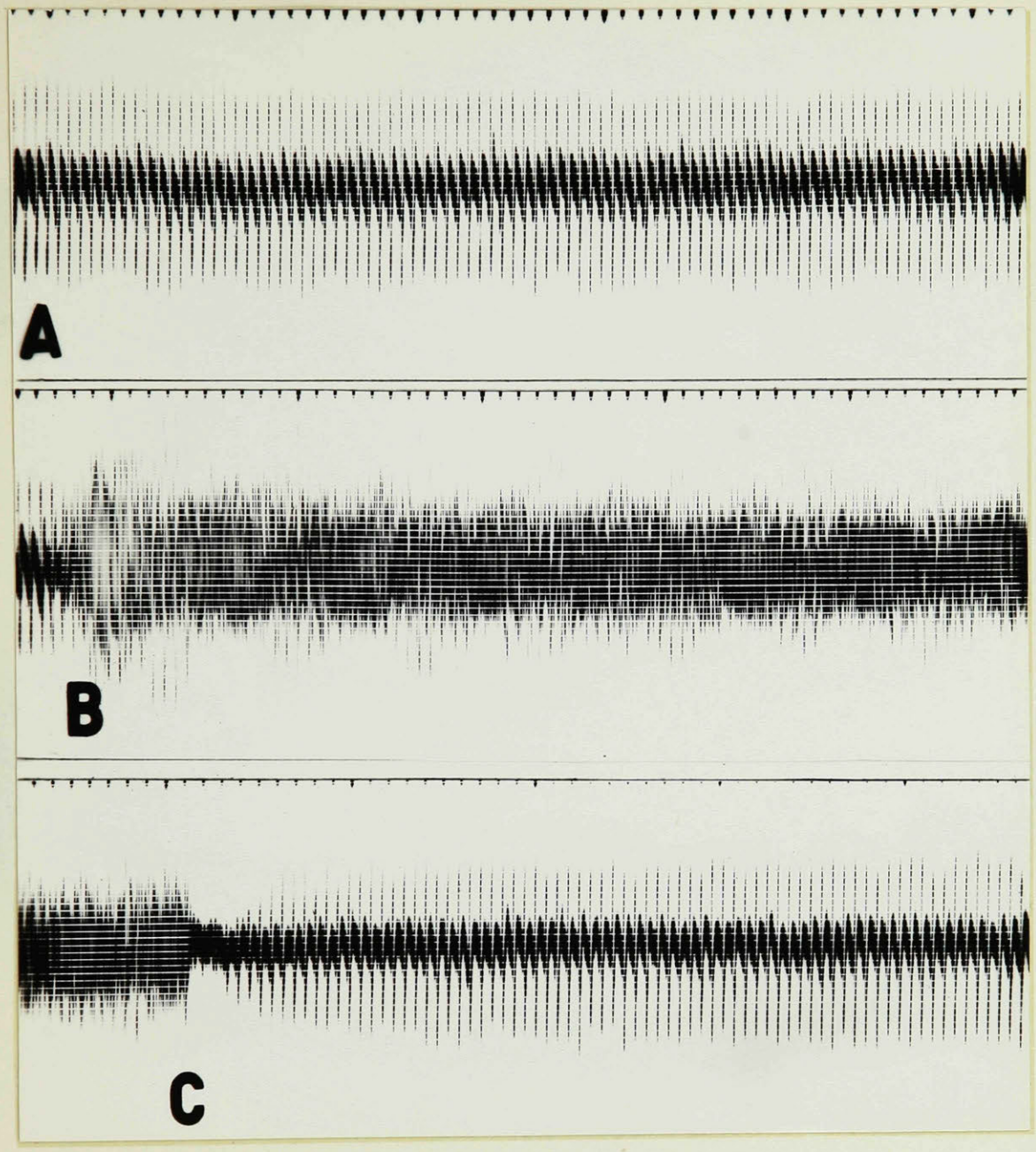

Figure 16. Inhibition of the action potentials evoked in response to an 85 cycle tone by an intense tone of 900 cps. Coincident stimulation. Time marker 0.2 and 0.02 seconds.

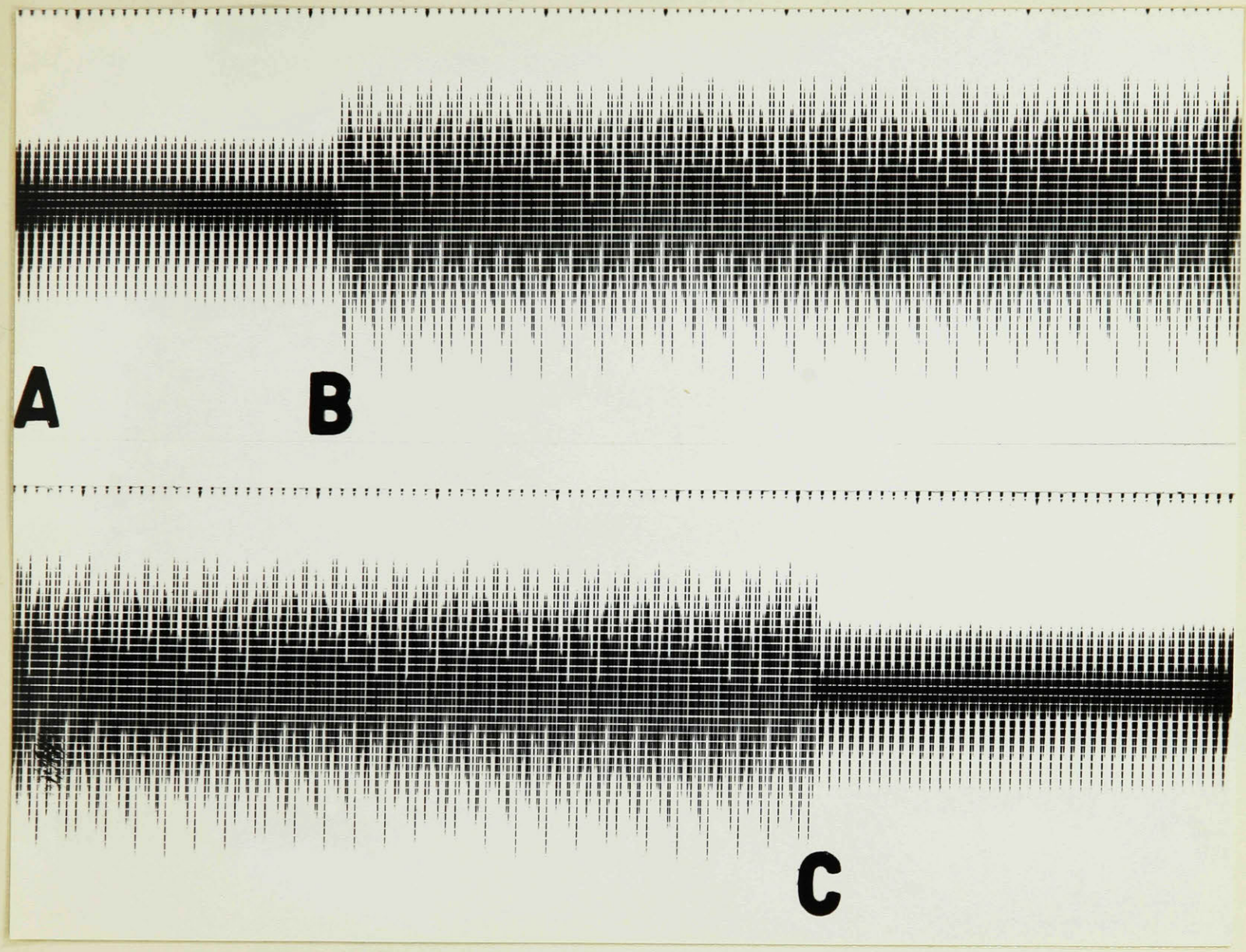

Figure 17. Cochlear potentials recorded in response to the same pattern of stimuli which produced the nerve records shown in Fig. 16. Note that there is no inhibition of the low tone potentials after cessation of the high tone at C. Time marker 0.1 and 0.01 seconds.

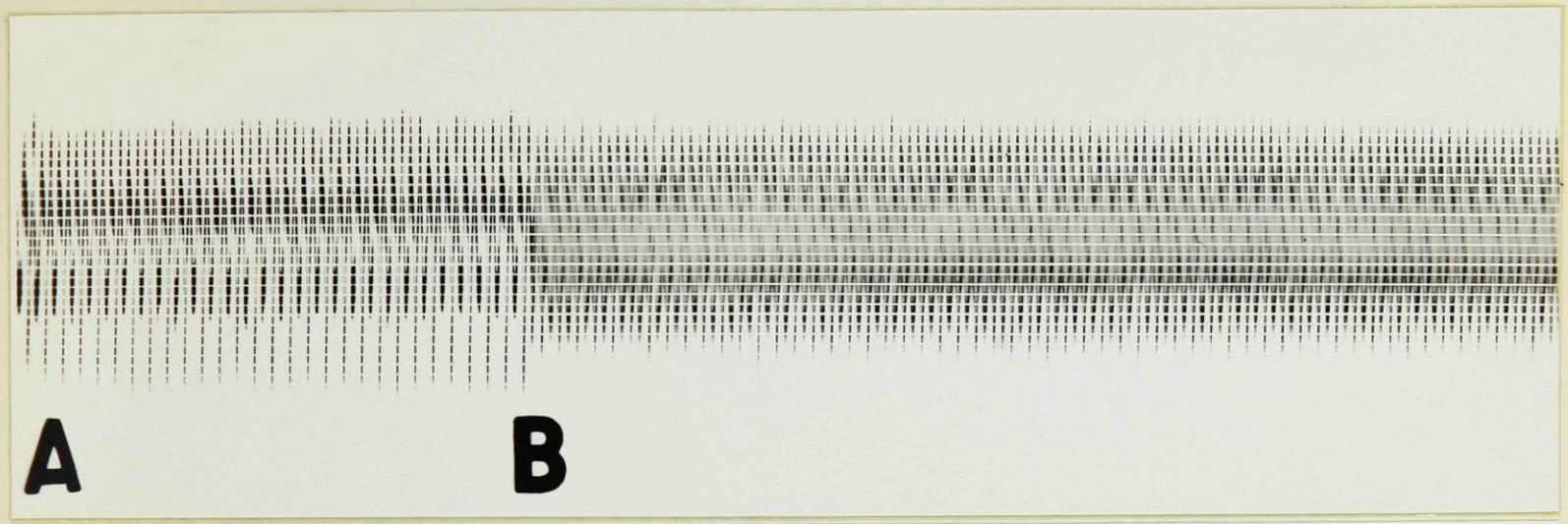

Figure 18. Photographic record showing cochlear potentials: A - B evoked by 70 cycle tone, B - C by 70 cycle and 800 cycle tone sounded together, C - by 70 cycle tone alone following cessation of the higher tone.

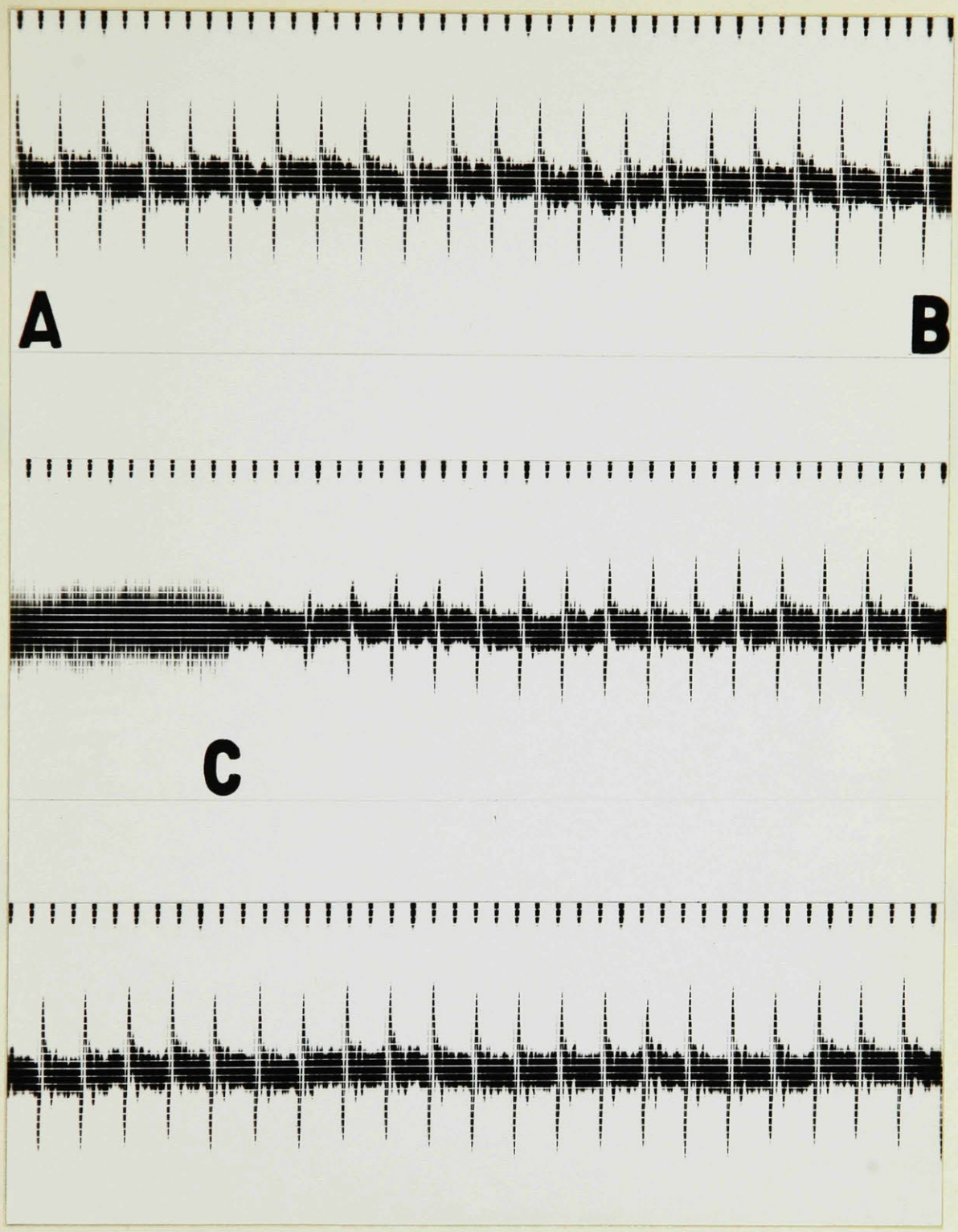

Figure 19. The inhibitory action of a 1000 cycle tone on the action potentials produced by click stimuli. Time marker 0.2 and 0.02 sec.

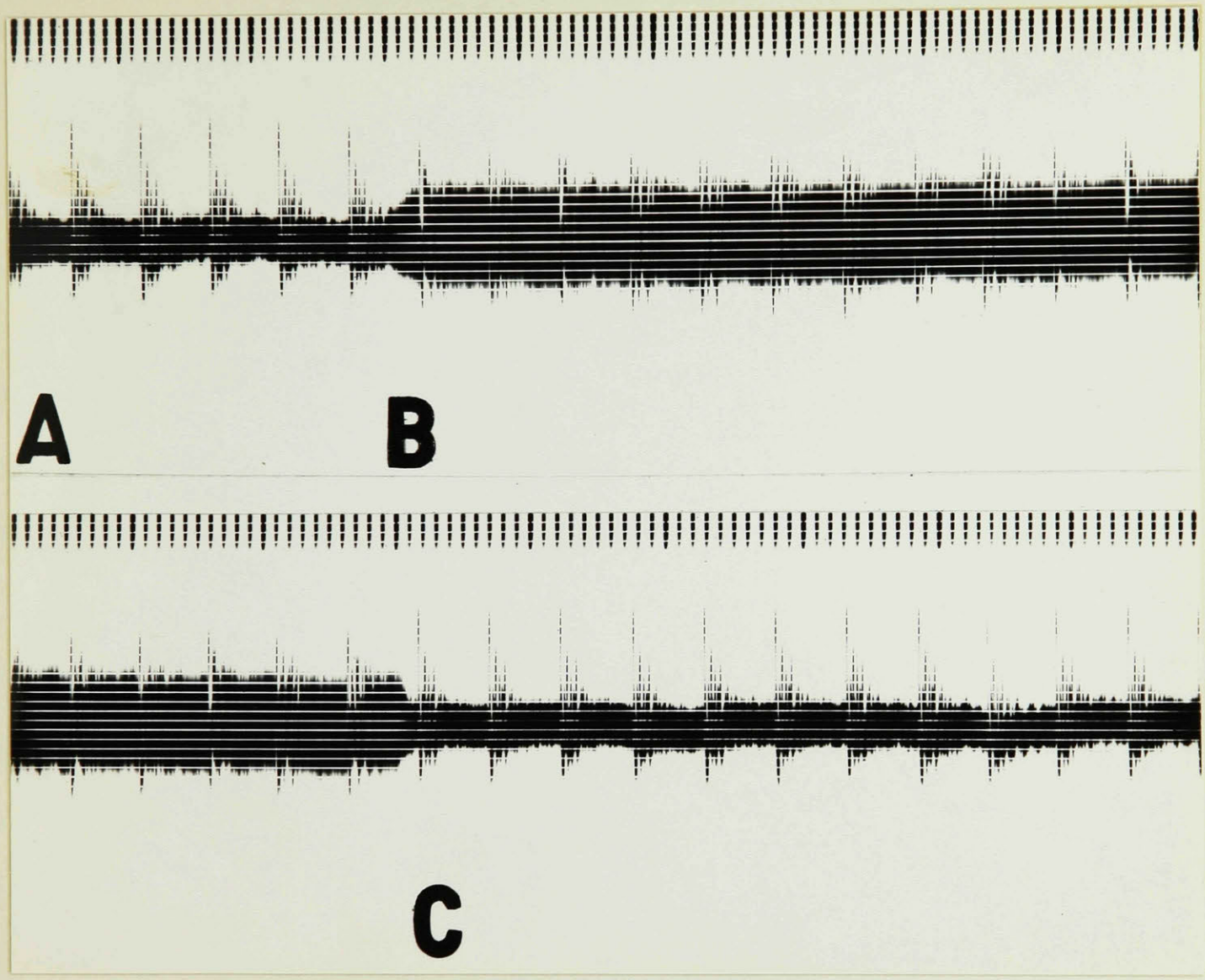

Figure 20. Cochlear potentials evoked by the same pattern of stimulation which produced the nerve records shown in Fig. 19. Time marker 0.1 and 0.01 seconds.

off. It is interesting to compare the record of the cochlear potentials obtained in response to the same stimuli (Figure 20): Here the click potentials are only slightly reduced in magnitude during presentation of the tone and regain their normal amplitude immediately following its cessation.

The Nature of the Inhibition

Up to the present time it has not been possible to ascribe the inhibition phenomenon to any specific process of nerve or sense organ, but several hypotheses have been considered and of these the following two appeared to be the most reasonable:

When first observed the effect was believed to be a manifestation of subnormality in the auditory nerve. It is a well-known fact that a nerve remains in a state of subnormal excitability for a considerable period after rapid tetanization (169). It was thought therefore that an intense high tone might cause all the fibers responding to it to fire at such a rapid rate that following withdrawal of the stimulus the fibers would be left in a state of depressed irritability. Because of the raised threshold the low tone would at first be only partially effective, but due to the slower rate at which the low tone would cause it to discharge the nerve would have a chance to recover -- hence, the gradual restoration of normal amplitude.

For the hypothesis to be valid it is necessary that the high tone should not only activate the nerve fibers which respond

to the low tone, but that it should initiate in these fibers a greater number of impulses than does the low tone itself. However, the only experimental data available concerning this factor indicates that while a single auditory fiber may respond when strongly stimulated to a wide range of frequencies, it responds maximally to only one specific frequency, and hence submaximally to all others (185). Thus it would be expected that low tone fibers would be tetanized most by tones of their own characteristic frequency and that if they responded at all to high tones it would be at a relatively slow rate; accordingly low tone fibers should develop a greater subnormality when stimulated by low tones than when stimulated by high tones. Nevertheless, subnormality was not immediately discarded as a possible cause of the inhibition effect because of the fact that there is evidence that the perception of low tones is not dependent upon the activation of a specific fiber or group of fibers. Although they made a "persistent search" for low tone fibers, Galambos and Davis did not succeed in localizing any having a characteristic frequency below 420 cps. When this is considered in the light of the clinical observation that partial section of the auditory nerve in man always causes losses to high tones but never to low tones, it becomes evident that the theory ascribing the physiologic correlate of pitch for low tones to the frequency and organization of the impulses passing up the auditory nerve, may indeed be correct. If it is, then the inhibitory action of a high upon a low tone may be satisfactorily explained in terms of nerve subnormality. In all the

experiments carried out by the writer and his associate it was found that tones below 400 cps were the ones most easily inhibited, and that tones of higher frequency were little or not at all affected by still higher tones. Nevertheless, attempts to alter the time course and magnitude of the phenomenon with agents which are known to exert a marked influence on subnormality were not successful.

Yohimbine, a drug which is known to prolong the duration of subnormality in nerve and markedly increase its depth, did not alter the dimensions of the auditory inhibition in any way whatsoever even though several methods of applying the drug to the acoustic nerve endings were tried including intravenous and intra-arterial injection, perfusion of the perilymph and infusion through the round window membrane. It is true that this might have been the result of a failure of the drug to reach the necessary site in sufficient concentration to produce an effect, but considered in the light of the fact that asphyxiation also does not influence the time course or magnitude of the inhibition, it seems clear that a subnormality of the responding nerve fibers cannot be the underlying mechanism of the inhibitory action of a high on a low tone.

It is conceivable that the inhibition phenomenon could be produced by reflex action of either central or peripheral origin. Cajal (187) has described centrifugal fibers in the auditory nerve which terminate around the cell bodies of the spiral ganglion. These are considered by Poliak (188) to be efferent fibers of the vasomotor nucleus and thus not directly concerned with auditory

function; it seems possible, however, that they may serve to prevent conduction through the ganglion cells which they inervate. An attempt has not been made to test the hypothesis by sectioning the nerve central to the recording electrode because this procedure invariably cuts off the blood supply to the cochlea with consequent loss of all electrical activity. A method of blocking the nerve below the electrode or of sectioning it without cutting the cochlear artery will have to be devised before an inhibition of central origin can be ruled out as a possible cause.

A peripheral inhibition mediated through the direct neural connections which exist between different parts of the cochlea is another possible explanation of the phenomenon. Lorente de Nó (187), Poliak (188), and others have described bundles of nerve fibers that run spirally within the ganglion, giving off collaterals "which enter several regions of the cochlea lying far apart from each other. There are also bundles of nerve fibers which run between the hair cells and the basilar membrane sending off fine collateral twigs to several of the external hair cells along their path (189). Very little is known concerning the origin and distribution of the intrganglionic and intracellular fibers, but if they serve, as they apparently do, to relay impulses from one part of the acoustic system to another then it may be that they act to depress excitability at a point distant from the region activated by the stimulus. Unfortunately the technical difficulties involved in subjecting the hypothesis to a critical test seem insurmountable, and the solution to the problem may not be

obtained until a refined microelectrode technic is devised whereby exploration of circumscribed regions of the auditory neuroepithelium is made possible.

IV. THE DEGREE OF DAMPING OF THE STRUCTURES RESPONSIBLE FOR THE GENERATION OF COCHLEAR POTENTIALS

The damping factor of the structures responsible for the production of cochlear potentials would not be of special interest were it not for the fact that there is considerable evidence that these structures are the hair cells of Corti's organ. The latter are closely attached to the basilar membrane and undoubtedly constitute the end-organs of the sense of hearing. The degree of damping to which they are subject will determine in large measure the character of their response. Now, the most widely accepted theory of frequency analysis maintains that the basilar membrane is composed of a graded series of resonators and that the discrimination of pitch depends upon the activation by the stimulus of a discrete and circumscribed region of the neuroepithelium thereon. But in order for a tone of a particular frequency to produce a significant displacement within a sharply defined and limited locus only, it is necessary that the damping factor of the responding element be very small: The greater the damping the more blunt will be the curve of resonance, and hence the wider will be the area of maximal displacement on the basilar membrane.* Thus it is clear that the damping factor of the vibrating elements of the inner ear

* This is illustrated by the equation $\frac{n^2 - p^2}{kp} = \sqrt{\frac{T_o - T}{T}}$ where T is the kinetic energy and T_o the maximal kinetic energy.

must be known before a satisfactory hypothesis concerning the mechanism by which the peripheral analysis of sound is achieved can be established.

The degree of damping of the element which generates cochlear potentials can be determined by examination of the wave form of these potentials at either the onset or cessation of the stimulating tone. According to Davis (190), "a pattern very closely resembling that resulting from a single isolated click" occurs both at the beginning and end of activity even when precautions are taken to switch the stimulus on and off without production of a gross physical transient. Experiments carried out in this laboratory do not, however, confirm these results. When care was taken to exclude clicks at the time of turning the tone on and off, the onset and cessation of cochlear electrical activity was always smooth and simple.

Due to the unavailability of the necessary apparatus it has not been possible to make satisfactory high speed photographs to illustrate this. However, the low speed records which have been obtained indicate that the forced and free oscillations of the element responsible for the production of cochlear potentials are typical of a system which is almost critically damped.

It will be recalled that the solution of the equation describing the motion of a simple vibrating system under the action of an external periodic force consists of two parts, a "transient" and a "steady" state. The former, which may be described by the

term $x_1 = e^{-kt}\left[C_1 \cos \omega t + C_2 \sin \omega t\right]$, expresses the temporary reaction of the system to any suddenly applied force: Its magnitude diminishes with time depending upon the size of k. The steady state term, $x_2 = a \cos (pt - \varepsilon)$, expresses the tendency of the system to follow the driving force, and after the initial transient has disappeared, constitutes a completely sufficient description of the motion unless further change in the driving force is made.

When damping is small the history of the system from t=o will be as follows: Starting from rest, the displacement will be the sum of the transient effect and the steady state effect, which are equal in magnitude but opposite in sign. During the initial stages of the motion the transient vibration, which is gradually diminishing in size, beats with the forced vibration, and the net result is a gradual asypmtotic rise in amplitude which continues until the steady state value is reached (when the transient effect finally dies out). While this increase in amplitude is taking place, the frequency of the vibration is neither that of the transient nor that of the impressed force, but is a variable composite of the two which gradually approaches the frequency of the steady state as the transient decays.

The duration of the period for which the transient is effective depends upon the value of k. If damping is appreciable then the transient displacement decays very rapidly and $x = a \cos(It - \varepsilon)$ becomes a sufficient and complete description of the motion within a much shorter space of time than in the case where k is small. In fact,

when k is large the first half cycle may have a greater amplitude than its successors due to the production of pseudo-beats.* This apparent paradox can be explained by the presence of the change of phase which causes the period of the resultant vibration to be longer while the free vibration lasts. The first "beat" maximum is always the greatest because at the beginning of the motion the free vibration is stronger than at any later time, while the amplitude of the forced vibration is constant. Theoretical and experimental proof of this fact has been provided by Blau (191). He has shown that even though the free vibration (transient) dies more quickly when damping is large, the maxima occur at such an early stage that the amplitude of the resultant motion is appreciably greater than the forced vibration of the steady state. With critical damping or almost critical damping, the first maximum occurs at the time of the first displacement of the system.

The alternating potentials generated in the cochlea in response to a tone of abrupt onset do not grow monotonically from zero as they would if the inner ear were a lightly damped system, but attain the steady state in both amplitude and frequency within the period of the first oscillation. As predicted for a damped system

* The term pseudo-beats is used after Blau because beats in the generally accepted sense of the term are possible only in an undamped system under forcing, or in systems in which the vibrations are separately maintained. The pseudo-beats which may occur in a damped system under forcing may have a greater or lesser frequency than the difference between the impressed and natural frequencies depending upon whether the impressed frequency is greater or smaller than the natural frequency of the system.

by theory, the first half cycle appeared to be a little larger than its successors, but an aperiodic wave pattern such as is produced by click stimuli was not observed in any of the records.

Conclusions

While the observations reported in this section demonstrate conclusively that the source of cochlear microphonic potentials is an almost critically damped element, they do not in themselves provide final proof that the structure responsible for the initiation of the auditory nerve impulses is similarly damped. However, as was mentioned earlier, most of the experimental data available tends to point to the hair cells of Corti's organ as the responsible source, and these cells are generally considered the end organs of hearing.

The question may be asked: If the inference is accepted that the cochlea is a highly damped system, will it then be necessary to deprecate the considerable empirical evidence that the analysis of pitch is accomplished in the cochlea by some mechanism which involves selective stimulation of localized areas of the neuroepithelium? The answer is no, for mechanical resonance is not the only principle by which a physical system can discriminate between vibrations of various frequencies. For example, Reboul (192) has set up a series of differential equations treating the cochlea as a hydraulic system contained in a vessel with elastic walls, and applying the theory of propagated disturbances in media constrained by elastic boundaries, he has been able to show that the basilar membrane will undergo a

maximal displacement at a position which is a function of the frequency of the force activating it. The fact that the positions of maximal displacement which Reboul calculated for several frequencies are in close agreement with figures obtained by various experimental methods, serves to emphasize the error of adhering unquestioningly to the Helmholtz' hypothesis in the face of its many inadequacies.

BIBLIOGRAPHY

1. Beauregard, H. and Dupy, E. C. R. Acad. Sci. Paris 1896, 122, 1565-67

2. Piper, H. Zbl. Physiol. 1906, 1, 293-297.

3. Piper, H. Med. Klin. 1906, 2, 1073-1078.

4. Buijtendijk, F.J.J. Konik, Akad. v. Wetensch. Amsterdam 1910-11, 13, 649-652.

5. Forbes, A., Miller, R.H. and O'Connor, J. Amer. J. Physiol. 1927, 80, 363-380.

6. Foa, C. and Peroni A. Arch. Fisiol. 1930, 28, 237-241.

7. Wever, E.G. and Bray, C.W. Proc. Nat. Acad. Sci. 1930, 16, 344-350.

8. Wever, E.G. and Bray, C.W. J. exper. Psychol. 1930, 13, 373-387.

9. Kreezer, G. Amer. J. Psychol. 1934, 46, 1-18.

10. Kreezer, G. and Darge, H. Science 1932, 75, 105.

11. Crowe, S.J. and Hughson, W. Trans. Amer. otol. Soc. 1932, 22, 125-136.

12. Hughson, W. and Crowe, S.J. Acta oto-laryng. Stockh. 1933, 18, 291-339.

13. Hughson, W., Crowe, S.J. and Howe, H.A. Acta oto-laryng. Stockh. 1934, 20, 9-23.

14. Crowe, S.J. Harvey Lectures 1931-32, 100-127.

15. Adrian, E.D., Bronk, D.W. and Phillips, G. J. Physiol. 1931, 73, 2P-4P.

16. Rademaker, G.G.J. and Bergansius, F.L. Arch. neerl. Physiol. 1931, 16, 346-349.

17. Elmquist, R. and Sjöström, P.M. Hospitalstidende, Dansk oto-laryng. Selsk. Forh. 1932-33, 76, 11-12.

18. Saul, L.J. and Davis, H. Trans. Amer. otol. Soc. 1932, 22, 137-145.

19. Davis, H. and Saul, L.J. Amer. J. Psychol. 1933, 45, 358-359.

20. Bast, T.H., Noer, R., West, R., Backus, O.L., Krasno, M. and Eyster, J.A.E. Proc. Soc. exper. Biol. 1933, 30, 638-640.

21. Hathaway, S. and Rasmussen, G.L. Proc. Soc. exper. Biol. 1932, 29, 412-414.

22. Fromm, B., Nylen, O., and Zotterman, Y., J. Physiol. 1934, 80, 3P-4P.

23. Fromm, B., Nylen, O., and Zotterman, Y. Acta oto-laryng. Stockh. 1935, 22, 477-486.

24. Hallpike, C.S. and Rawdon-Smith, A.F. J. Physiol. 1934, 81, 395-408.

25. Rinne, F.H. Ztsch. f. rat. Med. 1865, 24, 12-64.

26. Voltolini, F.E.R., Virchow's Archiv. 1885, 100, 27-41.

27. Rutherford, W. Brit. Med. J. 1898, 2, 353-358.

28. Adrian, E.D. J. Physiol. 1935, 71, 28-30.

29. Davis, H. and Saul, L.J. Science 1931, 74, 205-206.

30. Saul, L.J. and Davis, H. Arch. Neurol. & Psychiat. 1932, 28, 1104-1116.

31. Davis, H. and Saul, L.J. Amer. J. Physiol. 1932, 101, 28.

32. Wever, E.G., Bray, C.W. and Lawrence, M. Ann. Otol. Rhinol. & Laryngol. 1941, 50, 317-329.

33. Wever, E.G. and Bray, C.W. J. exper. Psychol. 1938, 22, 1-16.

34. Kemp, E.H., Coppée, G.E. and Robinson, E.H., Amer. J. Physiol. 1937, 120, 304-315.

35. Davis, H. J. Acoust. soc. Amer. 1935, 6, 205-215.

36. Brücke, E.v., Early, M. and Forbes, A. J. Neurophysiol. 1941, 4, 80-91.

37. Derbyshire, A.J. and Davis, H. Amer. J. Physiol. 1935, 113, 476-504.

38. Hallpike, C.S. Acta oto-laryng. Stockh. 1937, 26, 145-160.

39. Hallpike, C.S. Nature Lond. 1934, 134, 419-420.

40. Hallpike, C.S. and Rawdon-Smith, A.F. J. Physiol. 1934, 83, 243-254.

41. Guttman, J. Laryngoscope St. Louis, 1933, 43, 983-985.

42. Guttman, J. and Barrera, S.E. Amer. J. Physiol. 1934, 109, 704-708.

43. Guttman, J. and Barrera, S.E. Amer. J. Physiol. 1937, 120, 666-670.

44. Rawdon-Smith, A.F. and Hawkins, J.E. Proc. Roy. Soc. Med. 1939, 32 496-507.

22. Fromm, B., Nylen, O., and Zotterman, Y., J. Physiol. 1934, 80, 3P-4P.

23. Fromm, B., Nylen, O., and Zotterman, Y. Acta oto-laryng. Stockh. 1935, 22, 477-486.

24. Hallpike, C.S. and Rawdon-Smith, A.F. J. Physiol. 1934, 81, 395-408.

25. Rinne, F.H. Ztsch. f. rat. Med. 1865, 24, 12-64.

26. Voltolini, F.E.R., Virchow's Archiv. 1885, 100, 27-41.

27. Rutherford, W. Brit. Med. J. 1898, 2, 353-358.

28. Adrian, E.D. J. Physiol. 1935, 71, 28-30.

29. Davis, H. and Saul, L.J. Science 1931, 74, 205-206.

30. Saul, L.J. and Davis, H. Arch. Neurol. & Psychiat. 1932, 28, 1104-1116.

31. Davis, H. and Saul, L.J. Amer. J. Physiol. 1932, 101, 28.

32. Wever, E.G., Bray, C.W. and Lawrence, M. Ann. Otol. Rhinol. & Laryngol. 1941, 50, 317-329.

33. Wever, E.G. and Bray, C.W. J. exper. Psychol. 1938, 22, 1-16.

34. Kemp, E.H., Coppée, G.E. and Robinson, E.H., Amer. J. Physiol. 1937, 120, 304-315.

35. Davis, H. J. Acoust. soc. Amer. 1935, 6, 205-215.

36. Brücke, E.v., Early, M. and Forbes, A. J. Neurophysiol. 1941, 4, 80-91.

37. Derbyshire, A.J. and Davis, H. Amer. J. Physiol. 1935, 113, 476-504.

38. Hallpike, C.S. Acta oto-laryng. Stockh. 1937, 26, 145-160.

39. Hallpike, C.S. Nature Lond. 1934, 134, 419-420.

40. Hallpike, C.S. and Rawdon-Smith, A.F. J. Physiol. 1934, 83, 243-254.

41. Guttman, J. Laryngoscope St. Louis, 1933, 43, 983-985.

42. Guttman, J. and Barrera, S.E. Amer. J. Physiol. 1934, 109, 704-708.

43. Guttman, J. and Barrera, S.E. Amer. J. Physiol. 1937, 120, 666-670.

44. Rawdon-Smith, A.F. and Hawkins, J.E. Proc. Roy. Soc. Med. 1939, 32 496-507.

45. Ashcroft, D.W., Hallpike, C.S. and Rawdon-Smith, A.F. Proc. Roy. Soc. Lond. 1937, 122B, 186-197.

46. Howe, H.A. Amer. J. Physiol. 1935, 111, 187-191.

47. Howe, H.A. and Guild, S.R. Anat. Rec. Suppl. 1933, 55, 20-21.

48. Davis, H., Derbyshire, A.J., Lurie, M.H. and Saul, L.J. Amer. J. Physiol. 1934, 107, 311-332.

49. Lurie, M.H., Davis, H. and Derbyshire, A.J. Ann. Otol. Rhinol. & Laryngol. 1934, 43, 321-343.

50. Lurie, M.H., Laryngoscope St. Louis, 1934, 44, 488-498.

51. Hughson, W., Thompson, E. and Witting, E.G. Ann. Otol. Rhinol. & Laryngol. 1935, 44, 777-791.

52. McCrady, E. Ann. Otol. Rhinol. & Laryngol. 1935, 44, 715-719.

53. Larsell, O., McCrady, E. and Zimmerman, A. J. comp. Neurol. 1935, 63, 95-118.

54. McCrady, E., Wever, E.G. and Bray, C.W. J. exper. Zool. 1937, 75, 503-517.

55. McCrady, E., Wever, E.G. and Bray, C.W. J. comp. Psychol. 1940, 30, 17-21.

56. McCrady, E., Wever, E.G. and Bray, C.W. Arch. Otolaryngol. 1944, 40, 233-248.

57. Fowler, E.P. Jr. and Forbes, T.W. Proc. Soc. exper. Biol. 1935, 32, 827-829.

58. Eyster, J.A.E., Bast, T.H. and Krasno, M.R. Amer. J. Physiol. 1937, 119, 305.

59. Fowler, E.P. and Forbes, T.W. Amer. J. Physiol. 1936, 116, 51-52.

60. Fowler, E.P. and Forbes, T.W. Amer. J. Physiol. 1936, 117, 24-35.

61. Fowler, E.P. and Forbes, T.W. Ann. Otol. Rhinol. & Laryngol. 1936, 45, 859-864.

62. Wever, E.G. and Bray. C.W. Ann. Otol. Rhinol. & Laryngol. 1937, 46, 291-302.

63. Walzl, E.M. Amer. J. Physiol. 1939, 125, 688-698.

64. Bast, T.H. and Eyster, J.A.E. Ann. Otol. Rhinol. & Laryngol. 1935, 44, 792-803.

65. Eyster, J.A.E., Bast, T.H. and Krasno, M.R. Amer. J. Physiol. 1935, 113, 40.

66. Dubner, H., Gerard, R.W. and Kobrak, H. Amer. J. Physiol. 1936, 116, 38.

67. Kobrak, H.G., Lindsay, J.R., Perlman, H.B. and Dubner, H. Arch. Otolaryngol. 1938, 27, 59-66.

68. Gilse, P.H.G.v. Acta oto-laryng. Stockh. 1934, 20, 23-31.

69. Hughson, W., Thompson, E. and Witting, E.G. Laryngoscope St. Louis, 1937, 47, 480-491.

70. Stevens, S.S., Davis, H. and Lurie, M.H. J. Gen. Psychol. 1935, 13, 297-315.

71. Hinnen, A.B. Ned. Tidschr. Genseek. 1936, 80, 1268-1271.

72. Walzl, E.M. and Bordley, J.E. Amer. J. Physiol. 1942, 135, 351-360.

73. Hallpike, C.S. and Rawdon-Smith, A.F. Nature, 1934, 133, 614.

74. Culler, E.A. Ann. Otol. Rhinol. & Laryngol. 1935, 44, 807-813.

75. Culler, E.A., Willman, J. and Mettler, F.A. Amer. J. Physiol. 1937, 119, 292.

76. Culler, E.A., Coakley, J.D., Lowy, K. and Gross, N. Amer. J. Psychol. 1943, 56, 475-500.

77. Kemp, E.H. and Johnston, P. Science 1939, 90, 405.

78. Eyster, J.A.E., Bast, T.H. and Krasno, M.R. Laryngoscope St. Louis, 1937, 47, 461-479.

79. Grüneberg, H., Hallpike, C.S. and Ledoux, A. Proc. Roy. Soc. Lond. 1940, 129B, 154-173.

80. Leiri, F. Acta oto-laryng. Stockh. 1934, 19, 265-285.

81. Leiri, F. Acta oto-laryng. Stockh. 1935, 22, 111-123.

82. Leiri, F. Acta Soc. Med. Fennicae "Duodecim" 1935, 21B, 1-115.

83. Hallpike, C.S. and Rawdon-Smith, A.F. Ann. Otol. Rhinol. & Laryngol. 1937, 46, 976-990.

84. Hallpike, C.S. and Hartridge, H. Proc. Roy. Soc. Lond. 1937, 123B, 177-193.

85. Gatty, O. and Rawdon-Smith, A.F. Nature 1937, 139, 670.

86. Kupfer, E. Arch. f. Ohren-, Nasen,-u. Kahlkopfh. 1931, 128, 339-344.

87. Voss, O. Die Naturwissenschaften 1933, 21, 721.

88. Kupfer, E. Monatsch. f. Ohrenh. 1934, 68, 943, 1041, 1208, 1294, 1462.

89. Kupfer, E. J. Laryngol. 1938, 53, 16-31.

90. Hallpike, C.S., Hartridge, H. and Rawdon-Smith, A.F. Nature 1936, 138, 839.

91. Davis, H., In, Murchison C. (Ed). A Handbook of General Experimental Psychology, Clark University Press, Worcester, Mass. 1934, 962-986.

92. Derbyshire, A.J. and Davis, H. Amer. J. Physiol. 1935, 113, 35.

93. Brenner, R., Untersuchungen und Beobachtungen auf den Gebiete der Electrotherapie. Leipzig, 1868.

94. Jellinek, S. and Schreiber, T. Wien.klin. Wschr. 1930, 43, 417.

95. Gersuni, G.V. and Volakhov, A.A. J. Physiol. U.S.S.R. 1934, 17, 1259.

96. Stevens, S.S. J. acoust. Soc. Amer. 1937, 8, 191-195.

97. Arapova, A.A., Gersuni, G.V. and Volakhov, A.A. J. Physiol. 1937, 89, 122-131.

98. Kahler and Ruf. Z. Hals.-Nas.-u. Ohrenheilk. 1931, 29, 218-230.

99. Gersuni, G.V. and Volakhov, A.A. J. exper. Psychol. 1936, 19, 370-382.

100. Gersuni, G.V. and Volakhov, A.A. J. Physiol. 1937, 89, 113-121.

101. Perwitzschky, R. Z. Hals.-Nas.-u. Ohrenheilk. 1930, 26, 477.

102. Gersuni, G.V., Lebedinski, A.W. and Volakhov, A.A. J. Physiol. U.S.S.R. 1934, 17, 168.

103. Andreev, A.M., Gersuni, G.V. and Volakhov, A.A. J. Physiol. U.S.S.R. 1934, 17, 546.

104. Andreev, A.M., Gersuni, G.V. and Volakhov, A.A. J. Physiol. U.S.S.R. 1935, 18, 250-256.

105. Stevens, S.S. and Jones, R.C. J. Acoust. soc. Amer. 1939, 10, 261-269.

106. Jones, R.C., Stevens, S.S. and Lurie, M.H. J. Acoust. soc. Amer. 1940, 12, 281-290.

107. Craik, K.J.W., Rawdon-Smith, A.F., and Sturdy, R.S. J. Physiol. 1937, 90, 3P-5P.

108. Hartridge, H. J. Physiol. 1936, 86, 64P-65P.

109. Hartridge, H. Phys. Soc. Proc. 1936, 48, 145-152.

110. Hartshorn, L. Phys. Soc. Proc. 1937, 49, 194-197.

111. Hartridge, H. Brit. J. Psychol. 1921, 12, 142.

112. Kellaway, P. and Brighouse, G. J. exper. Psychol. 1943, 33, 514-516.

113. Barany, E. Nature 1937, 139, 633.

114. Wever, E.G. Psychol. Rev. 1929, 36, 402-523.

115. Hallpike, C.S., Hartridge, H. and Rawdon-Smith, A.F. Phys. Soc. Proc. 1937, 49, 190-193.

116. Hallpike, C.S., Hartridge, H. and Rawdon-Smith, A.F. Proc. Roy. Soc. Lond. 1937, 122B, 175-185.

117. Wever, E.G. and Bray, C.W. J. cell. comp. Physiol. 1933, 4, 79-93.

118. Wever, E.G. J. comp. Psychol. 1935, 20, 17-20.

119. Pumphrey, R.J. and Rawdon-Smith, A.F. Nature 1936, 137, 990.

120. Pumphrey, R.J. and Rawdon-Smith, A.F. Proc. Roy. Soc. Lond. 1936, 121B, 18-27.

121. Pumphrey, R.J. and Rawdon-Smith, A.F. J. Physiol. 1936, 87, 4P-5P.

122. Ashcroft, D.W. and Hallpike, C.S. J. Physiol. 1934, 81, 23P-24P.

123. Aschroft, D.W. and Hallpike, C.S. J. Laryngol. 1934, 49, 450-460.

124. Ross, D.A. J. Physiol. 1936, 86, 117-146.

125. Adrian, E.D., Craik, K.J.W. and Sturdy, R.S. Proc. Roy. Soc. Lond. 1938, 125, 435-455.

126. Wever, E.G. and Bray, C.W. Acta oto-laryng. Stockh. 1931, 16, 154-159.

127. Wever, E.G. and Bray, C.W. J. comp. Psychol. 1936, 22, 353-363.

128. Wever, E.G. and Bray, C.W. Psychol. Bull. 1936, 33, 607.

129. Wever, E.G. and Bray, C.W. Proc. Amer. phil. Soc. 1937, 78, 407-410.

130. Grossmann, F. and Spielmann, K. Monatsch. f. Ohrenh. 1937, 71, 537-539.

131. Crowe, S.J. and Hughson, W. Z. Hals.-Nas.-u. Ohrenheilk. 1931, 30, 65-70.

132. Bordley, J.E. and Hardy, M. Arch. Otolaryngol. 1937, 26, 649-657.

133. Guild, S.R. Ann. Otol. Rhinol. & Laryngol. 1936, 45, 736-754.

134. Wever, E.G. and Bray, C.W. Ann. Otol. Rhinol. & Laryngol. 1936, 45, 822-830.

135. Hughson, W., Thompson, E. and Witting, E.G. Ann. Otol. Rhinol. & Laryngol. 1936, 45, 844-848.

136. Crowe, S.J., Hughson, W. and Witting, E.G. Arch. Otolaryngol. 1931, 14, 575-580.

137. Wever, E.G. and Bray, C.W. Ann. Otol. Rhinol. & Laryngol. 1937, 46, 947-961.

138. Wiggers, H.C. Amer. J. Physiol. 1937, 120, 771-780.

139. Smith, K.R. J. exper. Psychol. 1943, 33, 96-107.

140. Thompson, E., Howe, H.A. and Hughson, W. Amer. J. Physiol. 1934, 110, 312-319.

141. Hughson, W. and Crowe, S.J. J. Amer. med. Ass. 1931, 96, 2027-2028.

142. Hughson, W. and Crowe, S.J. Ann. Otol. Rhinol. & Laryngol. 1932, 41, 332-348.

143. Finch, G., Culler, E.A. and Girden, E.S. Psychol. Bull. 1933, 30, 581.

144. Culler, E.A., Finch, G. and Girden, E.S. Sciencé, 1933, 78, 269-270.

145. Culler, E.A., Finch, G. and Girden, E.S. J. Psychol. 1936, 2, 409-419.

146. Hughson, W. Amer. J. Physiol. 1932, 101, 396-407.

147. Kellaway, P. Arch. Otolaryngol. 1944, 39, 203-210.

148. Kellaway, P. Arch. Otolaryngol. 1945, 41, 252-260.

149. Kellaway, P. Amer. J. Psychol. 1945, 63, 25-42.

150. Pflüger, E. Pflüger's Arch. 1891, 1, 337.

151. Thörner, W. Zeitschr. f. allg. Physiol. 1908, 1, 79.

152. Tigerstedt, C. Zeitschr. f. Biol. 1912, 63, 451.

153. Heinbecker, P. and Bishop, G.H. Amer. J. Physiol. 1931, 96, 613.

154. Scott, D. J. Physiol. 1934, 82, 321.

155. Haberlandt, L. Pflüger's Arch. 1911, 127, 435.

156. Gerard, R.W. and Marshall, W.H. Amer. J. Physiol. 1933, 104, 575-585.

157. Worozonow, D.S. Pflüger's Arch. 1935, 235, 96-102.

158. Titeca, J. Arch. Int. de Physiol. 1935, 41, 1.

159. Gasser, H.S. Amer. J. Physiol. 1935, 111, 35-50.

160. Graham, H.T. and Lorente de Nó, R. Amer. J. Physiol. 1938, 123, 326-340.

161. Field, H. and Brücke v., E.Th. Pflüg. Arch. ges. Physiol. 1926, 214, 103-111.

162. Bugnard, L. and Hill, A.V. J. Physiol. 1935, 83, 394-406.

163. Gerard, R.W. and Forbes, A. J. Physiol. 1928, 86, 178.

164. Boyd, T.E. and Gerard, R.W. Amer. J. Physiol. 1930, 92, 656.

165. Cattell, McK. and Gerard, R.W. J. Physiol. 1935, 83, 407-415.

166. Bugnard, L. and Hill, A.V. J. Physiol. 1935, 83, 416-438.

167. Brücke v., E.Th., Early, M. and Forbes, A. J. Neurophysiol. 1941, 4, 456-472.

168. Forbes, A. and Rice, L.H. Amer. J. Physiol. 1929, 90, 119-145.

169. Gasser, H.S. and Grundfest, A. Amer. J. Physiol. 1936, 117, 113-133.

170. Kato, G. The Further Studies on Decrementless Conduction, Tokyo, 1926, 112.

171. Trendelenburg, W. Arch. f. Physiol. 1903, 271-310.

172. Umrath, K. Z. Biologie, 1925, 83, 535-543.

173. Tigerstedt, R. Die Physiologie des Kreislaufes, Berlin, 1921, Vol. 2, 472.

174. Adrian, E.G., Cattell, J.M. and Hoagland, H. J. Physiol. 1931, 73, 377.

175. Hoagland, H. J. Gen. Physiol. 1933, 16, 911-923.

176. Echlin, F. and Fessard, A. J. Physiol. 1938, 93, 312-334.

177. Gotch, F. J. Physiol. 1910, 40, 250.

178. Bazett, H.C. J. Physiol. 1908, 36, 414-430.

179. Amberson, W.R. J. Physiol. 1930, 69, 60.

180. Adrian, E.D. J. Physiol. 1914, 48, 453-464.

181. Schoepfle, G.M. and Erlanger, J. Amer. J. Physiol. 1941, 134, 694-704.

182. Matthews, B.H.C. J. Physiol. 1931, 71, 64-110.

183. Bronk, D.W. J. Physiol. 1929, 67, 270.

184. Gerard, R.W. Amer. J. Physiol. 1930, 92, 498-541.

185. Galambos, R. and Davis, H. J. Neurophysiol. 1943, 6, 37-57.

186. Erlanger, J. and Blair, E.A. Amer. J. Physiol. 1931, 99, 108-128.

187. Lorente de Nó, R. Laryngoscope 1933, 43, 1-38.

188. Poliak, S. Z. ges. Neurol. Psychiat. 1927, 110, 1-49.

189. Tello, J.F. Trab. Lab. Invest. biol. Univ. Madrid 1933, 28, 152-186.

190. Stevens, S.S. and Davis, H. Hearing: Its Psychology and Physiology, John Wiley and Sons, Inc., New York, 1938.

191. Blau, L.W. Frank. Inst. J. 1928, 206, 355-378.

192. Reboul, J.A. J. de physique 1938, 9, 185-194.