Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*June* 14, 1956]

Some Ocular Effects of Diencephalic Stimulation in the Experimental Animal[1]

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CENTRAL nervous mechanisms have been considered of importance in the regulation of numerous bodily functions, and in the maintenance of the steady state of the internal environment. In particular, much attention has been paid to the diencephalon from clinical, anatomical and physiological aspects.

From the experimental standpoint it has been shown (Bard, 1928 ; Ranson and Magoun, 1933) that when structures within the posterior part of the hypothalamus are stimulated marked activity of the sympathetic nervous system results. These responses, found in such emergency states as fear and anger, are accompanied by vasoconstriction in the skin and gut, an increase in heart rate, contraction of the spleen, dilatation of the pupil and contraction of the nictitating membrane in animals which possess one.

In view of this influence, exerted on many viscera, is it likely that the eye is in any way specifically affected and does its clinical application extend to glaucoma? The idea that the diencephalon influences the intra-ocular pressure is not new and much speculation has been based on physiological and, in particular, clinical features. We are familiar with cases which suggest some such connexion; for instance glaucoma patients who produce a sudden rise in intra-ocular pressure as a result of an emotional disturbance, and the effect of barbiturates in lowering the tension or preventing the rise in similar cases is well known. In fact, certain authors, notably Magitot (1949), Elwyn (1938) and Thiel (1952), have postulated the existence of "centres" controlling ocular tension and are confident that they will be revealed by future work.

Present ideas on the association between the higher vegetative systems and the eye are based therefore more on speculation than physiological facts, and there is thus need for further experimental study. Our aim, therefore, is primarily a physiological one, the intention being to examine in more detail the responses in the eye to stimulation in an area which is known to produce autonomic responses.

Previous work on diencephalic stimulation dates back to Karplus and Kreidl (1909) who found that electrical stimulation of the antero-lateral hypothalamus resulted in sympathetic responses, and later they showed that these responses could be elicited even when the cerebral hemispheres had been removed sufficiently long before to allow degeneration of cortico-fugal fibres. Thus the idea was conceived that the hypothalamus contained "centres", and the theory of the presence of an integrative vasomotor centre was furthered by the reports of Magoun (1938) and Eliasson *et al.* (1954).

From a functional standpoint stimulation of the posterior part of the hypothalamus is known to be accompanied by sympathetic activity whilst stimulation in the middle and anterior parts is thought to evoke parasympathetic responses. This division is far from being clear cut; for example, pressor and depressor responses have been reported from the same area, whilst yet again similar responses have been obtained from stimulation of widely scattered points.

As far as structure is concerned the enthusiasm of anatomists has led to descriptions of much detailed cyto-architecture, and as many as 20 nuclear masses are reported in the hypothalamus (Ingram *et al.*, 1932), though no functional correlation to the anatomical detail has been demonstrated.

It is therefore hardly reasonable to expect that any nervous control of the intra-ocular pressure should be mediated by a discrete anatomical structure. For the present we would prefer not to impose any rigid anatomical limits upon a regulatory mechanism, if such exists.

[1]For publication the original paper has been shortened and much detail has of necessity been omitted, particularly regarding methods. This detail will be supplied in the publication of subsequent work.

Previous Work

Earlier work on the eye reactions was confined mainly to pupillary responses as incidental to more general effects. The work of Ranson and Magoun (1933) showed that pupillary dilatation could be obtained from almost anywhere in the hypothalamus but mainly from the lateral hypothalamic area, the region around the fornix and throughout the length of the hypothalamus. Hess (1939) showed that stimulation of the anterior and medial parts of the hypothalamus was accompanied by a fall of blood pressure and contraction of the pupil, the opposite effects being obtained when the posterior and lateral areas were stimulated.

Only recently has more specific attention been paid to the influence of the hypothalamus on intra-ocular pressure, for example by Schmerl and Steinberg (1950), Nagai *et al.* (1951), Weinstein (1954) and still more recently by von Sallmann and Loewenstein (1955). The last-mentioned approached the problem more critically and employed a better technique, although the area investigated was comparatively limited especially in the parasagittal direction. Their factual account of the results indicates the intricate nature of the matter. In general, stimulation of a ventral zone in the hypothalamus led to a mass sympathetic discharge accompanied by rises of blood pressure and intra-ocular pressure. From a more dorsal region they obtained changes in intra-ocular pressure which were isolated events bearing no constant relationship to blood pressure changes.

Our own experiments are similar in principle to those of previous investigators, but we felt that there was a need to use a standard stimulus throughout the series of animals in order that a fair comparison could be made between the observed effects. We have also extended the investigation into more lateral areas of the diencephalon.

METHODS

Cats weighing approximately 3 kg. were anæsthetized with intravenous chloralose (1% solution, 100 mg./kg.). For each experiment the head of the cat was fixed in a stereotaxic instrument and a dental drill employed for drilling holes in the skull in the appropriate position. Points within the brain were referred to the usual stereotaxic planes, our zero H level being the horizontal plane passing through the internal auditory meatuses and the lower orbital margins.

The femoral arterial blood pressure and intra-ocular pressures were continuously recorded photographically with the aid of optical manometers (*see* Greaves and Perkins, 1952). Movements of the nictitating membranes were recorded on the same record by means of a mirror fixed to a lever attached to the nictitating membranes.

Changes in pupil size were measured and correlated with blood pressure and intra-ocular pressure changes in the final assessment of the results of the experiment.

Stimulation

For this particular series of experiments we employed unipolar cathodal stimulation, the anode being placed within the rectum. The electrode itself was of 4/1,000 inch diameter nickel wire within a 0·8 mm. external diameter straight glass capillary tube, the whole mounted in a watchmaker's lathe chuck, and capable of being moved in three planes at right angles. A square wave pulse of 1 msec duration, 30 c/s was used, the circuit being arranged to give a current of 0·2 mA and to avoid variations due to polarization at the electrode tip. This stimulus was chosen by trial and error in preliminary experiments as being the lowest intensity causing full dilatation of the pupil in a suitable area. The electrode was placed in position at H+15 and after three minutes the first stimulus was applied for 60 seconds. Subsequent stimulations of 60 seconds duration were made at 5-minute intervals, the electrode being lowered 1 mm. between stimulations, each point in the brain receiving only one application of the stimulus. Two electrode tracks were made on each animal, one on each side of the mid-line, and generally separated by 7 mm. The position of the electrode was determined by subsequent histological examination of the brain, allowance being made for shrinkage of the tissue during fixation.

Diagrams modified from the Atlas of Jasper and Ajmone-Marsan were prepared for frontal planes separated by 1 mm. extending from A 9 to A 14 and the results of each experiment were plotted on these. After examination of the slide showing the needle tip it was possible to decide upon the appropriate frontal plane diagram to be used. The lateral points were decided by the relationship of the needle tracks to the anatomical structures seen on the slide.

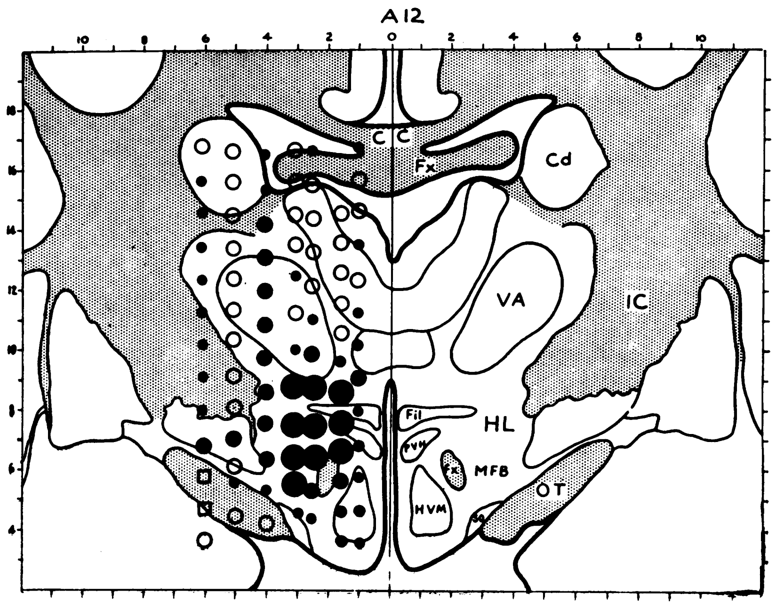
RESULTS

These results were obtained in 32 experiments in which 630 points in the diencephalon were stimulated. Only the main features can be given here. These will be reported under four headings, viz. (1) Pupillary responses; (2) Nictitating membrane effects; (3) Blood pressure effects, and (4) Intra-ocular pressure changes.

Pupillary Responses

Pupillary dilatations were elicited by stimulation of points which were scattered widely throughout the diencephalon, but the most marked effects were obtained from stimulation in the lateral part of the hypothalamus. The dilatations were usually bilateral and approximately equal on the two sides. The impression was gained that dilatations obtained from stimulation in the hypothalamus differed in some respects from those arising from stimulations elsewhere. Dilatations from stimuli in the thalamus were small (usually 1–2 mm.) and took place slowly. Dilatations from stimuli in the hypothalamus were larger and the pupil began to dilate rapidly as soon as the stimulus was switched on, reaching a maximum in 5–10 seconds. The pupil began to return to its initial size as soon as the stimulus was switched off.

Fig. 1 shows the pupil effects from stimulation of points in the diencephalon in the frontal plane A 12.



PUPIL RESPONSES

- O No effect
- • Pupil dilatation less than 3 mm.
- ● Pupil dilatation 3–6 mm.
- ⬤ Pupil dilatation more than 6 mm.
- □ Pupil constriction

FIG. 1.—Map showing points in the diencephalon from which pupillary responses were obtained. Frontal plane 12 mm. anterior to inter-aural line. The edges of the map are marked in divisions representing millimetres of brain tissue. The vertical scale zero is the horizontal (H) plane.

Contractions of the pupil were seldom elicited in these experiments, but two points in the optic tract from which small pupillary contractions were obtained can be seen in Fig. 1. Contractions were also obtained from points in plane A 8 which lies slightly posterior to the area in which we were mainly interested.

Nictitating Membrane Effects

Whereas pupillary responses were often observed, nictitating membrane effects were relatively uncommon and the changes were always small. Both contractions and relaxations of the membrane were recorded, but contractions occurred about twice as frequently as relaxations. It should be added that some changes in the nictitating membrane record must be interpreted with caution since they may be due to small movements of the rectus or orbicularis muscles.

Blood Pressure Responses

Alterations in the systemic blood pressure often induce changes in intra-ocular pressure in experimental animals and therefore a brief description will be given of the blood pressure changes observed in this investigation.

The most frequent blood pressure change was a simple rise or fall during stimulation, but complex effects also occurred. The response usually started promptly at the commencement of stimulation, and sometimes persisted for a time after the stimulus was switched off or was succeeded occasionally by a temporary change in the opposite direction.

Blood pressure effects were obtained from stimulation of many areas in the diencephalon but the most marked effects were elicited from the hypothalamus, where rises of blood pressure were obtained more frequently than falls.

Some correlation could be established between the type of blood pressure response and the site of stimulation, but this was not as consistent as the analogous correlation for the pupillary effects. This suggests that the pupillary response to hypothalamic stimulation is determined by a smaller number of factors than the blood pressure response.

Intra-ocular Pressure Effects

Since alterations in blood pressure frequently influence intra-ocular pressure, it is of comparatively little value to study the intra-ocular pressure changes without taking into account simultaneous blood pressure effects. If biphasic responses are excluded, there are nine possible combinations of intra-ocular pressure change and blood pressure change. When the results of 630 stimulations were analysed on the basis of this classification, the main conclusions were: (i) in slightly more than half the stimulations there was no change of intra-ocular pressure, (ii) the majority of intra-ocular pressure changes were accompanied by blood pressure changes in the same direction, (iii) changes of intra-ocular pressure which were independent of blood pressure changes resulted from slightly less than one-fifth of all stimuli, and (iv) the incidence of each combination of intra-ocular pressure and blood pressure was essentially the same in the two eyes and independent of the side of stimulation.

The most interesting intra-ocular pressure responses were those which could not be explained by simultaneous blood pressure changes, and two types of response requiring further consideration are: (1) a rise of intra-ocular pressure unaccompanied by a rise of blood pressure (Fig. 2), and (2) a fall of intra-ocular pressure accompanied by a rise of blood pressure (Fig. 3).

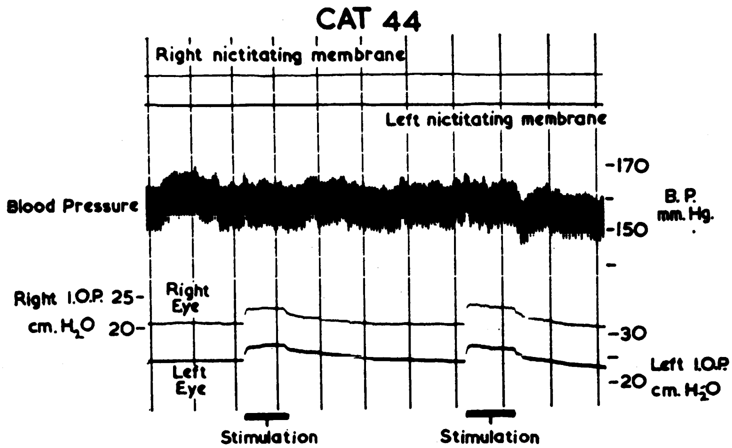


FIG. 2.—Tracing showing bilateral rises of intra-ocular pressure unaccompanied by blood pressure changes. (Interval between vertical time-marker lines=60 sec.)

With regard to the first of these, there are two observations which may explain how this rise of intra-ocular pressure occurs in the absence of a rise of blood pressure. Firstly, at times the rise in pressure and the subsequent return at the end of stimulation were rapid, and, secondly, they were occasionally accompanied by abrupt movements of the nictitating membrane record. These two observations suggest that the increase in intra-ocular pressure is sometimes due to pressure on the globe from contraction of striated or unstriated muscle within the orbit.

The combination of a fall in intra-ocular pressure with an increase in systemic blood pressure could be explained in several ways, but the fall in intra-ocular pressure resembles the effect of stimulation of the cervical sympathetic trunk. Therefore it is possible that, in the area of the hypothalamus yielding this response, stimulation evokes a sympathetic discharge which produces a rise of general blood pressure together with a marked vasoconstriction in a vascular territory which includes the eye. However, further experiments are needed to establish this hypothesis.

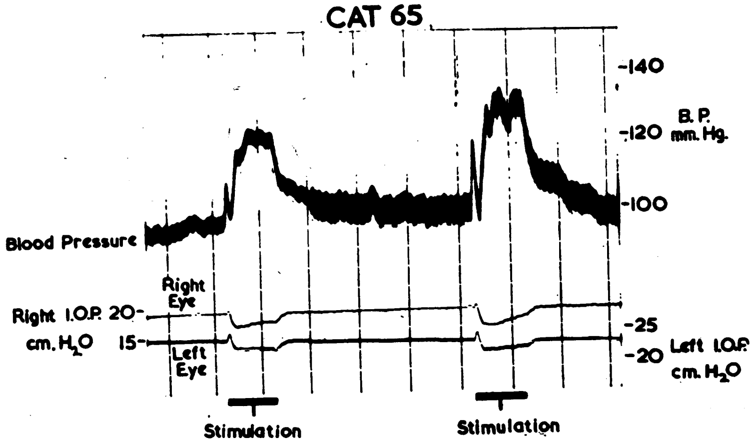


FIG. 3.—Tracing showing bilateral reduction of intra-ocular pressure accompanied by rise of blood pressure. (Interval between vertical time-marker lines = 60 sec.)

An attempt has been made to correlate the intra-ocular pressure responses which were independent of blood pressure changes with the site of stimulation in the diencephalon. The results for one frontal plane (A 11) are illustrated in Fig. 4. Intra-ocular pressure rises which were not associated with rises in blood pressure were elicited from points which, although widespread, occurred most frequently in the postero-dorsal region of the diencephalon. The points at which stimulation gave a fall of intra-ocular pressure with a simultaneous blood pressure rise were few in number, but, with one exception, were confined to the medial part of the hypothalamus and were grouped round the fornix. As far as can be judged from the present results, it appears that stimulation in this area elicits this type of response fairly consistently.

Comment.—The pupillary responses reported here do not differ substantially from those described by previous workers (e.g. Ranson and Magoun, 1933). Pupillary contractions were seldom elicited, but this is probably due in part to the use of chloralose anæsthesia which produced slit-like pupils in most of the cats.

The most interesting responses were those in which the intra-ocular pressure fell although accompanied by a rise in general blood pressure. The interest is heightened by the fact that they appear to be elicited from a comparatively well-defined area of the hypothalamus closely related to the anterior column of the fornix. It seems likely that the reduction of intra-ocular pressure is due to constriction of the ocular blood supply, but it is not yet clear whether this vasoconstriction is confined to the eye or is more generalized, involving perhaps the entire head region.

Our observations that diencephalic stimulation can cause changes of intra-ocular pressure which are not merely reflections of blood pressure variations suggest that efferent pathways may exist by which the central nervous system could influence the intra-ocular pressure. Nevertheless proof of the existence of such pathways would strengthen, but not establish, the concept of a nervous mechanism controlling the intra-ocular pressure, since it must be borne in mind that such a mechanism would require an afferent pathway for which there is at present no definite evidence. Finally, we must emphasize that our observations do not necessarily indicate that the diencephalon itself influences the intra-ocular pressure, since the responses obtained could have arisen from the stimulation of tracts which run through the diencephalon without interruption or which are relayed there. Thus, while the observations

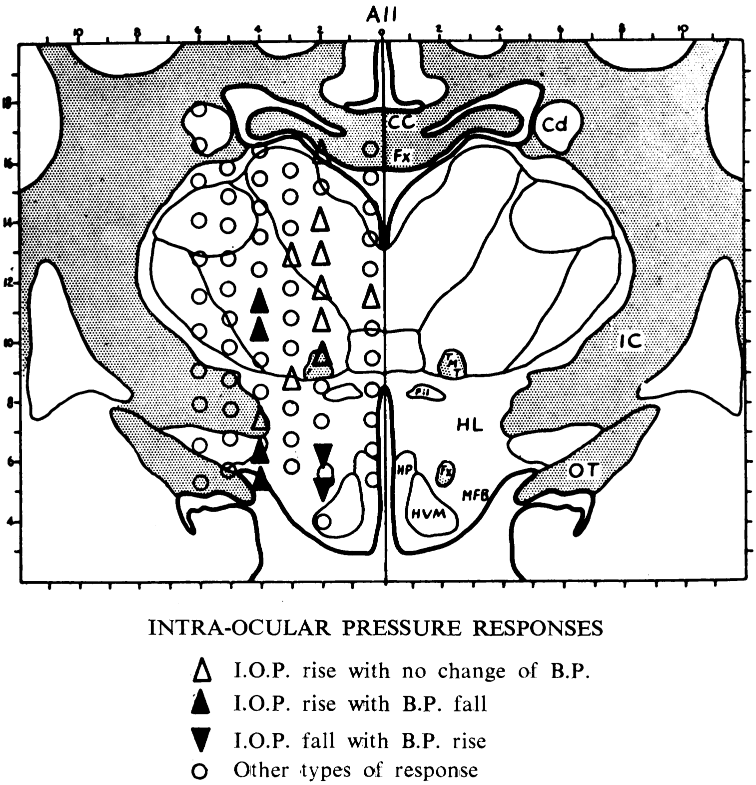


FIG. 4.—Map showing points in the diencephalon from which independent changes in intra-ocular pressure were elicited. Frontal plane 11 mm. anterior to inter-aural line.

which have been described provide a useful basis for further work, it may be necessary to extend the search beyond the diencephalon into other parts of the central nervous system.

Acknowledgments.—We are grateful to Sir Stewart Duke-Elder for his encouragement in this research and also for the help given by the Department of Medical Illustration. We should also like to acknowledge a grant from the Pigott Wernher Trust Fund covering the expenses of this work.

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