J. Physiol. (1950) 111, 335–346 611.814.1:612.492

HYPOTHALAMIC CONTROL OF THE ANTERIOR PITUITARY GLAND AND BLOOD LYMPHOCYTES

By J. de GROOT and G. W. HARRIS

From the Physiological Laboratory, University of Cambridge

(*Received* 6 *December* 1949)

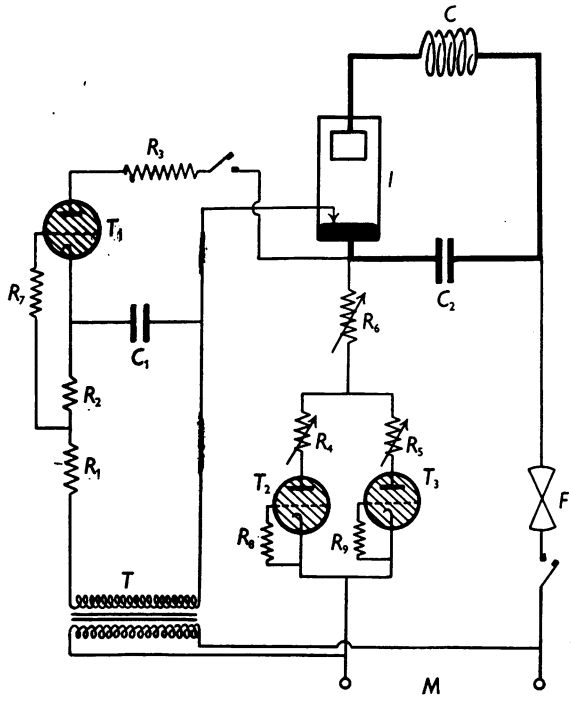
It has been shown that the secretion of the anterior pituitary gland is essential to the development of an acute lymphopenia following emotional stress (Dougherty & White, 1944; Colfer, de Groot & Harris, 1950). The probable sequence may be represented: emotional stress (nervous system)—adenohypophysis—adrenal cortex—lymphopenia. It was decided: (*a*) to stimulate various regions of the hypothalamus and pituitary gland electrically, to see whether secretion by the anterior pituitary with a resultant lymphopenia could be so induced; and (*b*) to place lesions in different parts of the hypothalamus and pituitary to see whether the lymphopenia that follows emotional stress in normal rabbits could be blocked. In this way it was hoped to obtain evidence relevant to hypothalamic control of pituitary secretion and the anatomical pathways by which any such control was mediated.

Although the lymphopenia that follows anterior pituitary secretion is the most rapid and easily observed indicator of such activity available, care must be taken in using this reaction that the animal is not subjected to incidental emotional stress in the course of the experiment. Therefore, in order to stimulate the hypothalamus and pituitary gland electrically in the unanaesthetized *quiescent* rabbit, it became necessary to use a specialized technique.

METHODS

Adult rabbits, between 2 and 3 kg. body weight, and usually female, were used. The method of performing blood counts and inducing emotional stress was as described by Colfer, de Groot & Harris (1950). Electrical stimulation of various regions in the hypothalamus and pituitary gland was performed by the remote control method in the conscious unrestrained animal. The implanted units were similar to those described previously (Harris, 1947*b*). In order to stimulate the animal whilst free to move in its usual cage, a large primary coil 3 ft. in diameter was used. A primary coil of these dimensions entails the use of high amperage current pulses, and to obtain these a modification of the method of Chaffee & Light (1934) was adopted. A single primary coil in the horizontal plane was used, since rabbits do not learn to rotate their heads voluntarily out of the plane of the coil. Short-lived variations in intensity of stimulation (due to movements of the head in eating or grooming the fur) were thought to be compensated by the prolonged periods of stimulation used

in these experiments, that is periods of 1 hr. The current pulses in the primary coil were produced by a circuit (Text-fig. 1) in which a 70 μF. condenser bank (C_2), charged from the mains (360 V. r.m.s.; 50 cyc./sec.) through two thyratrons (T_2, T_3, arranged in parallel and acting as rectifiers) to 500 V. is discharged at a later stage in the cycle through the ignitron (I) and the primary coil (C). The peak value of the current pulses through the primary coil is about 600 amp., and they recur at the frequency of the supply mains, 50 cyc./sec., i.e. at intervals of 20 m.sec. The point of discharge of condenser (C_2) is arranged to be about 15 msec. after the start of the charging pulse, and depends



Text-fig. 1. The primary circuit. The main charging-discharging circuit is on the right in the diagram, and the trigger circuit on the left. C, primary coil of $\frac{1}{2}$ in. copper tubing, 5 turns 3 ft. diameter. All connexions in heavy lines are made of $\frac{1}{2}$ in. copper tubing or 1 in. copper ribbon. C_1, 1 μF. condenser and C_2, 70 μF. condenser bank (condensers suitable for operation in a.c.); F, fuse; I, ignitron BK 24, water-cooled; M, mains supply, 360 V. r.m.s., 50 cyc./sec.; R_1, 1000 Ω.; R_2, 200 Ω.; R_3, 40 Ω.; R_4, R_5, R_6, 0–40 Ω.; R_7, R_8, R_9, 10 kΩ.; T, 1:1$\frac{1}{2}$ step-up mains transformer; T_1, T_2, T_3, thyratron valves, BT 5.

on a high voltage pulse (760 V.) being delivered through the ignitor or trigger circuit. This trigger pulse is obtained by charging condenser (C_1) via a 1:1$\frac{1}{2}$ step-up transformer from the mains, and then discharging through the thyratron (T_1) and ignitor of the ignitron, the timing of the discharge being determined by the phase difference in potential applied to the cathode and grid of the thyratron (T_1). Important technical points are that the connexions shown in heavy type in Text-fig. 1 have sufficient current-carrying capacity, that the ignitron be water-cooled, and that the condensers (C_1 and C_2) and resistances (R_4, R_5 and R_6) are able to withstand the applied voltages and currents. The mean current in the trigger circuit is about 0·14 amp., and in the ignitron circuit 2–3 amp. A small secondary coil similar to those implanted in the rabbits was found to develop a peak potential of 7·0 V. when placed in the centre of the field of the primary coil, and of 13·5 V.

when placed at the periphery of the field almost in contact with the primary coil. By restricting the size of the wooden cage containing the animal in the field of the primary coil, the induced voltage varies less than 2% for different positions in the cage. If a metal cage (of galvanized iron) is used, variations of up to 20% in the induced voltage may occur. Pl. 1, fig. 1, shows the wave-form of the pulse induced in a secondary coil. Stimulation of the hypothalamo-hypophysial region by this method produces the same visible signs in the rabbit as described previously (Harris, 1947*b*). The effect on the orbital structures is of value in standardizing the strength of the stimulus between different animals. The strength of stimulation may be most easily adjusted either by varying the resistance R_6 and thus the potential to which condenser C_2 is charged, or by varying the position of the animal's cage in the vertical plane of the primary coil. Electrical stimuli of this type have been shown previously to have a spread of $\frac{1}{2}$ mm. or less from the electrode tip so far as unmyelinated fibres of the supraoptico-hypophysial tract are concerned (Harris, 1947*b*, 1948*a*), and it seems likely that the effective spread for other unmyelinated hypothalamic fibres is of the same order of magnitude. The routine procedure was to place the animal in its cage within the primary coil and to find the appropriate strength of stimulus the evening before the experiment. The following day the initial blood sample was taken, stimulation applied for 1 hr., and further blood samples removed at $1\frac{1}{2}$ hr. intervals from starting stimulation. On the day of the experiment the animals were starved until the last blood sample had been taken. At least three experiments were performed on each animal, and usually on three consecutive days without removing the animal from within the primary coil, so that it became accustomed to the procedure and to its surroundings.

Electrolytic lesions have been placed in various parts of the hypophysis and hypothalamus. In preliminary experiments, the hypophysis was exposed from below by the parapharyngeal route of Jacobsohn & Westman (1940), a platinum electrode (anode) inserted into the gland and a direct current passed for 1 min. In all the later experiments that we describe below, the electrolytic lesion was made with the use of a stereotaxic instrument (Harris, 1937), the electrode insulated to within 0·5 mm. of its tip being inserted through a small trephine hole at bregma. The indifferent cathode was inserted rectally, and a direct current of 1·0 or 3·0 mA. passed for 1 min. This latter method was finally chosen as it involved less operative trauma, less risk of damage to the venous drainage of the gland and gave greater accuracy in placing the hypothalamic lesions. The lympho-penic response to the emotional stress stimulus was measured before operation and again on the first and third post-operative days, the animal being killed at the end of the last experiment.

Other operations. Cervical sympathectomy entailed bilateral removal of the superior cervical ganglion and upper part of the cervical sympathetic chain. In many excitable animals the caudal margin of each ear was denervated by removal of the great auricular nerve in order to facilitate the removal of blood.

Histological procedures. The rabbits bearing implanted coils were killed with chloroform, injected with 5% formol through the abdominal aorta, the head removed, trimmed and placed in 5% formol. The rabbits with electrolytic lesions were killed with chloroform, injected with 150 c.c. 1:3 indian ink solution through the carotid arteries, the head removed, trimmed and placed in 5% formol. After complete fixation all heads were decalcified in Bensley's solution, and a block of tissue, containing hypothalamus, base of skull and pituitary gland, embedded in celloidin. Serial sections, 100–250 μ. were cut and stained with haemalum and eosin.

RESULTS

Stimulation of hypothalamus and pituitary gland

Eighty-three experiments have been performed on fourteen rabbits in which different parts of the hypothalamus and pituitary gland have been stimulated electrically for hourly periods and the effect on the blood lymphocytes studied (see Table 1). The effect of stimulation on the lymphocyte count is expressed by giving the lymphocyte count at the third hour after beginning the stimulus

as a percentage of the initial (pre-stimulus) count. From the results of these experiments the animals fall into two groups.

TABLE 1. Lymphopenic responses to electrical stimulation of various regions of the hypothalamus and pituitary gland. The lymphopenic response is expressed by giving the lymphocyte count at the third hour after starting stimulation as a percentage of the initial count

Rabbit	Lymphopenic responses to electrical stimulation	Average	Response to emotional stress stimulus	Electrode position
152	80, 101, 113, 96, 113, 112	103	41	Between zona tuberalis and main part of pars distalis
161	66, 63, 78, 70, 82, 75, 75, 82, 64	73	78	Posterior region of tuber cinereum, slightly to right of midline
208	76, 94, 84, 85, 100, 105, 90, 109, 98, 92	93	77	In contact with right side of infundibular stem and into pars distalis and intermedia
210	111, 98, 85, 93, 103, 87, 86, 90	94	—	Through supraopticohypophysial tract in median eminence and in pars tuberalis*
214	98, 79, 89, 97, 100, 108	95	75	Pars distalis
219	67, 75, 73, 80, 82	75	52	Posterior region of tuber cinereum midline
222	92, 88, 89, 116, 106, 99, 91	97	73	Lateral tuber cinereum and in zona tuberalis
232	86, 90, 107, 114, 95, 114	101	77	High in tuber cinereum, 1·5 mm. above infundibular stem
237	98, 94, 93, 84, 99, 82, 73, 97, 112	92	62	In supraopticohypophysial tract in median eminence*
258	107, 98, 102	102	68	Third ventricle 0·5 mm. above infundibular stem
271	93, 96, 104	98	68	Left wall of tuber cinereum
272	54, 66, 65, 49, c.s., 66†, 63†	59	55	Mammillary body and in junction of infundibular stem and infundibular process
273	78, 80, 70, 62, c.s., 54†, 68†	73	68	Right posterior region of tuber cinereum*
274	96, 95, 93	95	66	Pars distalis and intermedia and adjacent to right side of infundibular stem*

c.s., cervical sympathectomy.

* See Pl. 1, figs. 2, 5.

† These figures excluded when calculating average of responses.

Positive response. In twenty-two experiments on four animals (161, 219, 272, 273) a marked fall in blood lymphocytes was observed to follow stimulation. This lymphopenic response was very similar in time relations and magnitude to that following the application of an emotional stress stimulus in these and other animals. The onset was acute, the maximal fall in number of lymphocytes occurred at about the third hour, and by the sixth hour the initial level was returning or had been regained. Microscopic examination of the brain and pituitary gland showed the electrode tip to have been situated in the posterior

region of the tuber cinereum (161, 219, 273) (Pl. 1, fig. 3) and in the mammillary body and neurohypophysis (272). The responses to stimulation in these rabbits were quite constant; a definite lymphopenia followed each period of stimulation.

Negative response. Sixty-one experiments on the other ten rabbits failed to demonstrate consistent lymphopenic responses in any animal. An occasional lymphopenia was observed in several of these rabbits, but in none was it constantly obtained. The following regions of the hypothalamus and pituitary gland were negative to stimulation: high in tuber cinereum, 1·5 mm. above the infundibular stem (232); anterior part of the tuber cinereum including the median eminence and the supraopticohypophysial tract (210, 237) (Pl. 1, figs. 2, 4); the lateral region of the tuber cinereum (222, 271); the infundibular stem (208, 274) (Pl. 1, fig. 5); the pars tuberalis and zona tuberalis (152, 210, 222); the pars intermedia (208, 274); and the pars distalis of the pituitary gland (152, 208, 214, 274).

Two rabbits (272, 273), that gave a marked lymphopenia following stimulation of the posterior region of the tuber cinereum, were submitted to bilateral cervical sympathectomy. On the first and fourth days after sympathectomy both animals were again stimulated for 1 hr., and the lymphopenic response was found to be unaltered (Table 1).

Lesions in hypothalamus and pituitary gland

Lesions have been made in various parts of the pituitary gland and hypothalamus in twenty-five rabbits and the effect of an emotional stress stimulus on the blood lymphocytes studied. The effect of an emotional stress stimulus on the lymphocyte count is expressed by giving the lymphocyte count at the third hour after beginning the stimulus as a percentage of the initial count. Before operation the lymphopenic response of twenty-three of these animals to the usual emotional stress stimulus was $69{\cdot}1 \pm 2{\cdot}3$ (S.E. of mean of twenty-three observations). After placing the lesion the response was measured again on the first and third post-operative days. The results are summarized in Table 2. The animals may be seen to fall into three groups according to whether the post-operative lymphopenic response was unchanged (++), diminished (+), or absent (0). Six rabbits showed what were considered to be diminished responses (249, 254, 259, 260, 261, 277). It should be mentioned that observations on rabbits 249 and 254 on the third post-operative day showed a light fall in blood lymphocytes to 90% of the initial figure $1\frac{1}{2}$ hr. after the stimulus; these figures are not given in Table 2.

The lesions made in the region of the hypophysial stalk usually damaged more than one structure. In Table 2 are listed all the structures involved in the lesions. By correlating the structures damaged with the lymphopenic responses in different rabbits it is possible to make the following statements.

TABLE 2. Lymphopenic responses to an emotional stress stimulus after placing lesions in different regions of the hypothalamus or pituitary gland. The response to emotional stress is represented by the lymphocyte count at the third hour after the stimulus given as a percentage of the initial lymphocyte count

		Lymphopenic response			
Rabbit	Pre-op.	1st day Post-op.	3rd day Post-op.	Group	Lesions
246	83	54	—	+ +	Single mid-line. Pars distalis
247	60	67	—	+ +	Single mid-line. Pars distalis
249	—	93	99	+	Single mid-line. Pars distalis, intermedia, infundibular stem, tuber cinereum
250	—	96	107	0	Single mid-line. Zona tuberalis*
251	69	76	63	+ +	Single mid-line. Pars distalis
252	68	69	73	+ +	Single mid-line. Posterior part tuber cinereum
253	77	82	82	+ +	Single mid-line. Pars distalis, intermedia and infundibular stem*
254	58	88	106	+	Single mid-line. Zona tuberalis, anterior part
255	69	104	101	0	Single mid-line. Zona tuberalis and infundibular stem
256	81	73	60	+ +	Single mid-line. Central part of mammillary body
257	81	65	86	+ +	Single mid-line. Pars distalis and intermedia. Infundibular stem and tuber cinereum*
259	77	93	84	+	Single mid-line. Posterior part of mammillary body
260	73	93	88	+	Single mid-line. Pars distalis
261	66	118	94	+	Single mid-line. Pars distalis, pars intermedia, infundibular stem and tuber cinereum
263	84	88	82	+ +	Single mid-line. High in posterior part of tuber cinereum
264	67	92	70	+ +	Single mid-line. Posterior to optic chiasma
265	69	111	98	0	Single mid-line. Tuber cinereum, infundibular stem and pars intermedia*
266	52	101	99	0	Single mid-line. Tuber cinereum, infundibular stem, pars intermedia and pars distalis
267	77	70	75	+ +	Single mid-line. Infundibular stem and tuber cinereum
268	59	80	64	+ +	Single mid-line. Above tuber cinereum
270	70	72	63	+ +	Single mid-line. Infundibular stem and tuber cinereum
277	56	84	94	+	Bilateral. Posterior region of tuber cinereum*
278	55	82	83	+ +	Bilateral. Posterior region of tuber cinereum
279	73	121	96	0	Bilateral. Posterior region of tuber cinereum
280	60	102	102	0	Bilateral. Mammillary body*

+ +, represents normal lymphopenic response to emotional stress stimulus after operation; +, diminished or slight response; 0, abolition of the response. The structures involved in the lesions, to a greater or lesser extent, are listed.

* See Pl. 2, figs. 6, 11.

(*a*) *Lesions of the pars distalis.* Large lesions confined to the pars distalis (exclusive of the zona tuberalis) do not interfere with the lymphopenic response (rabbits 246, 247, 251). Two rabbits (253, 257) (Pl. 2, figs. 6, 7) in which other parts of the pituitary were involved as well as the pars distalis, showed normal lymphopenic responses. In other cases (249, 261, 266) in which the tuber cinereum was damaged as well as the pars distalis, the response was diminished or abolished. In only one animal (260) was a diminished response seen to follow a lesion confined to the pars distalis.

(*b*) *Lesions of the pars intermedia.* In no case was this structure alone damaged. In two rabbits (253, 257; see Pl. 2, figs. 6, 7), extensive damage to the pars intermedia was associated with a normal lymphopenic response; in two (249, 261) with a diminished response; and in two others (265, 266) with abolition of the response.

(*c*) *Lesions of the zona tuberalis.* This specialized region of the pars distalis was involved in three cases. In rabbit 250 (Pl. 2, fig. 8) the lesion clearly involved the whole of the zona tuberalis and the bony margin of the sella turcica, but no other structure; the lymphopenic response was abolished. In rabbit 254, the anterior region of the zona tuberalis was damaged, and the response was diminished. In the third case (rabbit 255) the zona tuberalis and the infundibular stem were extensively involved, and the response abolished.

(*d*) *Lesions of the infundibular stem.* In no case was this structure alone damaged. However, it was completely interrupted in rabbit 257 (Pl. 2, fig. 7), almost completely interrupted in rabbit 267, and damaged in rabbits 253 and 270. These four animals showed normal lymphopenic responses. In other cases in which the tuber cinereum or zona tuberalis were damaged as well as the infundibular stem, the response was diminished or abolished.

(*e*) *Lesions of the tuber cinereum.* In nine rabbits a single mid-line lesion was found to involve the posterior part of the tuber cinereum. In two animals (265, 266) the lesion extended laterally the width of the tuber cinereum in the region of the posterior part of the pars tuberalis or the posterior part of the primary plexus of the hypophysial portal vessels (Pl. 2, fig. 9). In these two rabbits the lymphopenic response was abolished. In both cases the lesion also interrupted the infundibular stem and extended into the adenohypophysis. In two other rabbits (249, 261) the lesion involved the pars distalis, pars intermedia, infundibular stem and the posterior part of the tuber cinereum. The tuberal lesion was again situated in the posterior part of the primary plexus but more localized to the mid-line. These animals showed a diminished lymphopenic response. In rabbit 257 the lesion involved the same structures but the tuberal lesion was confined to the mid-line and the lymphopenic response was normal. Rabbits 267 and 270 that had small mid-line lesions in the tuber cinereum behind the primary plexus, and rabbits 252 and 263 that had larger mid-line lesions more posteriorly, also showed normal lymphopenic responses.

In three rabbits (277, 278, 279) bilateral lesions involved the posterior part of the tuber cinereum. One animal (278) gave a normal lymphopenic response, one a diminished response (277) (Pl. 2, fig. 10) and in one (279) the response was abolished.

(*f*) *Lesions of the mammillary body.* In three animals the lesion was found to involve the mammillary body. In rabbit 259 the posterior part of this structure was damaged and the lymphopenic response found to be diminished; in rabbit 256 the lesion was confined to the mid-line part of the mammillary body and the response found normal; and in rabbit 280, a bilateral lesion completely destroyed the mammillary body without damage to surrounding structures (Pl. 2, fig. 11) and the lymphopenic response was abolished.

(*g*) *Other hypothalamic lesions.* In two rabbits that gave normal responses median lesions were found to be situated posterior to the optic chiasma (264) and above the tuber cinereum (268).

The evidence indicates that lesions of the zona tuberalis abolish the lymphopenic response, and that similar lesions in the pars distalis, pars intermedia or infundibular stem are compatible with a normal lymphopenic response. Lesions which extend transversely in the posterior region of the tuber cinereum or in the mammillary body are often associated with a loss or diminution of response.

DISCUSSION

The lymphopenic response has been found of great value in the present study in indicating anterior pituitary activity. When using this response it is essential to work without anaesthesia and with quiescent animals. For this purpose the method of electrical stimulation used was very satisfactory. Incidental emotional stress during the course of an experiment may produce a lymphopenia which repetition of the experiment shows was not due to the electric stimulation. A single positive response in an animal is not significant, whereas a single negative result is highly significant. We should also like to stress the importance of being able to repeat an experiment many times on any individual animal. This allows the elimination of many variable factors (changes in diet, external temperature, phase of sex cycle and so on), and enables definite conclusions to be drawn from the study of fewer animals than would otherwise be possible.

It has been shown that emotional stress produces a lymphopenia in the normal, but not in the hypophysectomized rabbit (Colfer *et al.* 1950). The mechanism by which the nervous system causes anterior pituitary secretion (of probably the adrenocorticotrophic hormone) and so a lymphopenia has received little attention in the past. The observation of Mikkelsen & Hutchens (1948), that electric shock therapy in man is followed by a lymphopenia 3 hr. later, made it seem likely that some part of the neural mechanism underlying the response would be excitable to electric stimulation. This is so, for localized

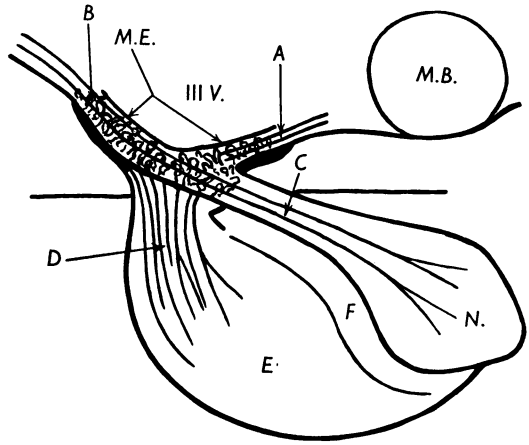
stimulation of the posterior part of the tuber cinereum or mammillary body has been found to produce a lymphopenic response similar to that following emotional stress. The evidence indicates that transverse lesions in the posterior part of the tuber cinereum or mammillary body, or lesions in the zona tuberalis of the pituitary gland, abolish the response to emotional stress. It is felt that the evidence derived from study of the lesions is not so clear cut as that derived from the study of stimulation. However, both lines of approach indicate the same conclusions.

The stimulus from hypothalamus to hypophysis does not pass by way of the cervical sympathetic system, as shown by the fact that cervical sympathectomy does not abolish the lymphopenia following stimulation of the tuber cinereum. The tubero-hypophysial tract of nerve fibres runs through the posterior wall of the tuber cinereum (Fisher, Ingram & Ranson, 1935) and is possibly concerned with the transmission of the stimulus. The most likely anatomical pathway involved between hypothalamus and adenohypophysis is the hypophysial stalk. Following Rioch, Wislocki & O'Leary (1940), the term hypophysial stalk is taken to include the neural stalk together with its sheath of portions of the glandular lobe. There are two possible pathways between hypothalamus and the anterior pituitary gland in the hypophysial stalk: either the hypothalamo-hypophysial nerve tract, or the hypophysial portal vessels contained in the pars and zona tuberalis (see Text-fig. 2).

Transmission of stimuli to anterior pituitary cells by means of the hypothalamo-hypophysial nerve fibres seems unlikely. Most workers find that nerve fibres passing from neurohypophysis to adenohypophysis are very scanty in number, if present at all. A few fibres have been described, however (see Harris, 1948*c*), as passing from the supraoptico-hypophysial tract in the median eminence to the pars and zona tuberalis, and from the infundibular stem and process to the pars intermedia. It appears unlikely that either of these sets of fibres is concerned in the lymphopenic response for the following reasons: (i) stimulation of the supraoptico-hypophysial tract in the median eminence (*B*, in Text-fig. 2) or the infundibular stem (*C*) does not evoke a lymphopenia; (ii) stimulation of the zona tuberalis (*D*) does not evoke a lymphopenia; (iii) interruption of the infundibular stem (*C*) does not prevent a lymphopenic response following emotional stress.

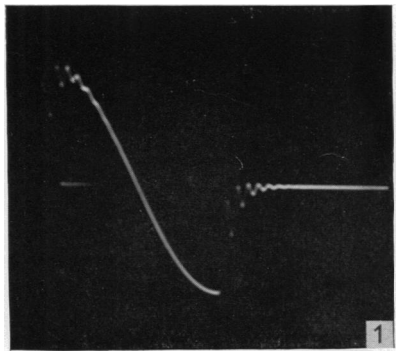
Transmission of stimuli to anterior pituitary cells by means of a humoral agent carried from the median eminence to the pars distalis via the hypophysial portal vessels seems probable. It has been suggested (Harris, 1944; Green & Harris, 1947) that the hypothalamus may influence anterior pituitary secretion by a two-link chain: nerve fibres passing from the hypothalamus to the median eminence where they liberate a humoral transmitter into the hypophysial portal vessels, which in turn carry the substance to the pars distalis. This theory is in accordance with the facts noted in the present work. Electrical stimulation of

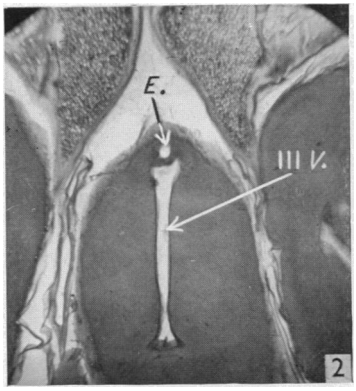
the posterior part of the tuber cinereum evokes a lymphopenia, possibly through stimulation of nerve fibres which are passing to the primary plexus of the portal vessels in the median eminence. The fact that a lymphopenia is not produced by electrical stimulation of the pars distalis, pars intermedia, pars or zona tuberalis of the pituitary gland may be because the adenohypophysis lacks a secreto-motor nerve supply and is humorally controlled. Again lesions of the zona tuberalis block the lymphopenia which normally follows emotional stress (even though electrical stimulation of this structure does not evoke the response), and this may be due to the fact that all the portal vessels traverse the zona tuberalis in passing to the main part of the pars distalis (Harris, 1947*a*).

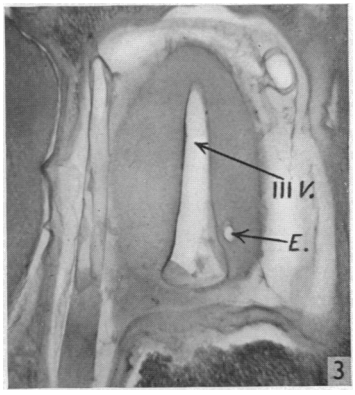


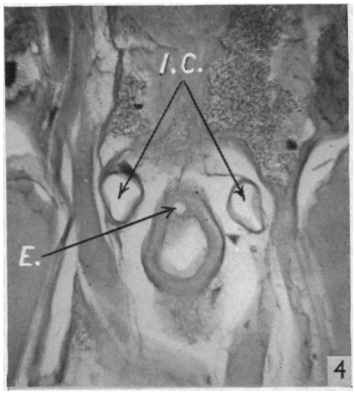
Text-fig. 2. Diagram of a sagittal section through the hypothalamus and pituitary gland of a rabbit, to illustrate the anatomy and to summarize the results obtained. *A*, posterior wall of the tuber cinereum containing the tuberohypophysial tract (stimulation evokes lymphopenia; most lesions here block lymphopenic response to emotional stress); *B*, anterior wall of the tuber cinereum containing the supraopticohypophysial tract (stimulation negative); *C*, infundibular stem (stimulation negative; lesions do not abolish lymphopenic response); *D*, zona tuberalis containing the trunks of the portal vessels and possibly some nerve fibres from the supraopticohypophysial tract (stimulation negative; lesions block lymphopenic response to emotional stress); *E*, main part of pars distalis (stimulation negative; subtotal lesions do not block lymphopenic response); *F*, pars intermedia; *M.B.*, mammillary body; *M.E.*, median eminence, surrounded by the very vascular collar of pars tuberalis, and containing the primary plexus of the hypophysial portal vessels; *N.*, neural lobe of the hypophysis; III *V.*, third ventricle.

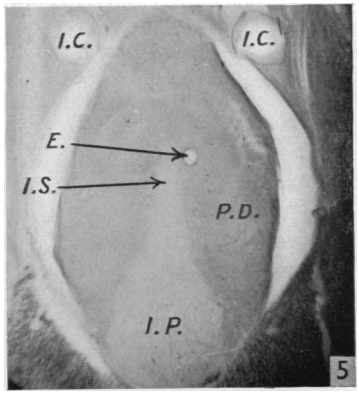
It is of interest that the evidence indicates the hypophysial portal vessels as the pathway underlying humoral control of the secretion of gonadotrophic hormone(s) in the rabbit (Harris, 1948*b*) and in the rat (Harris, 1950). The work of Markee and his colleagues (Markee, Sawyer & Hollinshead, 1948; Sawyer, Markee & Townsend, 1949; Sawyer, Everett & Markee, 1949; Everett, Sawyer & Markee, 1949) indicates that an adrenergic substance humorally excites the secretion of gonadotrophic hormone(s), and that the action of this substance may be blocked by sympatholytic drugs, such as dibenamine. It





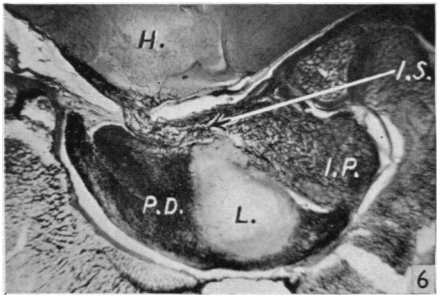


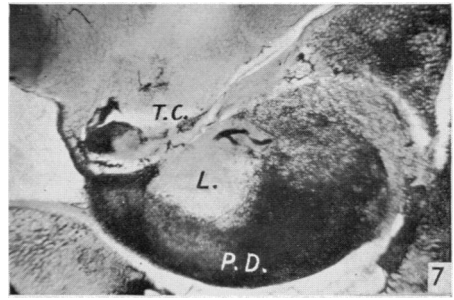


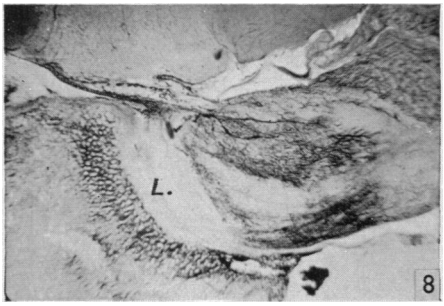


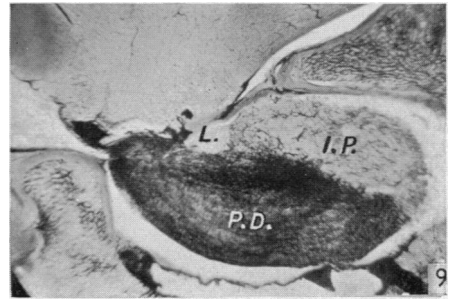
Figs. 1–5.

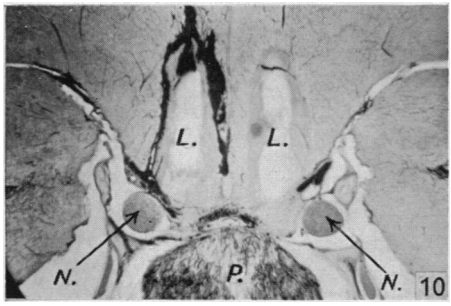
To face p. 344

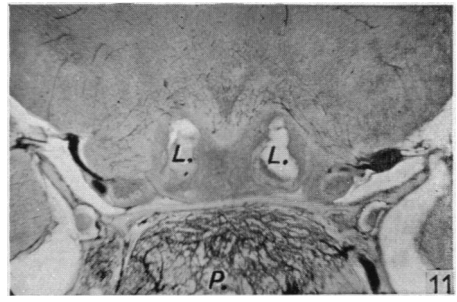












Figs. 6–11.

would be of interest to see whether sympatholytic drugs also blocked the lymphopenic response to emotional stress.

SUMMARY

1. Electrical stimulation of the posterior region of the tuber cinereum or of the mammillary body, of unanaesthetized, unrestrained rabbits resulted in a lymphopenia, which was similar in time relations and magnitude to that following an emotional stress stimulus. Cervical sympathectomy did not abolish this response. Electrical stimulation of certain other regions in the hypothalamus (including the supraopticohypophysial tract), of the pars and zona tuberalis, pars distalis, pars intermedia and infundibular stem of the pituitary gland did not elicit the response.

2. The lymphopenic response which follows an emotional stress stimulus in normal rabbits was abolished by lesions in the zona tuberalis (two cases), and, in most cases, was abolished or diminished by transverse lesions in the posterior region of the tuber cinereum or in the mammillary body. Similar lesions in the pars distalis and pars intermedia, and lesions which interrupt the infundibular stem, were compatible with normal responses.

3. The conclusion is drawn that anterior pituitary secretion (of probably the adrenocorticotrophic hormone) is under neural control via the hypothalamus and the hypophysial portal vessels of the pituitary stalk.

We are grateful to Mr L. Hatton for the radiography and microphotography involved in this work, and to Mr R. R. W. Dye for valuable technical assistance and for his care of the animals. Our thanks are also due to Mr L. Herbert, of the Research Laboratories of the British Thompson-Houston Company, Ltd., Rugby, for advice on the ignitron circuit.

REFERENCES

Chaffee, E. L. & Light, R. U. (1934). *Yale J. Biol. Med.* **7**, 83.
Colfer, H. F., de Groot, J. & Harris, G. W. (1950). *J. Physiol.* **111**, 328.
Dougherty, T. F. & White, A. (1944). *Endocrinology*, **35**, 1.
Everett, J. W., Sawyer, C. H. & Markee, J. E. (1949). *Endocrinology*, **44**, 234.
Fisher, C., Ingram, W. R. & Ranson, S. W. (1935). *Arch. Neurol. Psychiat., Chicago*, **34**, 124.
Green, J. D. & Harris, G. W. (1947). *J. Endocrinol.* **5**, 136.
Harris, G. W. (1937). *Proc. Roy. Soc.* B, **122**, 374.
Harris, G. W. (1944). Thesis for M.D. degree. Cambridge University.
Harris, G. W. (1947*a*). *J. Anat., Lond.*, **81**, 343.
Harris, G. W. (1947*b*). *Philos. Trans.* B, **232**, 385.
Harris, G. W. (1948*a*). *J. Physiol.* **107**, 412.
Harris, G. W. (1948*b*). *J. Physiol.* **107**, 418.
Harris, G. W. (1948*c*). *Physiol. Rev.* **28**, 139.
Harris, G. W. (1950). *J. Physiol.* **111**, 347.
Jacobsohn, D. & Westman, A. (1940). *Acta Physiol. Scand.* **1**, 71.
Markee, J. E., Sawyer, C. H. & Hollinshead, W. H. (1948). *Rec. Progr. Horm. Res.* **2**, 117.
Mikkelsen, W. P. & Hutchens, T. T. (1948). *Endocrinology*, **42**, 394.
Rioch, D. McK., Wislocki, G. B. & O'Leary, J. L. (1940). *Res. Publ. Ass. nerv. ment. Dis.*, **20**, 3.
Sawyer, C. H., Everett, J. W. & Markee, J. E. (1949). *Endocrinology*, **44**, 218.
Sawyer, C. H., Markee, J. E. & Townsend, B. F. (1949). *Endocrinology*, **44**, 18.

EXPLANATION OF PLATES

PLATE 1

Fig. 1. Photograph of an oscilloscope tracing of the pulse wave from a secondary coil (similar to the implanted coils) placed in the field of the primary coil. Duration of pulse 0·5 msec.

Fig. 2. Microphotograph of a horizontal section through the hypothalamus and surrounding tissue of rabbit 210. Note the electrode site, *E.*, situated in the anterior tuber cinereum, immediately adjacent to the anterior end of the third ventricle, III *V*. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 3. Microphotograph of a horizontal section through the hypothalamus and surrounding tissues of rabbit 273. Note the electrode site, *E.*, situated in the posterior tuber cinereum, just lateral to the third ventricle, III *V*. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 4. Microphotograph of a horizontal section through the tuber cinereum and surrounding tissues of rabbit 237. Note the electrode site, *E.*, in the region of the supraopticohypophysial tract in the anterior wall of the tuber cinereum. *I.C.*, internal carotid artery. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 5. Microphotograph of a horizontal section through the pituitary gland and surrounding tissues of rabbit 274. Note the electrode site, *E.*, in the pars distalis, *P.D.*, and adjacent to the infundibular stem, *I.S.* *I.C.*, internal carotid artery. *I.P.*, infundibular process. Section 200 μ. thick. Haemalum and eosin. × 10.

PLATE 2

Fig. 6. Microphotograph of a sagittal section through the hypothalamus and pituitary gland of rabbit 253. Blood vessels injected with indian ink. Note the lesion, *L.*, in the pars distalis, *P.D.*, and pars intermedia of the pituitary and partially involving the infundibular stem, *I.S.* *H.*, hypothalamus. *I.P.*, infundibular process. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 7. Microphotograph of a sagittal section through the hypothalamus and pituitary gland of rabbit 257. Blood vessels injected with indian ink. Note the lesion, *L.*, involving the pars distalis, *P.D.*, pars intermedia, infundibular stem and the posterior region of the tuber cinereum, *T.C.* Section 250 μ. thick. Haemalum and eosin. × 10.

Fig. 8. Microphotograph of a sagittal section through the hypothalamus and pituitary gland of rabbit 250. Blood vessels injected with indian ink. Note the lesion, *L.*, involving the zona tuberalis at the anterior pole of the pituitary gland. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 9. Microphotograph of a sagittal section through the hypothalamus and pituitary gland of rabbit 265. Blood vessels injected with indian ink. Note the lesion, *L.*, involving the posterior region of the tuber cinereum, infundibular stem and pars intermedia of the pituitary gland. *I.P.*, infundibular process. *P.D.*, pars distalis. Section 250 μ. thick. Haemalum and eosin. × 10.

Fig. 10. Microphotograph of a transverse section through the hypothalamus and pituitary gland of rabbit 277. Blood vessels injected with indian ink. Note the bilateral lesions, *L.*, extending to the floor of the hypothalamus, in the posterior part of the tuber cinereum. *N.*, third nerve. *P.*, pituitary gland. Section 200 μ. thick. Haemalum and eosin. × 10.

Fig. 11. Microphotograph of a transverse section through the hypothalamus and pituitary gland of rabbit 280. Blood vessels injected with indian ink. Note the bilateral lesion, *L.*, situated in the mammillary body. *P.*, pituitary gland. Section 200 μ. thick. Haemalum and eosin. × 10.