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OVARIAN STIMULATION FOLLOWING CEREBRAL LESIONS IN FERRETS

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SUMMARY

Bilateral electrolytic lesions have been made in the thalamus, caudate nucleus or adjacent areas, in fourteen anoestrous ferrets; in another ten animals control operations were performed which were identical except that an electrolytic current was not passed.

Most of the experimental animals came into heat precociously. This effect was independent of the size, position, or even the presence of an electrolytic lesion, but depended only upon operative interference with the cerebrum.

It was concluded that these procedures acted as a non-specific stimulus for the production of gonadotrophic hormone and that more specific interpretations of the results of similar investigations involving central nervous lesions were, therefore, not necessarily valid.

The precocious activation of the ovaries of anoestrous ferrets which are exposed to artificial light after sunset during the winter months is primarily due to stimulation of the retina [Thomson, 1951, 1954], and is dependent on the presence of the anterior pituitary gland [Hill & Parkes, 1933]. Considerable research has, however, failed to explain the physiological connexion between these two conditions, and, in particular, to show how impulses passed along the optic pathways trigger the release of gonadotrophin from the pituitary. One view is that the ovarian response is merely part of some general effect which retinal stimulation has on the 'total activity' of the body. This conclusion derives from the fact that anatomical study has failed to reveal any direct connexion in the ferret between the optic tracts and the subthalamus or hypothalamus [Jefferson, 1940]. Another view, based essentially on argument by exclusion, is that nervous impulses are relayed from the optic pathways to a 'sexual centre' in the hypothalamus, where the chain of stimulation is continued by means of 'chemotransmitters' that are passed down the pituitary portal vessels into the pars distalis of the pituitary [Donovan & Harris, 1956].

Efforts to track nervous pathways which the impulses that are fired along the optic tracts could follow on their way to the hypothalamus have, however, failed [Le Gros Clark, McKeown & Zuckerman, 1939; Jefferson, 1940]. Experiment has also shown that the ovarian response can still be elicited when the pituitary is separated from the floor of the third ventricle in a way which leaves no possibility of any vascular or nervous connexion between the gland and the hypothalamus, and therefore no direct channel for the passage of hypothetical chemotransmitters [Thomson & Zuckerman, 1953, 1954; Zuckerman, 1954, 1955, 1958].

A critical and general review of the evidence that the hypothalamus is the seat of a sexual centre (or centres) will be presented elsewhere [Herbert, to be published]. The present paper is concerned only with the claim that such a centre exists in the anterior hypothalamus of the ferret, and that it inhibits the liberation of follicle stimulating hormone (FSH) from the pituitary during anoestrus [Donovan & van der Werff ten Bosch, 1956]. This view was based on the observation that bilateral lesions in the anterior hypothalamus made between 30 December and 21 January resulted in precocious oestrus some 4–7 weeks later. No artificial light was used in these experiments, and no account has yet been given of the size or precise location of the effective lesions.

The experiments described in the present paper suggest an alternative conclusion to that advanced by Donovan & van der Werff ten Bosch. Our observations, of which a preliminary note has already been published [Herbert & Zuckerman, 1957], relate to experiments in which lesions were made in the thalamus, corpus striatum and fornix, and in which the hypothalamus was never directly affected.

MATERIALS AND METHODS

(1) *Animals*

All animals used in this investigation were mature female ferrets of unknown genetic history. They were fed on fish and milk, and were caged in pairs, each pair consisting, as a rule, of a ferret bearing lesions and its corresponding sham-operated control. The animal room was lit by daylight through a large window, no artificial light being provided after sunset. The environmental conditions of the experiment were thus basically the same as in the experiments of Donovan & van der Werff ten Bosch [1956].

(2) *Experimental procedure*

Bilateral electrolytic lesions were made in various parts of the brains of fourteen ferrets between 19 September and 13 December 1956. An additional animal died soon after operation and was excluded from the analysis. Control operations were made in ten animals, and eight animals were left unoperated. (Table 1)

(*a*) *Apparatus.* A stereotaxic device modelled after the one described by Cort & Harding [1953] was used, with the head-piece adapted to fit the ferret's skull. Electrodes were 1 in. lengths of stainless steel wire 0·017 in. in diameter, insulated, except for about 1 mm of their tips, with 'Demarda' lacquer. The indifferent electrode consisted of a copper plate, upon which was placed a cotton-wool pad soaked in saline. The power source was an instrument designed to deliver a steady direct current whose strength could be varied at will.

Approximate co-ordinates of different parts of the diencephalon and corpus striatum were determined by dissection and trial operation. The exact position of the lesions in each animal was subsequently determined histologically.

(*b*) *Operative procedure.* The animal swere weighed and anaesthetized with 'Nembutal' (1·0 ml./kg unfed body weight). The top of the skull and the lower thorax (which was in contact with the indifferent electrode) were shaved. A median incision along the sagittal line of the skull revealed the underlying temporalis muscles, which were reflected laterally to the required extent. The calvarium was drilled with a no. 8 round dental burr at the chosen site, and the electrode lowered to a predetermined depth. After an electrolytic current had been passed and the electrode removed, the burr holes were packed with a sterile gelatinous foam preparation ('Sterispon'). The wound was insufflated with a powder consisting of a mixture of penicillin and sulphonamide, the muscles sutured together with catgut, and the skin incision closed with Michel clips. Sterile precautions were taken throughout.

Control operations were identical except that an electrolytic current was not passed. They were carried out on the same or the day following the one on which lesions were made in the 'experimental' animals.

100,000 i.u. of a long-acting penicillin preparation were injected into the hamstring muscles immediately after operation, and in some cases, for a few days post-operatively.

(*c*) *Size and positions of lesions.* From Table 1 it will be seen that a current flow of 50 mA/sec was used in producing the majority of lesions, the current being raised to 4 mA in 5 sec and maintained at that value for a further 10 sec. A flow of 30 mA/sec was used in the animals of series III.

Table 1. *Details of operation*

Series	Variety	No. of animal: With lesion	No. of animal: Sham operation	Date of operation*	Electrolytic current (mA/sec)
I	Albino	1283	1286	19. ix. 56	50
I	Albino	1285	1288	20. ix. 56	50
I	Albino	1287	1289	26. ix. 56	50
I	Albino	1290	1291	28. ix. 56	50
I	'Polecat'	1375	—	13. xii. 56	50
I	'Polecat'	1376	—	13. xii. 56	50
I	Albino	1378	—	14. xii. 56	50
II	Albino	1329	1328	31. x. 56	50
II	Albino	1341	—	1. xi. 56	50
II	Albino	1340	—	2. xi. 56	50
III	Albino	1296	1297	2. x. 56	30
III	'Crossed'	1292	1293	4. x. 56	30
III	'Polecat'	1295	1294	22. x. 56	30
IV	Albino	1331	1332	29. x. 56	50
IV	Albino	(1330)†	1337	29. x. 56	50

* This refers to animals in which lesions were made: corresponding sham-operations were carried out either on the same day or the following one. † Died.

Each animal of series I, II and III had a single pair of bilateral cerebral lesions. All animals of series I had lesions of the same size (as measured by the amount of current), lateral and vertical disposition, but with different antero-posterior co-ordinates. In series II the lesions were placed 2 mm more ventrally. An example of the type of lesion produced is shown in the Plate.

In series III the lesions were placed as in series I, but were smaller.

The single experimental animal of series IV had three pairs of lesions placed bilaterally.

(*d*) *Examination of animals.* Animals were weighed, and the state of their genital region, eyes and pelts examined weekly.

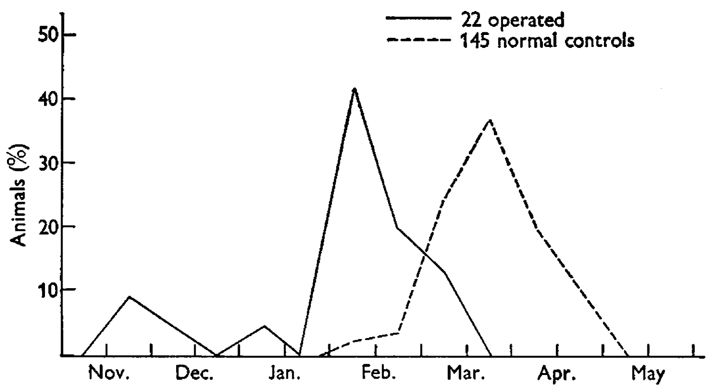
The first definite signs of swelling of the vulva was taken as the onset of oestrus.

Eight unoperated normal animals served as controls. The oestrous records of 137 normal unoperated ferrets observed over the past 10 years in this laboratory were also available (Text-fig. 1).

(3) *Autopsy and histology*

The animals were killed with chloroform during the latter part of March 1957, and the upper part of their vascular system was perfused with 10 % formol-saline solution injected through the left ventricle. The part of the brain in which the lesion was made was then fixed in 10 % formol-saline. The ovaries, adrenals, thyroids and, in some cases, the reproductive organs were placed in alcoholic Bouin's solution.

Frontal serial sections at 20 μ were made of the blocks of brain tissue, one section in every five being mounted and stained with aqueous cresyl-violet. The ovaries and adrenals were cut serially at 10 μ and stained with haematoxylin and eosin. In some cases representative sections of the uterus were also prepared in a similar manner.



Text-fig. 1. Time of onset of oestrus in normal and operated (including sham-operated) ferrets.

RESULTS

In the subsequent account, the letter 'L' following an animal's number indicates that it was one in which an electrolytic lesion was made. The letter 'D' implies a sham operation.

(1) *Onset of oestrus*

Table 2 and Text-fig. 1 show the time of onset of oestrus in the operated and control animals. Operated animals with and without lesions generally came into oestrus much earlier than did the controls.

(2) *Relation of date of operation to date of oestrus*

Table 3 shows that there was no obvious relation between the time of the operation and the date of the subsequent onset of oestrus.

(3) *Changes in weight*

Most ferrets gained weight during the experimental period. There were considerable individual variations, but none which could be correlated with the time animals came into heat.

(4) *Histological findings*

Animals which came into oestrus in late November

1285 L. After this animal had been in oestrus for nearly 7 weeks, its vulval swelling began to subside on 15 January, and the animal again became anoestrous. It was then killed.

The left lesion had destroyed much of the medial part of the caudate nucleus.

The right lesion was situated more medially and ventrally, and involved

Table 2. *Time of onset of oestrus in normal and experimental animals**

	Exptl. animals		Normal animals	
Onset of oestrus	With lesions	Sham-operated	Unoperated controls	Previous laboratory data
End of November	2	—	—	—
Beginning of December	—	1	—	—
End of December	—	—	—	—
Beginning of January	—	1	—	—
End of January	—	—	—	—
Beginning of February	5	5	—	3
End of February	4	1	2	4
Beginning of March	3	—	2	34
End of March	—	—	1	53
Beginning of April	—	—	2	27
End of April	—	—	—	15
Beginning of May	—	—	1	1
Total	14	8	8	137

* There were ten 'sham-operated' ferrets but one of them, 1288D, was killed in January when still anoestrous, while another, 1286D, failed to come into oestrus at any time during the summer.

Table 3. *Interval between operation and the subsequent onset of oestrus*

Onset of oestrus	No. of animal	Date of operation	Date of onset of oestrus	Interval (days)
November/December	1285L	20. ix. 56	27. xi. 56	68
	1287L	26. ix. 56	27. xi. 56	62
	1291D	28. ix. 56	4. xii. 56	67
First half January	1297D	3. x. 56	2. i. 57	92
First half February	1329L	31. x. 56	4. ii. 57	96
	1340L	2. xi. 56	29. i. 57	88
	1296L	2. x. 56	10. ii. 57	132
	1292L	4. x. 56	4. ii. 57	123
	1378L	14. xii. 56	10. ii. 57	58
	1289D	29. ix. 56	4. ii. 57	128
	1293D	4. x. 56	4. ii. 57	123
	1294D	22. x. 56	4. ii. 57	105
	1332D	30. x. 56	29. i. 57	92
	1337D	31. x. 56	4. ii. 57	96
Second half February	1283L	19. ix. 56	12. vi. 57	—
	1341L	1. xi. 56	16. ii. 57	107
	1331L	29. x. 56	24. ii. 57	116
	1376L	13. xii. 56	16. ii. 57	65
	1328D	31. x. 56	16. ii. 57	108
First half March	1290L	28. ix. 56	2. iii. 57	155
	1295L	22. x. 56	14. iii. 57	143
	1375L	13. xii. 56	8. iii. 57	85

the anterior column of the fornix and part of the anterior commissure of that side.

Histological examination of the ovaries showed several medium-sized follicles undergoing atretic changes but no corpora lutea.

1287 L. Eight weeks after coming into oestrus this animal was mated with a male which had been brought into a state of reproductive activity by exposure to light. The female subsequently became pseudopregnant and then exhibited renewed signs of oestrus.

The left lesion lay mainly in the nucleus medialis dorsalis of the thalamus, destroying the medial two-thirds of that nucleus. The right lesion had been placed a little more laterally, involving the nucleus centralis lateralis as well as adjacent areas of adjoining nuclei.

Both ovaries contained several developing follicles which were in general smaller than those seen in an oestrous ovary, as well as numbers of others in earlier states of development. The uterus was larger and more congested than usual, with prominent blood vessels. The histological appearance indicated a recent phase of pseudopregnancy.

Animal which came into oestrus in early December

1291 D. This (sham-operated) animal was mated on 21 January (7 weeks after the onset of oestrus). It became pseudopregnant, and was killed when signs of vulval swelling reappeared.

A track made by the electrode was visible on the left side of the brain, but not on the right.

The right ovary contained several follicles in various stages of maturation. The left ovary was shrunken but contained two follicles in early stages of development.

Animal which came into oestrus in early January

1297 D. After being mated on 22 January this (sham-operated) animal became pregnant. It delivered one young 43 days later. Renewed signs of oestrus were then observed and the animal was killed on 14 March.

The right cortex was damaged below the hole in the calvarium. The left cortex appeared normal.

The left ovary contained three large follicles and a degenerating corpus luteum. The right ovary contained three large and several other follicles in less advanced stages of development. The uterus showed typical regressing parturient changes.

Animals which came into oestrus during February

(*a*) *First half of the month. Animals with lesions*

1296 L. The more anterior part of the caudate nucleus was destroyed on both sides.

Both ovaries contained several large mature follicles.

1292 L. The lateral part of the fornix was destroyed on the right side. On the left side the lesion lay in the caudate nucleus and the anterior part of the internal capsule.

Each ovary contained several corpora lutea (see below).

1340 L. The lesions had destroyed the lateral part of the nucleus ventralis medialis, the medial part of ventralis anterior and part of the internal medullary lamina and mammillo-thalamic tract on the right side. The lesion involved mainly the nucleus medialis dorsalis, especially its more caudal regions. On the left side the nucleus centralis lateralis was entirely destroyed, together with the contiguous part of medialis dorsalis (see Plate).

Both ovaries contained several large follicles.

1378 L. The right lesion lay in the caudate nucleus just dorsal to the anterior part of the thalamus. On the left side the lesion lay more medially, in the lateral ventricle itself, damaging the adjacent part of the corpus callosum and the caudate nucleus.

Both ovaries contained several mature follicles.

1329 L. Histological sections through the brain were too poor to permit identification of the position of the lesions.

Both ovaries contained four to five fully-grown follicles.

Sham operations

1289 D. The drilling of the calvarium had damaged both sides of the cortex.

Neither ovary contained fully-grown follicles, although each contained several nearing complete maturation.

1293 D. There were no lesions in the brain.

Both ovaries contained several follicles in intermediate stages of growth.

1294 D. The drilling of the calvarium had damaged both sides of the cortex.

Both ovaries contained several large corpora lutea (see below).

1337 D. The cerebral cortex was undamaged.

Both ovaries contained a few large follicles.

1332 D. There was slight thickening of the dura mater with minimal damage to the underlying cortex at one point on the right side.

Both ovaries contained numbers of large follicles.

(*b*) *Second half of the month. Animals with lesions*

1283 L. The lesions were restricted to the medial parts of the two caudate nuclei.

Both ovaries contained large follicles, which were smaller than those seen at full oestrus.

1341 L. The lesions destroyed a large part of the anterior commissure and the basal part of the fornix. Small parts of the caudate nucleus and internal capsule were also involved.

One ovary contained one and the other two fully-grown follicles.

1331 L. This animal had three pairs of lesions placed bilaterally. On the right side, an area extending throughout the medial thalamus (involving the nuclei anteroventralis, medialis dorsalis, habenularis lateralis and centrum medianum) had been destroyed, as well as the most cranial part of the pretectal area, and adjacent parts of nuclei lateralis intermedius and posterior.

On the left side, the greater part of nucleus anteroventralis and a smaller area of medialis dorsalis were involved. More posteriorly, the corpus callosum and the hippocampus were involved.

A total of seven large and several somewhat smaller follicles were observed in the ovaries.

1376 L. The lesion on the left side involved adjacent areas of the caudate nucleus, fornix and lateral ventricle; on the right side a small part of the caudate nucleus was involved.

There were two or three large follicles in each ovary.

Sham operations

1328 D. Histological examination revealed no abnormal features in the brain.

Both ovaries contained several large follicles.

Animals which came into oestrus in March

All experimental animals which came into oestrus in March did so during the first fortnight of the month.

1290 L. On the right side, the lesions interrupted the corpus callosum dorsally, and damaged the nuclei medialis dorsalis (both the small-celled and the large-celled parts), parataenialis, paraventricularis, and posteriorly, the nucleus habenularis lateralis.

On the left side, the nucleus centralis lateralis was almost completely destroyed and the medial part of ventralis pars arcuata and a large part of centrum medianum were damaged caudally.

Each ovary contained several large follicles of less than the maximum size seen at oestrus.

1295 L. The left-sided lesion had destroyed about half the nucleus lateralis anterior, the cranial region of the large-celled part of medialis dorsalis, and the caudal half of anteroventralis.

On the opposite side, more laterally situated structures were also damaged (parts of nuclei ventralis anterior and lateralis pars intermedius, as well as the ventral part of lateralis anterior and the caudal anteroventralis).

Several large follicles, and others in earlier states of maturation, were present in each ovary.

1375 L. A large part of the caudate nucleus was destroyed on the right side, and the adjacent area of the internal capsule and anterior commissure were also involved.

The lesion was smaller on the left side, but the same structures were damaged. Part of the caudate nucleus not directly involved by the lesion had degenerated.

Of the remaining two animals, 1288 D was killed when still anoestrous on 29 January 1957, and 1286 D remained anoestrous throughout 1957.

(5) *Spontaneous ovulation*

Two ferrets, 1294 D and 1292 L, both of which were caged with another female and neither of which was mated, are believed to have ovulated spontaneously.

1294 D. This animal underwent a sham operation on 22 October, and started to come into oestrus on 4 February. It was in full oestrus on 16 February. On 2 March the vulval swelling began to collapse. The animal was killed on 23 March. The uterus was very congested, and histological examination revealed several large corpora lutea in each ovary, all of them looking healthy and functional.

1292 L. Bilateral cerebral lesions were made on 4 October, and the animal showed signs of incipient oestrus on 4 February and full oestrus on 10 February. The vulval swelling started to regress on 2 March, and autopsy on 22 March showed a similar picture to that seen in 1294 D.

(6) *Mating behaviour*

Hypothalamic lesions associated with abnormalities of the sexual cycle have also been reported as preventing mating behaviour, an effect apparently independent of the resultant endocrine disturbances [see Dempsey & Rioch, 1939; Brookhart, Dey & Ranson, 1941]. The mating response of animals in which cerebral lesions had induced precocious oestrus was therefore tested with a male whose reproductive organs had been activated by means of artificial light. The behaviour of the animals was also compared with that of two unoperated ferrets which had been brought into oestrus in the same way.

All five mated normally, ovulation occurring in each case.

Details of the experiment are given in Table 4.

Table 4. *Results of mating in normal and experimental animals*

No. of animal	Mated	Result	Date of reappearance of oestrus or of parturition	Interval (days)
		Normal animals		
1264	29. i. 57	Pregnant	13. iii. 57	43
1303	22. i. 57	Pseudopregnant	13. iii. 57	50
		Operated animals		
1287 L	23. i. 57	Pseudopregnant	14. iii. 57	50
1291 D	21. i. 57	Pseudopregnant	19. iii. 57	57
1297 D	22. i. 57	Pregnant	6. iii. 57	43

DISCUSSION

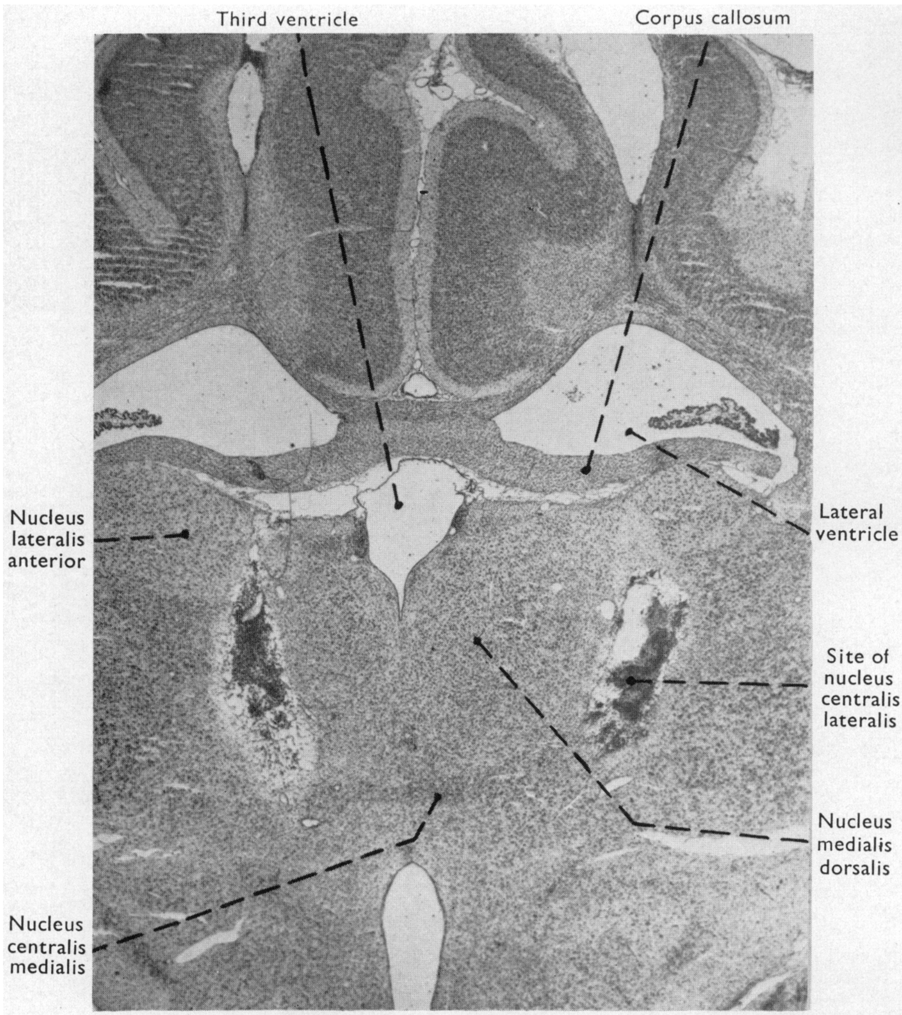
None of the eight control animals kept under observation during the course of the present experiment started to come into heat till the end of February. In contrast, four out of the twenty-four animals in the experimental group (cf. Tables 1, 2) were in oestrus by the end of January, and all but three were in heat before the beginning of March. The difference appears even more striking when the records of the eight control animals of the present series are combined with those of 137 other normal ferrets that have been kept under observation in this laboratory over the past ten years (Text-fig. 1). Of the total of 145 normal animals, only nine started coming into oestrus before the onset of March, and no signs of oestrus were ever observed in a normal animal before the beginning of February (Table 2). The differences between the present series of experimental animals and the controls is demonstrated graphically in Text-fig. 1.

It is clear that most operated animals came into heat precociously. It is equally clear that oestrus occurred precociously both in animals in which electrolytic lesions were made and in those in which a current was not passed down the electrode. It follows, therefore, that neither the size, position nor even the presence of a lesion had any necessary influence on the time at which any particular ferret came into oestrus. The only possible conclusion is that the operative procedure itself in some way brought about the response. Such an explanation might also apply, in spite of the different circumstances of the experiments, to the findings of the earlier study reported by Le Gros Clark *et al.* [1939] on the possible pathways by which the light stimulus is transmitted. These authors reported that the acceleration of the onset of oestrus in ferrets following their exposure to additional illumination was not prevented by extirpating parts of the optic cortex and midbrain, and suggested alternative nervous pathways along which impulses could pass from the retina to influence the anterior pituitary. A non-specific effect of the operative trauma must now be considered as a possible factor in their results.

In view of the above conclusion, the interpretation which Donovan & van der Werff ten Bosch [1956] have put upon their observations of the effects of hypothalamic lesions in ferrets is not necessarily valid. There is, however, one difference between their observations and ours which is worth noting. Their animals seem to have come into oestrus relatively more quickly following operation than those described in the present paper. One explanation for this difference is that they operated on their animals later in anoestrus than was the case in the present set of experiments (i.e. between 30 December and 21 January). Another possibility is that to the 'stimulus' which their surgical procedure (and ours) gave to the pituitary has to be added a second factor constituted by those normal physiological changes which precede the onset of oestrus. These changes are in operation long before the breeding season actually begins. In the male, for example, Allanson [1932] has described normal testicular activation as early as December. Moreover, it is reasonable to suppose that the stimulus of artificial light during anoestrus does little more than disturb or modulate a normal rhythm which operates in the ferret regardless of external events. This is the only reasonable explanation for the fact that ferrets which are completely blind still come into heat at the normal time in the spring, although failing to respond to the stimulus of artificial light [Thomson, 1954].

It is not inconceivable, of course, that lesions situated in the hypothalamus might have a greater disrupting effect on reproductive mechanisms than lesions in other parts of the brain. Without bearing at all on the question of specificity, this possibility follows from the fact that the hypothalamus is concerned in a variety of metabolic and other bodily processes which could secondarily affect reproductive performance. Non-specific factors could also stimulate secretion of gonadotrophin in the ferret in a manner similar to that demonstrated in the rat by Mandl & Zuckerman [1952] (cf. also Zuckerman [1952]).

Spontaneous ovulation in the ferret is not usual, or even common [Marshall, 1904; Robinson, 1918; Hammond & Marshall, 1930]. Therefore, the fact that two females in the present series—a rather high proportion of the animals concerned—ovulated in this way, appears significant. Eckstein & Zuckerman [1954] have argued that the threshold stimulus for ovulation is higher in species not ovulating spontaneously than in cyclical animals, rather than that there is any fundamental difference between the two. If this view is valid, it might be that all that had happened in the present experiments is that the stimulus of the operation had lowered the threshold for ovulation.


Third ventricle
Corpus callosum
Nucleus lateralis anterior
Lateral ventricle
Site of nucleus centralis lateralis
Nucleus medialis dorsalis
Nucleus centralis medialis

The fact that the experimental ferrets which were mated subsequently became either pregnant or pseudopregnant demonstrates that, in addition to FSH, the pituitary was able to secrete adequate amounts of luteinizing hormone and prolactin [Astwood, 1941].

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DESCRIPTION OF PLATE

Bilateral lesions in thalamus (ferret 1340L). × 13.