SOME EFFECTS OF METHYL-PHENIDATE (RITALIN) AND AMPHETAMINE ON NORMAL AND LEUCOTOMIZED MONKEYS

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Introduction

In a previous report (Cole and Glees, 1956) on methyl-phenidate (Ritalin) as an antagonist to reserpine (Serpasil) in monkeys we referred to a similar effect produced by amphetamine. Following up this work we have now studied and compared the effects of methyl-phenidate and amphetamine when given separately without reserpine to normal and leucotomized monkeys.

Leucotomized animals were used for two reasons: first, in order to study the reaction of a brain-damaged monkey to these drugs, and secondly to investigate whether the interruption of pallido-diencephalic and fronto-diencephalic connections would aid in the location of these drugs' "target area" in the central nervous system.

Material and Methods

Fourteen monkeys were used in the experiment, four *Macaca nemestrina* and ten *Macaca mulatta* varying in weight between 2·5 kg. and 4 kg.

For this particular experiment the *M. mulatta* proved more suitable than the *M. nemestrina* as the latter shows less spontaneous activity, and it was this activity which we proposed to use as a measure of the effects of the drugs.

All the monkeys were observed before and after the administration of the drugs, and the activity of seven was measured in a specially designed cage; of these seven, three had had a bilateral leucotomy eight, ten and thirty-six weeks respectively before testing.

The testing cage, through which passed a beam of infra-red light focussed on an electric photo-cell, enabled us to record the day and night movements of the monkey. These were registered on a counter and at the same time marked on recording paper so that we not only obtained the number of movements in any given period, but also their distribution. In this way the animal's normal activity and the changes produced by the drugs were plotted. This method was particularly useful in obtaining data on the monkey's sleeping habits, which we found to be a very sensitive indicator of the effect of the drug.

The electrical apparatus we used was designed and constructed by Dr. R. H. Kay of this laboratory to whom our sincere thanks are due.

When in the recording cage, the monkey was kept in a room by itself in order to avoid social stimulation by other monkeys, and was observed by one of us (J.C.) from the next room through a panel of one-way vision glass.

The counter and movement recorder were also in the observer's room so that readings could be taken at will without disturbing the monkey.

All monkeys were allowed at least a week in the recording cage in which to adjust to the environment. During this time they were carefully observed and an experiment was not begun until their pattern of daily activity had settled down to a constant level.

Dosage Used

One of the chief problems encountered in designing our experiment was to decide what were equivalent doses of the two drugs used. In this matter we were advised by the manufacturers of methyl-phenidate, who suggested that amphetamine was approximately twice as potent as methyl-phenidate. We therefore used the one to two ratio and experience has tended to confirm its validity, but it is possible that a ratio of two to five may be even more accurate.

We used single doses of 10 mg. of methyl-phenidate or 5 mg. of amphetamine, given by subcutaneous injection at 10 a.m.; this enabled us to observe their effect on normal daytime behaviour. In no case was either drug administered with less than three days' interval between doses.

Method of Leucotomy

The three *M. mulatta* monkeys operated on were anaesthetized with nembutal and a small opening cut on each side of the skull either with a trephine or dental drill. The openings were made in all cases with their posterior edge bordering on the coronal suture. After the pia had been incised with an iridectomy knife, bilateral lesions were made laterally, medially and down to the orbital plate of the base of the skull with scissors and a spatula (Fig. 1). The

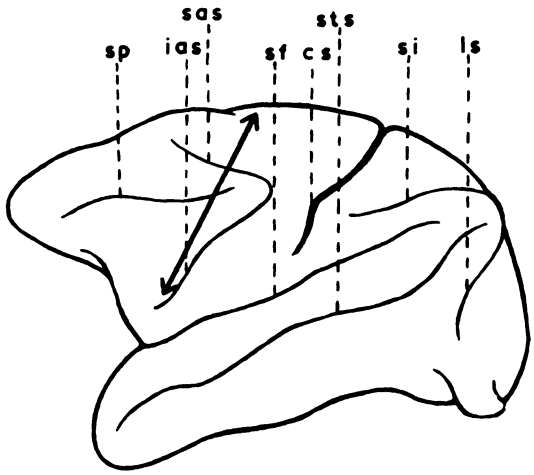

FIG. 1.—Lateral view of the left hemisphere of a Macaca mulatta. The arrow drawn in an oblique transverse plane on the frontal lobe illustrates the level of leucotomy carried out in M.S.10.

Abbreviations for sulci are as follows:

c.s.	=	central sulcus
i.a.s.	=	inferior ramus of arcuate sulcus
l.s.	=	lunate sulcus
s.a.s.	=	superior ramus of arcuate sulcus
s.i.	=	sulcus intraparietalis
s.t.s.	=	sulcus temporalis superior
s.f.	=	Sylvian fissure
s.p.	=	sulcus principalis

dura was closed, but not sutured, the bone replaced, the area dusted with penicillin, and the subcutaneous fascia and scalp sewn with multiple sutures.

Two of the monkeys showed typical post-leucotomy confusion and some "tameness"; all within a few days developed marked hyperactivity during the daytime which, up to the time of writing, has persisted in one animal for fourteen months. No monkey showed any evidence of paralysis after operation, and with the exception of the aspiration of some fluid from under the scalp in one case convalescence was normal and uneventful.

Results

Our findings can most easily be given under the headings of the drugs' effects on the daytime activity and the sleep pattern of the monkeys, considering in each case first the intact animals and then those that had been leucotomized.

Effect of Drugs on Daytime Activity

1. Unoperated Monkeys

(*a*) *Methyl-phenidate*

The first visible effect of the drug was an increase in cage pacing, then within three to six minutes of the injection multiple small tic-like movements of the hands and feet, of the scalp, ears and eyes, and especially of the lips and mouth were seen. There was also frequent touching of the naso-labial region, "smelling" and sucking of the fingers, chewing movements and biting of the cage bars. This activity of the mouth, nose and lips was a most striking and consistent phenomenon. With the increase of the tic-like movements cage-pacing decreased and the monkey sat or stood in one corner of the cage or clung to its side. Responses to external stimuli such as noise were exaggerated and fear reactions intensified. The animals also scratched themselves far more than normally and frequently picked over their hair as if looking for lice.

When the effect of the drug was wearing off, the small movements gradually ceased, those of the lips and mouth lasting longest, and then for a period of from two to three hours gross locomotory movements around the cage showed an increase, thus repeating in reverse the phenomena seen during the onset of the drug's effect. Throughout the six- to eight-hour period during which the drug was producing its maximum effect, the monkey's tail appeared to be more rigid, and in the case of *M. mulatta* was often held horizontal as the animal walked around. During the twenty-four hours measured from one hour before the giving of the drug its total movements showed an increase over normal.

(*b*) *Amphetamine*

All the effects produced by methyl-phenidate appeared after the injection of amphetamine, but to a greater degree. For instance, locomotion showed first an increase then a greater decrease, the period during which the drug's effect was most pronounced was prolonged and the "rebound" increase of activity continued far longer than after methyl-phenidate. The monkey also had a greater tendency to climb as high up its cage as possible and remain there in the position assumed by the normal monkey when alarmed. The total locomotory movements during twenty-four hours were usually in excess of those recorded for the same period after methyl-phenidate, as we reported in an earlier paper (Cole and Glees, 1956), and their distribution differed in the way we have mentioned.

2. LEUCOTOMIZED MONKEYS

(*a*) *Methyl-phenidate*

All the effects seen in the unoperated monkeys were produced when methyl-phenidate was given to those that had had a leucotomy, and although the period after operation varied from eight to thirty-six weeks, this made no difference to the results. All the operated animals showed the tic-like movements during the period of the drug's maximum effect, the temporary fall in cage pacing was greater than in the intact animals, but over the twenty-four hours, as in the case of the intact monkeys, the total number of movements recorded showed an increase.

(*b*) *Amphetamine*

The various signs observed during the daytime in the intact monkeys were all seen in the leucotomized animals which were given amphetamine.

There was, however, one striking difference.

Whereas in the intact monkeys after amphetamine the total of the recorded movements during the twenty-four hours showed an increase, in those that had been leucotomized it showed a decrease.

EFFECT ON SLEEP PATTERN

The fact that in every case the monkeys were given their injection at 10 a.m. is important when considering the effects of the drugs on the sleep pattern, because it means that the periods of multiple small movements and of the rebound increase in activity had both occurred and passed before the animals' usual time for sleep.

The normal monkey settles to sleep at sunset; during the night it makes few movements, but becomes fully active within half an hour of sunrise. This pattern is seen both before and after leucotomy (Figs. 2(*a*) and (*d*), 3(*a*) and (*d*)).

1. UNOPERATED MONKEYS

(*a*) *Methyl-phenidate*

After methyl-phenidate the monkey settles for the night at sunset as usual and thereafter few, if any, movements are recorded until sunrise (Fig. 2(*b*)).

In the morning the activity pattern follows a normal course, i.e. transition from sleep to full activity is extremely rapid (Fig. 3(*b*)).

(*b*) *Amphetamine*

After amphetamine the result was different. All the monkeys remained restless and active after sunset—for three hours in one case; throughout the night short bursts of activity were recorded and early morning activity occurred before sunrise (Figs. 2(*c*) and 3(*c*)). This disturbance of the sleep pattern after amphetamine was in sharp contrast to the normal undisturbed night after methyl-phenidate, and is the most striking and consistent difference between the effects of the two drugs which we have recorded.

2. LEUCOTOMIZED MONKEYS

(*a*) *Methyl-phenidate*

The sleep pattern of the leucotomized monkeys given methyl-phenidate was—as in the case of the unoperated animals—normal. The animal settled

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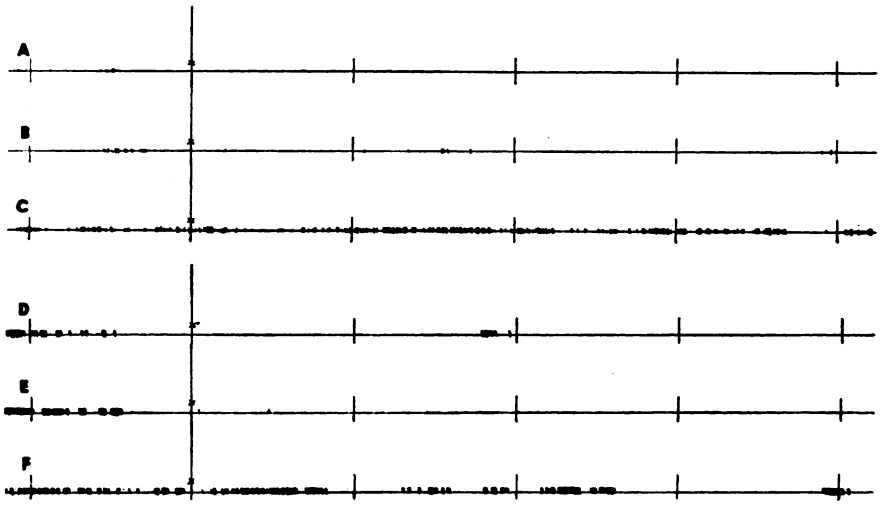

FIG. 2.—Vertical lines indicate 30 min. periods; the line marked with X gives the time of sunset.

Records A, B, C are from an intact monkey.

Records D, E, F are from a monkey three months after bilateral leucotomy.

A and D are without drugs.

B and E are after 10 mg. of phenidylate given at 10.00 hours.

C and F are after 5 mg. of amphetamine given at 10.00 hours.

Note the restlessness continued well into the normal sleeping period after amphetamine, and the normality of the sleep pattern in the phenidylate records.

The small burst of activity one hour after sunset in record D was caused by the accidental disturbance of the monkey.

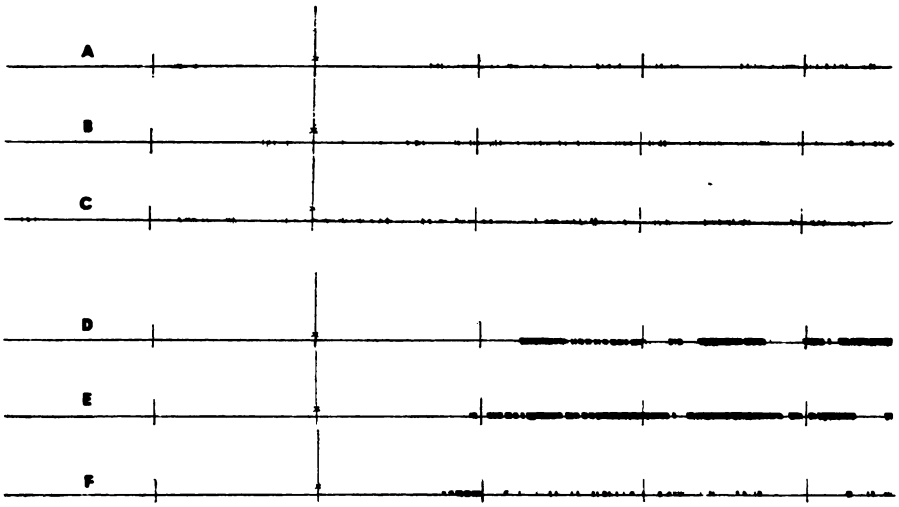

FIG. 3.—Vertical lines indicate 30 min. periods; the line marked with X gives the time of sunrise.

Records A, B, C are from the same intact monkey as in Fig. 2.

Records D, E, F are from the same operated monkey as in Fig. 2.

A and D are without drugs.

B and E are the morning after 10 mg. of phenidylate given at 10.00 hours.

C and F are the morning after 5 mg. of amphetamine given at 10.00 hours.

Note the early restlessness in records C and F and particularly the intermittent and decreased activity after sunrise in F compared with D and E.

at dusk, very few movements were recorded during the night, and with sunrise activity followed a normal pattern (Figs. 2(*e*) and 3(*e*)).

(*b*) *Amphetamine*

Amphetamine given to leucotomized monkeys affected their sleep pattern for, like the intact animals, they continued active long after sunset (Fig. 2(*f*)) But in contrast to the intact animals, once they had settled, their night remained undisturbed. In the morning their activity began at the usual time, but was much less and far more intermittent than normal (Fig. 3(*f*)). This effect of amphetamine on the early morning activity pattern in the leucotomized monkeys differs both from their own early morning records after methyl-phenidate (Fig. 3(*e*)) and also from those of the intact monkeys after amphetamine (Fig. 3(*c*)).

The ability of the leucotomized monkeys to remain asleep during the night, combined with the decrease in their early morning cage pacing accounts for their less than normal activity over a twenty-four hour period after amphetamine. As stated in a previous paragraph this decrease during the twenty-four hours in which amphetamine is given, is one of the most significant ways in which the reactions of the leucotomized and intact monkeys differ.

In order to eliminate the possibility that the different effects, and particularly the change in sleep pattern seen after amphetamine were due merely to a quantitative difference in the dose, we gave a double amount, i.e. 20 mg. of methyl-phenidate to two leucotomized and to two intact monkeys. This failed to produce, in all four monkeys, the long delay in settling to sleep; in the intact animals the restless night and in the leucotomized monkeys the decrease in spontaneous activity in the morning which were such typical effects of amphetamine (Figs. 2 and 3).

With regard to the daytime activity in the leucotomized monkeys, a temporary but very considerable increase in cage pacing occurred over that recorded after 10 mg. of methyl-phenidate and in sharp contrast to the fall seen after amphetamine. The intact animal on the other hand did show a drop in activity more nearly corresponding to that produced by amphetamine, but at the same time less evidence of agitation and tension. Furthermore, the effects produced by the drugs were not observed after the subcutaneous injection of similar amounts of saline.

Discussion

Our findings that both methyl-phenidate and amphetamine decrease the spontaneous daytime cage pacing of monkeys, at least for some hours, needs to be considered alongside the report of Meier, Gross and Tripod (1954) that both these drugs produce a fourfold increase in the activity of mice. At first sight their results appear to conflict with ours. By the courtesy of Dr. Gross one of us (J.C.) examined the type of "jiggle cage" used in their experiments and found that it registered in the mouse many of the small fidgeting movements of the kind observed in our monkeys, and that it did not distinguish between the locomotory movements of the mouse as it ran round the cage and restless movements made in a very limited area; in fact it summed all movements of both types.

In contrast, our cage gave us no record of the multiple small movements, but distinguished between these and locomotion by selecting and recording only the latter. This explains the apparent contrast of our findings with those of Meier, Gross and Tripod.

Turning to the consideration of the drugs' effect on the monkeys' sleep pattern, particularly that of the leucotomized animals, we would relate this to observations made on the use of methyl-phenidate in psychiatry. Ferguson (1955) studying the stimulating effect of methyl-phenidate in patients depressed by reserpine, uses their sleep pattern as a criterion of mental tension and writes: "the further from the normal towards insomnia or other sleepless patterns, the more tense the patient" (p. 106).

Although terms such as "mental tension" must be used with caution when applied to animals, it is, nevertheless, helpful to avail ourselves of this concept to explain the way in which the reaction of the leucotomized monkey to amphetamine differed from that of the unoperated animal. The operated monkeys given amphetamine, though late in settling to sleep, showed records of undisturbed nights, but the intact animals after the same dose remained restless throughout the night. We suggest, therefore, that leucotomy by cutting the fronto-diencephalic circuit prevents the storage of afferent impulses to the frontal lobe and the consequent building-up of a "state of tension".

From this it would follow that in the intact animal given amphetamine the disturbed sleep pattern indicates a state of tension which is impossible after leucotomy. For the operated monkey once it is deprived of external stimuli and especially of light is able to remain asleep because the amphetamine without the self-sustaining nervous circuit from the frontal areas to act upon cannot produce nor maintain the state of tension, which manifests itself in nocturnal restlessness. This is also probably valid for man, since Partridge (1950) notes that his leucotomy patients experienced deep and dreamless sleep.

Neurohistological and Functional Aspects of Leucotomy

Leucotomy, as previously stated, was used in our experiment in order to estimate the effect of the drugs on the activity of brain damaged monkeys. In their study of leucotomy, Freudenberg *et al.* (1950) found that this operation produces in the monkey long lasting restlessness and perambulation. A state of hyperactivity was also seen by Glees *et al.* (1950) after lesions in the cingular gyrus, which involved adjacent parts of the frontal lobe. But this restlessness began immediately after operation in contrast to the hyperactivity following leucotomy which begins after about ten days. The increase of cage pacing by the leucotomized animal depends on "triggering" by outside stimuli and ceases when these are excluded. This was clearly established by the improved method of continuously recording movements which was used in this study. Cage pacing is also more marked the further posterior the lesion is made.

In Freudenberg *et al.* (1950) neurohistological observations revealed that the prefrontal cortex of the monkey has a strong afferent connection with the dorso-medial nucleus of the thalamus, and Glees, Meyer and Meyer (1946) showed that fibres from this nucleus reach the frontal cortex. Leucotomy therefore interrupts a circuit which passes to the thalamus and from there back again to the frontal cortex.

In addition to interrupting these pathways it also involves the basal ganglia, in particular the globus pallidus (Fig. 4) and causes degeneration of the pallido-hypothalamic tract. This fibre bundle connects the globus pallidus with the ventro-medial nucleus of the hypothalamus. Its course and termination have been studied experimentally in the monkey and discussed by Glees (1945).

The interruption of these pathways (Fig. 5), the fronto-thalamic, the thalamic-frontal and the pallido-hypothalamic appears to be a causal factor in producing increased perambulation.

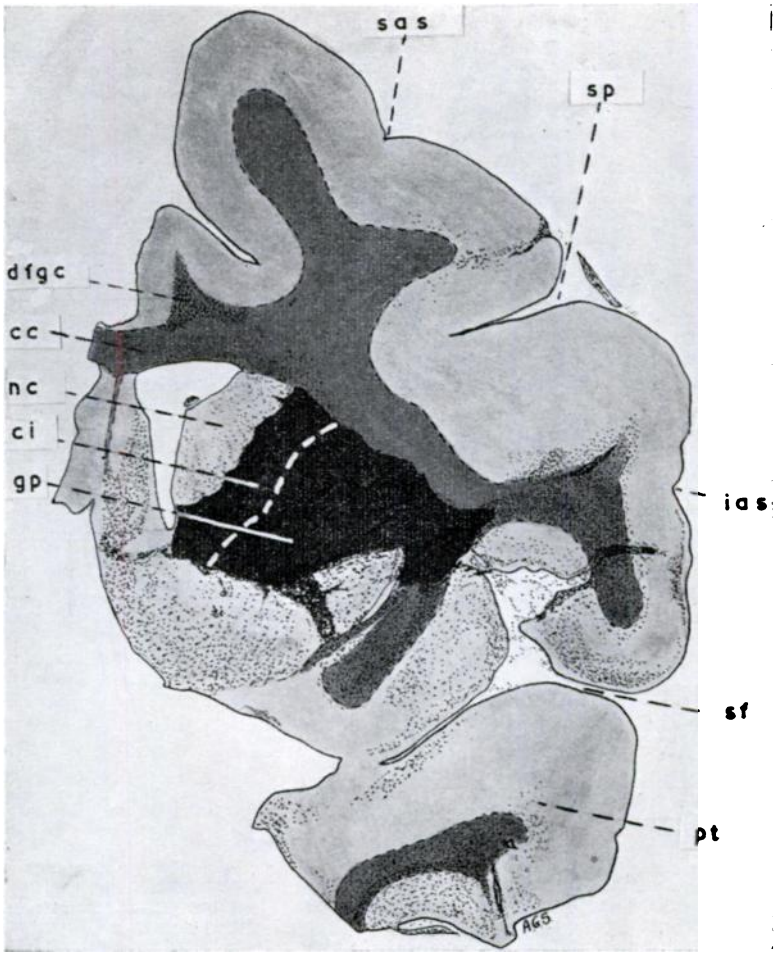

FIG. 4.—Section through the plane of leucotomy in the right hemisphere of M.S.10 stained with the Marchi-technique. The area drawn in black shows the area of necrosis and involves the anterior limb of the internal capsule and the lentiform nucleus (putamen and globus pallidus). The dotted areas show fibre degeneration and also cell changes.

Abbreviations:

c.c.	=	corpus callosum
c.i.	=	capsula interna
d.f.g.c.	=	degenerated fibres in white matter of gyrus cinguli
g.p.	=	globus pallidus
i.a.s.	=	inferior ramus of arcuate sulcus
n.c.	=	nucleus caudatus
p.t.	=	temporal pole
s.a.s.	=	superior ramus of arcuate sulcus
s.f.	=	Sylvian fissure
s.p.	=	sulcus principalis

Fulton (1948) discussing the function of the orbital gyri which are also involved in our lesions, holds the opinion that injury to this region is responsible for the increase in spontaneous activity. Wall *et al.* (1951), in studying the fibre connections of this orbital area, demonstrated the termination of fibres, mainly from area 13, within the ventro-medial and paraventricular nuclei of

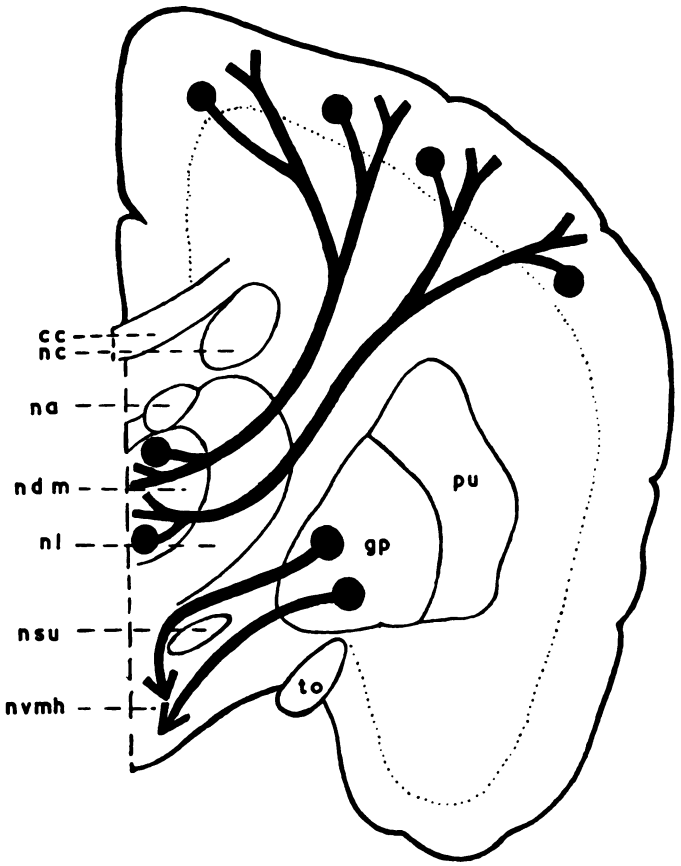

FIG. 5.—A diagrammatic representation of the fronto-thalamic and thalamic-frontal connections of the globus pallidus with the hypothalamus. The connections referred to in the text between orbital lobe and hypothalamus (Wall *et al.*, 1951) run in a horizontal plane and are not shown.

Abbreviations:

c.c.	=	corpus callosum
n.a.	=	nucleus anterior
n.c.	=	nucleus caudatus
n.d.m.	=	nucleus dorsalis medialis thalamii
n.l.	=	nucleus lateralis
n.su.	=	nucleus subthalamicus
n.v.m.h.	=	nucleus ventro-medialis hypothalamii
g.p.	=	globus pallidus
pu.	=	putamen
t.o.	=	tractus opticus

the hypothalamus. This is the same region which receives fibres from the globus pallidus. We suggest, therefore, that the daytime restlessness in our leucotomized monkeys is essentially due to the removal of a damping influence from the orbital regions of the frontal lobe and from the globus pallidus. In attempting to discover the target area or areas for amphetamine and methyl-phenidate it is highly significant that both drugs change drastically the motor pattern by almost stopping perambulation and bringing about the much finer tic-like movements.

Effects of Leucotomy, Amphetamine and Methyl-phenidate on the Hypothalamus

We stated in a previous paper (Cole and Glees, 1956) that the increase in parasympathetic-like activity seen after large doses of reserpine could be reversed by methyl-phenidate or amphetamine, and suggested that these two drugs increased the sympathetic outflow. One of the sympathetic centres in the hypothalamus is the ventro-medial nucleus referred to above which therefore might well be a "target area" for methyl-phenidate and amphetamine. Further evidence for the activation of the sympathetic nuclei in the hypothalamus by these drugs is the marked restlessness and alertness which they cause in the unoperated monkey. The reason for this statement is the well-established fact that lesions in the sympathetic centres of the hypothalamus (posterior hypothalamus) produce among other symptoms the opposite effect, namely, complete abolition of spontaneous movements (Collins, 1955). The catatonic-like effect of such lesions closely resembles that seen after an injection of a large dose of reserpine (Cole and Glees, 1956). A similar state of catatonia and stupor was also found by Feldberg and Sherwood (1955) after intraventricular injection of bulbocapnine or anticholinesterases.

We believe that the two drugs under consideration reverse the reserpine syndrome by greatly increasing sympathetic activity. Moreover, in the leucotomized monkey these drugs, acting on a nervous system which has already lost the inhibiting influence of the frontal lobes and the globus pallidus, produce more marked effects than in the normal animal. For while the motor system in the leucotomized monkey reacts to the absence of the inhibiting influence of the damaged areas by excessive daytime perambulation, when the drugs are given the increased sympathetic activity overwhelms the orderly movements and produces the generalized tics. Therefore it is because of the presence of the intact inhibiting cortical and subcortical systems in the unoperated monkey that the effects of the drugs are less marked and of shorter duration in these animals than in those that have been leucotomized.

The significance of hypothalamic functions for neuropsychiatry—and our work is relevant to this field—has been repeatedly stressed and recently been summarized by Gellhorn (1956) and by Feldberg (1956). We, too, for the reasons stated, hold the view that the hypothalamus is the most likely "target area" for centrally stimulating or depressing drugs. The important data on the reticular system gathered by Magoun, French and their co-workers have also to be considered in the interpretation of our results. In this connection their interesting finding that the frontal cortex influences the activity of the ascending reticular system (French *et al.*, 1955) deserves special attention. For some of the effects of leucotomy could be produced by the interruption of the fronto-reticular system which they describe. The hypothalamus, however, is a link in the chain of the reticular system and is an integrated part of that portion of the reticular system which exercises an "alerting" influence on the cortical E.E.G. so that our hypothesis is not at variance with their results.

General Comment

A point of some significance, both for our experiment and for wider issues, and one which became increasingly definite as our work proceeded, is that there appears to be no such thing as a standard monkey, for directly these animals are studied in detail, important individual differences appear.

Thus, while it is true that monkeys settle to sleep about sunset and during

the night make few movements, but become fully active around sunrise, nevertheless individual animals have a characteristic and consistent sleep pattern, which, while conforming to the general pattern in outline, differs from it in minor details. For instance, one unoperated monkey always had two small bursts of activity during the night, another consistently showed a period of movement about an hour before sunrise. For this reason we made a careful and detailed study of each individual monkey's pattern of activity throughout the twenty-four hours before we attempted to test the effects of the drugs.

The same individuality was also apparent in the animals' reactions to the drugs; there was always an overall similarity of reaction, but this when analysed in detail revealed consistent individual traits.

While in all monkeys methyl-phenidate and amphetamine caused a decrease in activity, then a period of rebound activity, we found on comparing and analysing several records of monkeys No. 5 and No. 9, that No. 9 responded to both drugs by a shorter period of decreased activity and a much greater rebound period than did No. 5.

We would stress this point of the individual differences appearing within a general conformity to a broad pattern, because the findings reported in this paper are mainly concerned with the broad pattern of reaction to the drugs used. Moreover, we would expect to find in the clinical use of these drugs similar individual variations of responses in human patients to those we have observed in our monkeys.

Furthermore, we are of the opinion that studies of the effect of drugs on primates can give valuable indications for their use in clinical psychiatry. Closer co-operation between those engaged in experimental studies of drugs and clinicians would therefore be advantageous in the field of psychiatric research, by facilitating the advance of our knowledge and avoiding some of the divergences of opinion as to the clinical value of a particular drug to which Shepherd (1956) draws attention.

Summary

1. Fourteen monkeys were given on different days 10 mg. of methyl-phenidate (Ritalin) and 5 mg. of amphetamine.
2. The day and night activity of eight was recorded by means of a special cage. Of these eight, three had had a bilateral leucotomy and five were intact.
3. Both drugs caused a decrease in daytime locomotion, but a marked increase in small tic-like movements and fidgeting. The effect of amphetamine was the more marked and prolonged.
4. Methyl-phenidate in contrast to amphetamine had no effect on the sleep pattern of any of the monkeys.
5. A double dose (20 mg.) of methyl-phenidate given to two intact and two leucotomized monkeys failed in both cases to produce the same effects as amphetamine.
6. Histological studies of the brains of the leucotomized monkeys showed that pathways from the frontal lobe to the dorso-medial nucleus of the thalamus and in the reverse direction had been interrupted in addition to pathways from the orbital area of the frontal lobe and the globus pallidus to the posterior hypothalamus.
7. The increase in locomotion after leucotomy is probably due to the interruption of these pathways, particularly those to the hypothalamus.
8. The effect of the drugs on both the intact and operated monkeys would indicate the posterior hypothalamus as a possible "target area".
9. It is suggested that testing the effects of drugs on primate behaviour can supply information useful in psychiatry.

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