The cells contained no chromophil granules but were more or less uniformly basophilic and resembled the normal intermediate lobe cells in every respect except that they were considerably larger and somewhat less basophilic than the latter. The anterior lobe of the same hypophysis contained 2 small chromophobe adenomata of the type which is usually produced by prolonged oestrin treatment (Fig. 2).

Intermediate lobe tumors are exceedingly rare; in fact, outside of the small adenoma reported in our previously mentioned communication and the tumor described in this paper, to our knowledge no growth of this type has ever been reported. Among the many pituitaries of rats from our colony, we have never seen intermediate lobe tumors either in untreated animals or in rats belonging to other experimental series. Although we have no proof that the 2 intermediate lobe tumors which we observed are the result of oestrin treatment, we feel that, considering the great rarity of these tumors, they should be reported and emphasis should be laid on the fact that both of them occurred in oestrin-treated animals. It is also noteworthy that in the case here reported, the pituitary showed obvious signs of stimulation by oestrin inasmuch as two independent chromophobe adenomata such as are usually produced by oestrogenic substances were present in the anterior lobe.

Summary. A pigmented adenoma of the intermediate lobe of the hypophysis is described. This is the second time such a tumor has been observed and both cases were seen in rats chronically treated with oestrogenic preparations.

10369

The Action of Toxic Doses of Atropine on the Central Nervous System.

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Scattered data concerning stimulation and depression of the central nervous system following the administration of atropine are both numerous and contradictory. Albertoni[1] reported that atropine in doses from 2-10 mg per kg increases the electrical excita-

[1] Albertoni, *Arch. Exp. Path. Pharmakol.*, 1882, **15**, 248.

bility of the motor cortex and facilitates the production of epileptiform seizures following stimulation of motor areas in dogs and monkeys, and stated that fatal or nearly fatal doses exert depressant or paralysant effects (terminating in paralysis of the limbs and respiratory muscles) without previous stimulation. Fraser[2] and Issekutz[3] described after initial depression the appearance of strychnine-like convulsions in frogs.

Joel,[4] Garcia,[5] Silver[6] and Friedberg[7] reported that the combination of atropine or hyoscyamine or scopolamine with morphine, ether, sodium phenobarbital or pernoston enhances the action of these narcotics. These authors used nearly anesthetic doses of the aliphatic depressants and supplemented these with doses from 25 to 50 mg of atropine per kg, immediately or a few minutes later. It is significant that Friedberg states that the synergism does not occur if the atropine is given one-half hour after injection of the barbiturates. All these experiments were carried out in rodents and it is obvious that a possible shock-producing effect of atropine given immediately on top of a sizeable dose of a central depressant, was not eliminated.

Very recently Schweitzer and Wright[8] have shown that 0.5-3.0 mg of atropine per kg depress the knee jerk owing to a central action and that these doses do not markedly antagonize either the excitatory action of physostigmine or the characteristic central inhibition produced by larger doses of acetylcholine.

The following experiments were carried out to study separately the stimulant and depressant actions of atropine and subject them to pharmacodynamic analysis. This was found possible only if large doses of this drug were employed.

A. *Frogs.* In *Rana pipiens* ("winterfrogs") intramuscularly administered doses of atropine sulfate from 50 to 400 mg per kg (20 animals) produced no observable effects; doses of 500 mg* (9 animals) produced sensory and motor depression lasting from 7 to 48 hours, following the depression 4 of the 9 animals showed hyperexcitability and an occasional convulsion upon sensory stimulation which persisted after destruction of the forebrain, became less pronounced after destroying the medulla and disappeared after pithing

2 Fraser, *Trans. Roy. Soc. Edinburgh,* 1869, **25**, 450.

3 Issekutz, *Z. Exp. Path. Therap.,* 1917, **19**, 99.

4 Joel, *Arch. Exp. Path. Pharmakol.,* 1928, **132**, 63.

5 Garcia, *Arch. Exp. Path. Pharmakol.,* 1928, **134**, 148.

6 Silver, *Arch. Exp. Path. Pharmakol.,* 1930, **158**, 219.

7 Friedberg, *Arch. Exp. Path. Pharmakol.,* 1931, **160**, 276.

8 Schweitzer and Wright, *J. Physiol.,* 1937, **89**, 384.

* All doses used are expressed in mg per kg of body weight; for the sake of brevity the last phrase is omitted.

the cord. Doses of 750 mg of atropine (5 animals) produced similar effects (2 of the 5 frogs developed hyperexcitability and spasticity), but 2 animals died within 6 days following administration. Doses of 1000 mg or more (10 animals) were invariably fatal, the sensory, motor and respiratory paralysis developing shortly after administration, persisting until death; no convulsions and in the majority of cases no curariform effects (judged by sciatic stimulation) were observed.

B. *Mammals.* Dogs, and to a lesser degree, cats are fairly tolerant to large doses of atropine. A preliminary survey of the toxicity of intravenously administered doses of this drug revealed that all but 2 dogs receiving 50 mg (12 animals) survived, 2 dogs receiving 60 mg survived, 4 of 5 animals receiving 75 mg recovered, while of those receiving 100 mg, 3 died and 3 survived. The drug seems to be more toxic for older than for younger animals. Atropine is far more toxic for cats, but doses from 30 to 40 mg are usually tolerated. The administration of these large doses of atropine is followed by a curious mixture of depression and stimulation. Immediately after injection depression predominates, the animals show muscular weakness, prostration, assume a lateral position and occasionally show relaxation and anesthesia of brief duration. They may fall asleep, but can be roused. It may take hours, but often only 15-30 minutes until the animals are able to stand or walk. A rapid fall of blood pressure following atropinization may be a contributing factor in the production of depression. In this series only dogs given 60 mg of atropine or more showed almost immediate typical epileptiform convulsions but occasionally dogs receiving the smaller doses exhibited other phenomena of central nervous stimulation: spontaneous elicitation of scratch reflex in rapid succession, stimulation of respiration, howling, retching and vomiting, hyperexcitability and spasticity. One dog, receiving 40 mg developed 2 hours after atropine administration clonic spasms. All these signs of stimulation, including the convulsions with higher doses are immediately stopped by small doses of barbiturates (*e. g.,* 10-15 mg of nembutal). The convulsions are not asphyxial; they continue in spite of vigorous artificial respiration and often cause death.

The following experiments were devised to ascertain whether the depression and stimulation are primary effects of atropine on the central nervous system or are secondary to drug injury of other structures.

Seven dogs each receiving 50 mg and 1 cat receiving 30 mg of atropine sulfate showed only a brief depression and within 30 min-

utes were able to stand and walk. Each of these animals received about one hour later 15 mg nembutal by vein and almost immediately following injection showed complete muscular relaxation and "surgical" anesthesia, (corresponding to an effect produced by 35-40 mg in control animals) recovering in 3½ to 4½ hours. On each of 4 successive days the same animals were again given 15 mg of nembutal and showed relaxation and anesthesia of gradually diminishing durations until on the fourth or fifth day following the administration of atropine they showed only motor incoördination and somnolence, *i. e.*, an effect 15 mg of nembutal usually produces in an untreated animal. One dog died on the next day following atropinization after the injection of 15 mg of nembutal. Two dogs receiving 50 mg of homatropine showed similar synergism with 15 mg of nembutal, but showed a normal reaction to the barbiturate on the third day. Similar results were obtained in 6 additional dogs by using 50-75 mg of sodium barbital instead of nembutal.

A typical condensed protocol may serve as an illustration:

Dog 9.2 kg; male		November 9, 1938
10:35	A.M.	50 mg of atropine SO_4 by vein
10:37	"	Animal falls, defecates, howls
11:00	"	Able to stand
11:15	"	15 mg nembutal, vein; falls
11:16	"	Anesthesia, relaxation
12:18	P.M.	Running movements, shivering
1:10	"	Attempts to right itself; howls
2:20	"	Crawls about
4:10	"	Able to stand
		November 10, 1938
10:00	A.M.	Animal appears normal
10:35	"	15 mg nembutal; falls
10:36	"	Anesthesia, relaxation
11:28	"	Shivering, running movements
12:00	P.M.	Attempts to right itself
1:35	"	Recovery (able to stand without support)
		November 11, 1938
9:45	A.M.	Animal normal
10:10	"	15 mg nembutal, falls
10:20	"	Anesthesia, relaxation
10:50	"	Shivering
11:20	"	Attempts to sit up
12:18	P.M.	Recovery
		November 13, 1938
10:12	A.M.	15 mg nembutal
10:15	"	Lies down, holds up his head (no anesthesia or relaxation)
10:21	"	Sits up
12:00	M.	Complete recovery

Doses of atropine less than 20 mg or of nembutal less than 10 mg cannot be used to demonstrate the above described phenomenon; by using 20-25 mg of atropine it is often possible to show severe depression following 15 mg of nembutal on the first day, but even then there is no anesthesia or complete relaxation. Smaller doses of nembutal (5-10 mg) do not produce complete relaxation and anesthesia irrespective of the dose of atropine.

Six dogs received 0.075 mg of strychnine sulfate (by vein); to 3 additional dogs the same dose was given twice within one hour without producing convulsions. To 5 dogs a dose of 50 mg of atropine was given which produced motor depression ("weakness of the limbs") and somnolence. Each of these 5 dogs received in about 30 minutes a dose of 0.075 mg of strychnine. Every one of these animals stood up almost immediately following injection, showed motor excitement and developed within a few minutes typical strychnine convulsions. Two of these 5 dogs died of convulsions. The surviving animals were given the same dose of strychnine the following day, but no convulsions were noted.

These experiments prove that (a) atropine, until appreciable elimination occurs, shows synergism with an aliphatic hypnotic; (b) large doses of the same drug synergize with a spinal convulsant, and (c) hypnotics may antagonize atropine stimulation and convulsants may oppose atropine depression. It other words, atropine, like morphine, has a twofold action on the central nervous system. Whether or not these actions can be explained by the acetylcholine-blocking effect of atropine still remains to be determined.

10370

Anaphylaxis in the Pregnant Rat.

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Attempts have been made to elucidate the rôle of the endocrine glands in determining the susceptibility of animals to anaphylactic shock. Kepinow and Lanzenberg[1] found that thyroidectomy protected the guinea pig and rabbit against anaphylactic shock by in-

[1] Kepinow, L., and Lanzenberg, A., *Compt. rend. Soc. de Biol.*, 1922, **86**, 204, 906.