partially reversed lipemia which had already appeared. This action could have resulted by blocking production of a clearing factor inhibitor or from stimulation of the lipid transporting system.

Summary. Dextran in doses of 1 to 1.5 g/day inhibited production of cortisone hyperlipemia in rabbits and partially reversed the hyperlipemia produced by cortisone. Alterations in fat transport, fat mobilization or in clearing factor action are considered as the basis for antagonism between dextran and hyperlipemic action of cortisone.

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Some Pharmacological Actions of Amphenidone* A New Psychotherapeutic Drug. (25880)

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A new chemical structure, 1-m-Aminophenyl-2-pyridone (amphenidone), is of interest in that it induces emotional stability without depression of psychic or motor functions(1). Because of promise shown in clinical trials, some of its pharmacological actions are described below.

Methods. Potentiation of a subhypnotic dose of hexobarbital (50 mg/kg) by amphenidone and other drugs was measured as reported(2). Inhibition of the effects of LSD in the mouse (CF #1) was investigated using Haley's method(3). Anticonvulsant activity was determined in the mouse, using maximal electroshock (MES) and Metrazol (Met) seizures(4) and in the cat, in which clonic convulsions were evoked by injecting 50 mg/kg Metrazol, subcutaneously. Analgesic activity was assayed according to Eddy and Leimbach(5), using a 40-second exposure to the hot plate at 54-55°C. Cardiovascular and respiratory effects in the anesthetized (pentobarbital) dog were recorded kymographically using a Hg manometer and an Anderson inspirometer. Studies of isolated cat and rabbit hearts were conducted according to Langendorff(6). Effects on the nictitating membrane were studied using the method of Plummer *et al.*(7). Whenever linearity of dose-response relationships permitted, ED_{50}'s with 95% fiducial limits were computed graphically(8) and, in general, 10 or more animals were used at each of 3 or more doses.

Results. Loss of the righting reflex was noted only in response to toxic doses of the drug, *e.g.,* 500 mg/kg i.v. and 1000 mg/kg

* Amphenidone manufactured under trade-name Dornwal by Maltbie Labs., Wallace & Tiernan.

† With technical assistance of Domicele P. Skeivis, Richard B. Lawlor, and Bernice R. Strauss.

TABLE I. Hexobarbital Potentiation.

Compound	ED_{50} (95% limits), mg/kg p.o.	Mean sleeping time at ED_{50}, min.
Amphenidone	132 (106-165)	37
Hydroxyzine	250 (167-375)	51
Meprobamate	123 (108-140)	24
Phenaglycodol	62 (41- 94)	15

p.o. in the mouse, 400 mg/kg i.p. in the rat and 600 mg/kg i.v. in the dog. Doses within the toxic range for the cat (400 mg/kg p.o.) and dog (400 mg/kg i.v.) were not hypnotic.

When given together with subhypnotic dose of hexobarbital, amphenidone precipitated loss of the righting reflex presumably through central depression, although cord and vestibular mechanisms are not entirely excluded. Potent central depressants such as phenothiazines, reserpine, and phenobarbital characteristically gave low ED_{50}'s(2) in contrast with the large values listed for the first 3 compounds in Table I.

Amphenidone completely blocked the effects of LSD in the mouse. Unprotected animals exhibited Straub tail, tremors, aggressive behavior, and hyperexcitability(9). The oral ED_{50} of 110 (73-165) mg/kg provides a large margin of safety, the therapeutic index being 12. The rationale of this test involves the assumption that LSD or one of its congeners has a role in development of psychic disturbances. That this concept represents an oversimplification of complicated processes (10,11) is undoubtedly true. That it has a certain empirical value for the pharmacologist, however, has not been excluded(12).

Results summarized in Table II indicate anticonvulsant activity, particularly against Metrazol. In general, tranquilizers do not have this property; for example, the convulsant dose of Metrazol was lowered following reserpine(13), minimal electroshock seizure threshold was decreased significantly by chlorpromazine(14), and convulsions were actually precipitated in monkeys following chronic administration of chlorpromazine (15). Exploring the brain of unanesthetized monkeys with the aid of implanted electrodes, Delgado(16) found that amphenidone decreased spontaneous electrical activity of the cortex, septal areas, basal ganglia and thalamus. The decreased thalamic excitability suggests possible effectiveness against *grand mal* seizures.

Amphenidone appeared to exert an analgesic effect in the mouse. In the Eddy and Leimbach test the ED_{50}'s of amphenidone and codeine were 480 (445-520) and 145 (116-181) mg/kg p.o., respectively. At this high dose amphenidone may exert analgesic activity by suppression of motor function. Amphenidone did not reduce activity of morphine. In contrast to these findings, reserpine had no analgesic activity and actually reduced the effectiveness of morphine(17). Other studies, to be reported, indicate that perception of pain may be interrupted by amphenidone at cord levels. Peripheral sites of action appear to be excluded.

In the anesthetized dog no significant cardiovascular or respiratory effects were induced by intravenous doses of 25, 50, or 100 mg/kg of the drug. The ECG pattern (lead 2) was unchanged and actions of epinephrine, norepinephrine, acetylcholine, and serotonin on blood pressure were not affected. Electrically and chemically induced contractions of the nictitating membrane of the cat were not altered, even after large intravenous doses (200 mg/kg) of amphenidone. Perfusion of the isolated heart with massive doses (1000 μg) of the drug induced no changes in the coronaries or in amplitude or rate of ventricular contractions. In these experiments amphenidone was devoid of cardiovascular, respiratory, and autonomic activity.

Summary. Overt signs of CNS depression were elicited only in response to toxic doses of amphenidone. Selective central depressant activity was revealed by 1) blockade of

TABLE II. Anticonvulsant Activity.

Compound	ED_{50} (95% confidence limits), mg/kg p.o. MES*	Met†
Amphenidone	180 (165-190)	120 (97-149)
Paramethadione	175 (149-220)	110 (90-135)
Phenacemide	109 (98-122)	126 (107-149)
Diphenylhydantoin	11 (8- 16)	Nil
Trimethadione	Nil	470 (415-530)

* Maximal electroshock seizures.
† Metrazol convulsions.

stimulant effects of LSD; 2) anticonvulsant activity against electrically and chemically induced seizures; and 3) analgesic activity. In the anesthetized dog and cat, blood pressure and respiration were affected only by lethal doses of the drug. Large doses of amphenidone did not alter blood pressure responses to acetylcholine, epinephrine, norepinephrine or serotonin. Contractions of nictitating membrane in response to electrical or chemical stimulation were not altered by amphenidone. Normal functioning of isolated heart was not affected by addition of massive doses of the drug to perfusion fluid, nor, in the intact dog, was the ECG (lead 2) changed.

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Standardization of Electrocardiographic Recording in Repeated Experiments on Supine Anesthetized Dogs.* (25881)

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There is great difficulty in obtaining reasonably constant electrocardiographic contour in repeated experiments upon dogs because the dog's heart is so mobile. This has been shown in this department(1) and also by Harris and Hussey(2) and Gross and Benison (3). The lateral position is no more successful as shown by Peterson, *et al.*(4), and the data of Lalich, *et al.*,(5). The former group(4) found better reproducibility in the supine position. This is the position we employed, taking not only limb leads but chest leads as well. Our study showed that the position employed minimized or eliminated the instability of serial records as seen in previous studies.

Materials and methods. A total of 32 electrocardiograms were taken on 12 healthy mongrel dogs weighing from 12 to 20 kg. One dog had 10 serial records and most had 3. The records were generally taken 3 days apart. The dogs were anesthetized with Pentothal Sodium, 20 mg/kilo, and placed supine on a V-shaped wooden table and tied down by means of lateral traction on the limbs. The electrode areas were shaved and coated with conducting jelly (Sanborn Redox). German silver plate electrodes were strapped on the 4 limbs just above the paws. Previous trials had shown that other limb positions or

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