references cited that the level of ATP found in the brain tissue was lower than that reported in the present communication. Although the reason for the slower degradation of ATP and PC in the brains of animals treated with depressants is unknown at present, a part of the retardation is probably due to depressed body temperatures in some of the animals.

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¹ LePage, G. A., Amer. J. Physiol., 146, 267 (1946).

² Grenell, R. G., Tranquilizing Drugs, 61 (Amer. Assoc. Adv. Sci., 1957).

¹⁹⁵⁷.
 ⁸ Schwemmle, K., and Heim, F., Med. Experimentalis, 1, 351 (1959).
 ⁸ Mandel, P., and Harth, S., J. Physiol. (Paris), 52, 166 (1960).
 ⁵ Gerlach, E., Doring, H. J., and Fleckenstein, A., Pflüg. Arch. ges. Physiol., 266, 266 (1958).
 ⁶ Koransky, W., Arch. Exp. Path. Pharmak., 234, 46 (1958).
 ⁷ Doring, H. J., Knopp, A., and Martin, T., Pflüg. Arch. ges. Physiol., 269, 375 (1959).

⁸ Minard, F. N., and Davis, R. V. (unpublished results).

PHYSIOLOGY

Effect of 'Metrazol' on the Isolated, **Perfused Mammalian Heart**

CONTEMPORARY pharmacological tests state that 'Metrazol' (pentamethylene-tetrazole) has no direct effect on the myocardium. Conflicting opinions are recorded in the literature¹. Goodman and Gilman² claim that the electrocardiographic changes are due to central nervous system influences, an opinion shared by Bircher et al.³. Since the direct role of 'Metrazol' on the heart did not seem to be settled, we undertook the following experiments.

Rabbit and cat hearts were rapidly removed from animals killed by pentobarbital and perfused through the aorta (Langendorff preparation) with mammalian Ringer's solution. The preparation would remain stable for several hours. Several concentrations of 'Metrazol' were injected into the perfusion tube immediately before the aorta so that a 'slug' of 'Metrazol' passed quickly through the coronary arteries one time and was not recirculated. No experiments were done with uniform concentrations of 'Metrazol' in the perfusate. Recordings were made with Sanborn equipment from the auricle and the ventricle. Depending on the quantity of 'Metrazol' injected, cardiac slowing, dysrhythmias, or arrest were produced. Fresh preparations fully recovered in 2-3 min. 200 mgm. 'Metrazol' produced 22 per cent slowing when injected over 8 sec., with complete recovery in 90 sec., while 250 mgm. produced first slowing, then complete asystole after 18 sec. that lasted 10 sec. Recovery was initiated in the auricle with a regular rate of 45 beats/min. without auricularventricular conduction. Then occasional ventricular extrasystoles appeared, followed by a short period of irregular auricular-ventricular dissociation with normal ventricular complexes appearing after Pwaves, followed for 60 sec. by a 2-1 auricularventricular block, with complete recovery in 3.5 min. This series of alterations could be repeated several times in any one preparation reliably. When doses greater than 250 mgm. were used, slowing and asystole occurred more rapidly and recovery was delayed.

We attempted to block these effects with atropine (0.1-1.0 mgm.) injected immediately before or with the 'Metrazol'. Only incomplete protection occurred. 'UK-738' (n-ethyl-nortropine-benzydrylether-hydrobromide) also afforded incomplete protection from the 'Metrazol'. More complete studies regarding protection and mechanism are in progress.

Rabbits' hearts appear to be more sensitive to 'Metrazol' than cats' hearts. Smaller doses consistently produced comparable changes. No attempt was made to relate injection-rate with effect beyond one test when the rate was reduced by a factor of ten for a 250-mgm. dose, and no effects were seen. No attempt was made to relate effect with heart weight or perfusion-rate.

A specific interpretation of these experiments is premature. The conflicting data recorded in the literature suggest that the experiments are not comparable. In all our experiments the P-R interval increased after 'Metrazol', while the QRS complex did not seem altered when present until isolated extra-systoles occurred. These were usually seen during recovery and may represent evidences of metabolic changes rather than the specific recovery pattern after 'Metrazol'. As recovery times were always longer than induction times one might suspect that 'Metrazol' dissociates from a receptor site more slowly than it combines.

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- ¹ Haury, V. G., and Gruber, C. M., J. Pharmacol. and Exp. Therap., 65, 227 (1939). Eichler, O., and Hildebrandt, F., Arch. Exp. Path. u. Pharm., 116, 110 (1926). Stoland, O. O., and Ginsberg, A. M., J. Pharmacol. and Exp. Therap., 60, 396 (1937).
 ² Goodman, L. S., and Gilman, A., The Pharmacological Basis of Therapeutics, second ed. (Macmillan, New York, 1956).
 ² Bircher, R. P., Kanai, T., and Wang, S. C., Fed. Proc., 19 (1), 111 (1960).

Transplantation Non-antigenicity of the Fœtal Placenta

THE feetal part of the placenta may be looked on as a homograft. With the exception of intra-inbred matings, it should possess a different genetic constitution from the mother's tissues, and its syncytium is in close contact with maternal blood in the intervillous spaces and to some extent with the endometrium and even the myometrium.

Mature female mice of the inbred strain A, mated with males of CBA strain, were used. Under sterile conditions, $A \times CBA F_1$ hybrid placentæ of the 16th-21st day of pregnancy were deprived of the remnants of fœtal membranes, weighed, cut into fragments in physiological saline and injected subcutaneously or intraperitoneally into normal adult (2 to 7 months old) male or female recipients of the parent strains. A dose of 100-200 mgm. corresponded to 2-3 placentæ per recipient. Three to six days after application, skin from the back of 2-4 month old $A \times CBA F_1$ hybrids or CBA strain mice was grafted on the recipient, following the technique of Billingham, Brent and Medawar. Seven days after transplantation, grafts were fixed in 10 per cent formol, embedded and examined histologically.