to the method described by Venning.[1] In cases of toxemia of pregnancy values below those for normal pregnancy have been obtained. In all cases of severe toxemias, clinically pre-eclamptic, none of the compound could be recovered.

In all the normal pregnant cases studied at various months of pregnancy, the values obtained for sodium pregnandiol glucuronidate were in keeping with those reported by Browne, Henry and Venning,[2] with three exceptions. In one of these three cases, no sodium pregnandiol glucuronidate was recovered in the fifth month, in another none of the compound was recovered in the ninth month, and in the third, a lower amount than normal was recovered. The urine of these three patients, however, when extracted for the unconjugated form of pregnandiol by a new method, was shown to contain the free form of the compound, pregnandiol. This free form of pregnandiol was recovered in amounts somewhat lower than the expected normal values calculated on the basis of the amounts excreted of the combined form of pregnandiol in other normal cases at corresponding periods of pregnancy.

In the course of these studies it was found that sodium pregnandiol glucuronidate in the urine is unstable and begins to hydrolyze at room temperature within a week and is almost completely hydrolyzed at the end of two weeks. The compound is rapidly hydrolyzed if the urine is allowed to stand at 37 degrees Centigrade for twenty-four hours. This form of hydrolysis in incubated urine results in very little loss of pregnandiol. Free pregnandiol has also been recovered from the fresh urine in those cases mentioned above, and in some cases of toxemia, by the same method, as is used to recover the free form after hydrolysis.

The details of this method as well as the values obtained for both the conjugated and the non-conjugated forms of pregnandiol, in the study of a series of cases of normal pregnancy and of the toxemias of pregnancy will be reported shortly.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD FOR STUDYING AND INFLUENCING CORTICO-HYPOTHALAMIC RELATIONS

THE immediate effects of direct hypothalamic stimulation have been shown by many investigators to be rise in systemic blood-pressure, change in respiratory rate, dilatation of the pupils, elevation of hairs and movement of the nictitating membrane and, in addition, slower appearing metabolic effects. I have devised a method by which hypothalamic stimulation can be effected through the intact skull without entering and damaging the nervous tissue and hence it is also applicable to the human.

The hypothalamus of the cat lies about the posterior part of the hard palate at a site easily located by stripping the mucous tissues and periosteum and finding a midline bleeding point, the source of which is a vein lying in a bony canal, a remnant of the embryological craniopharyngeal duct. With experience this point can be located without reflection of the soft tissues. A probe is simply passed down to the bone in the midline at this point, making a circular opening of several millimeters in diameter in the mucosa. The outer table is tapped for a few turns and a small bakelite core screwed in. This bakelite core contains a silver electrode covered with cotton moistened with silver chloride solution. The electrode simply makes contact with the surface of the bone. Its end penetrates the top of the bakelite and an insulated lead-off wire is looped over it. An ordinary indifferent electrode is applied to the shaved neck. Relatively weak interrupted currents from an inductorium evoke typical hypothalamic responses, mentioned above, while stronger currents produce muscle movements in addition. Pain-producing stimuli in the neighborhood and elsewhere do not evoke these responses. It is suggested that the electrode may be left in place and stimuli applied to the conscious animal, repeated when desired, in order to study the slower acting effects of hypothalamic excitation within the metabolic field.

The electrode in the bone close to the hypothalamus has been used to lead off currents to amplifiers of an electroencephalograph made by Mr. Franklin Offner under the direction of Professor Ralph Gerard. The resulting waves have been compared to the cortical brain waves. In the electrohypothalamogram there are few alpha waves and definitely characteristic slow regular waves of low voltage. Preliminary studies show that stimulation of the hypothalamus produces changes in the cortical waves of an excitatory character, increasing the voltage of the alpha waves which become clearer and devoid of spikes and increasing the frequency of the alpha bursts. After stimulation fast beta waves increase in the cortical lead. Immediately after stimulation through the hypothalamic electrode the amplifier is switched back and the result of stimulation has been found to be an increase in frequency and voltage of the slow hypothalamic waves. Preliminary pharmacological studies indicate that intra-

[1] Eleanor Hill Venning, *J. Biol. Chem.*, 119: 473, 1937.
[2] J. S. L. Browne, J. S. Henry and E. H. Venning, *J. Clin. Investigation.*

venous adrenalin produces effects similar to hypothalamic stimulation, while pilocarpine causes effects in the opposite direction.

The human hypothalamus lies on the clivus of the sphenoid bone, either above or behind the sphenoid air sinus. There is much individual variation. A simple drilled steel cylinder slightly curved at the top, insulated with dripped celluloid, except for a few millimeters at the sharp pointed silver-plated tip, is used as a unipolar electrode. The turbinates are shrunk with adrenalin and, using an endoscope in one nostril, the electrode is passed through the other to the posterior pharynx. It is inserted far back in the vault of the pharynx, and at the junction of the roof and posterior wall it is pressed deeply through the mucous tissue until a crunching noise is heard. The electrode can be firmly embedded in the bone. Only slight pain occurs at its insertion. The patient is able to walk about and swallow normally with the electrode in place. No untoward results appear after its removal.

Stimulation of the hypothalamic electrode causes the usual signs of hypothalamic excitation, pupils dilating and blood pressure rising as high as 80 mm of mercury. In the human, too, a characteristic electrohypothalamogram can be elicited and the effects of hypothalamic stimulation on cortical brain waves studied. Pharmacological effects and other experimental situations may be studied by this method of comparing hypothalamic and cortical leads to an encephalograph as in the experimental animal. Larger currents sent through the hypothalamic electrode produce convulsive movements and marked changes in blood pressure, respiration and circulation. These cease gradually on cessation of stimulation. This method will be used to produce shock effects in schizophrenia as a substitute for insulin or metrazol, as it offers a safer, easier graded and quickly interrupted method of changing cerebral circulation. It seems more rational than the other methods because it directly influences the vegetative regulatory centers concerned with circulation and blood pressure, at the same time evoking the identical secondary effects by producing muscle twitchings. If the effect of "shock" in schizophrenia is psychological, the above method is equally adapted.

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THE CULTURE OF CHAOS CHAOS

PROFUSE cultures of *Chaos chaos,* Type A, Schaeffer strain, have been obtained by the following method:[1]

Prepare each finger bowl in the manner suggested by Brandwein—namely, by covering the bottom with a thin (1–2 mm) sheet of 1 per cent. aqueous solution of agar and implanting the agar, while it is still soft, with five preheated rice grains, distributed evenly on the surface. After the agar has hardened, add 80 cc of the general culture solution,[2] a few drops of a rich culture of *Blepharisma lateritia*[3] and several specimens of *Chaos chaos.* Maintain the culture at 17–19° C. Maximum growth is reached in about four weeks, and then sub-culturing is advisable.

Blepharisma lateritia, Actinophrys sol., Stentor coeruleus, Paramecium bursaria and *Paramecium caudatum* also propagate rapidly in the foregoing solution, used in conjunction with the agar and rice. In such cultures, Chilomonas also appears in abundance and, apparently, this small ciliate serves advantageously as food for the larger organisms.

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[1] A modification of the method of Paul F. Brandwein, *American Naturalist,* 69: 628, 1935.

[2] General Culture Solution: NaCl 1.20 gms, KCl .03 gm, $CaCl_2$ .04 gm, $NaHCO_3$ .02 gm, Phosphate Buffer Solution, pH 6.9–7.0, 50 cc; add distilled water to 1 liter. For use, dilute 1: 10, with distilled water (see footnote 1).

[3] *Chaos chaos* ingests Blepharisma in preference to Paramecium, Stentor and other ciliates which have been tried. In the cultures every specimen shows numerous food vacuoles containing the pinkish remnants of the digesting Blepharisma.

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