scar formation. The scars are usually focal and disseminated. The massive hyperemia with cavernous dilatation of the sinusoids is usually unaccompanied by any inflammatory reaction; occasionally small lymphoid cells accumulate about cavernous sinusoids. Kupffer cells and large epithelioid cells of undetermined character filled with yellow-brown pigment giving a diffuse yellowish hue to their cytoplasm are present in variable numbers about cavernous sinusoids. There appears to be an increase in the number of Kupffer cells and endothelial cells about many sinusoids. The presence of scattered small hemopoietic foci seen about sinusoids of these mice has also been noted in normal animals at comparable ages.

The character and pathogenesis of this liver damage remain to be determined. The possibility that it is due to a virus carried by and only accidentally associated with granulosa cell carcinoma is unlikely, since in the earlier stage of this liver damage, inflammatory reactions or other changes known to be produced by viruses are absent. It is more probable that it is due to substances derived from the tumor cells. Similar changes have not been described in mice receiving estrogens over a long period of time (*cf.* [6]) or in mice with transplanted granulosa cell carcinoma originating in a non-irradiated mouse.[7] The liver is known to receive and inactivate estrogens, and may undergo swelling with hyperemia during menstruation, and is sometimes profoundly damaged in the course of pregnancy (*cf.* [8]). Thus it can be postulated that a substance of hormonal nature reaches the liver in small quantities under physiological conditions, and that this substance is produced or initiated by granulosa cell carcinoma of the ovary and is discharged in large quantities in animals carrying transmitted granulosa cell growth thereby leading to liver damage. It is also possible that this hypothetical substance is related to, but is not identical with, normal steroid hormones.

Summary. Three granulosa cell tumors of the ovary induced in mice by X-rays have been successfully grafted to related mice, indicating the neoplastic character of this growth.

Associated with the transplantable granulosa cell carcinoma No. 1 is a cavernous dilatation of liver sinusoids, which leads to thrombosis and scar formation. The relation of sex hormones to liver changes is discussed.

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Hypothalamic Facilitation of the Motor Cortex.

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Observations in this laboratory upon a monkey paralyzed from experimental poliomyelitis suggested that emotional states accompanied by hypothalamic activity may elicit cortically induced movements not otherwise operative. It was therefore decided to study the effect of direct stimulation of hypothalamic and adjacent forebrain nuclei upon skeletal muscular responses evoked by electrical stimulation of the cortical motor areas in the experimental animal, in the hope of further clarifying cortico-hypothalamic relations.[1-4]

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[2] Morison, R. S., Finley, K. H., and Lothrop, G. N., *J. Neurophysiol.*, 1943, **6**, 243.

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[4] Kennard, M. A., *J. Neurophysiol.*, 1943, **6**, 405.

Materials and Methods. In cats (dial-urethane) bipolar, steel electrodes (the tips .5 mm apart) were inserted stereotactically (Horsley-Clarke instrument) into the hypothalamic region. Cortical stimulation (bipolar silver electrodes, 2 to 4 mm apart) was effected by use of a Goodwin stimulator, with intensities of from 3 to 5.5 volts, frequencies of 5.5 to 90 impulses per second, and duration of impulse 20 sigma. After the cortex had been stimulated at threshold for 10 seconds, the hypothalamus was stimulated separately for 15 seconds (Harvard inductorium, 3 V, c.d. usually at 8 cm) and the occurrence or absence of sympathetic response (contraction of the nictitating membrane and maximal pupillary dilatation) was observed. Then hypothalamic and cortical stimulation were combined, the former preceding the latter by 5 seconds. Stimuli were spaced at intervals of 2 minutes.

Results. Over 350 experiments were made, on 20 animals, with stimulation of various points in the hypothalamus and adjacent nuclei and with simultaneous stimulation of various cortical areas. In general, the effect of stimulation of a "responsive" area in the basal forebrain nuclei upon simultaneous stimulation of the motor cortex consisted of intensification of the motor response, spread of the response to involve other muscular groups contralateral to or ipsilateral with the motor cortex, shortening of the period of latency of motor response, or—most often—a combination of all three effects. These results were interpreted as being due to facilitation of the motor cortex by stimulation of the hypothalamus.

Exact location of the hypothalamic and adjacent nuclei, discharge of which was found to facilitate the cortical response awaits histological confirmation. However, it is apparent that positivity of a facilitatory effect from hypothalamic stimulation is associated with activation of a nuclear zone productive of sympathetic autonomic effects. 335 experiments were conducted to "map out" the facilitatory area in the basal forebrain. Of the 149 hypothalamic points which were positive for cortical facilitation, stimulation of 120 of these points, or 80%, resulted in retraction of the nictitating membranes and dilatation of the pupils, while the remaining 29 positive facilitatory nuclear points (20%) were negative for concomitant sympathetic response. On the other hand, of the 186 hypothalamic points which did not result in cortical facilitation, 174 points, or 93%, were negative for both types of effect.

That facilitation of the cortex from hypothalamic stimulation does not, however, depend upon associated discharge of the sympathetic nervous system was demonstrated by a series of experiments in which the cervical sympathetic trunks were severed and the adrenals ligated, and by another series in which the medulla oblongata was transected at the point of junction with the cervical spinal cord. In the peripherally and partially sympathectomized animals results were surprising in that far from decreasing the hypothalamic facilitatory effect, facilitation was intensified. Complete elimination of sympathetic effects *per se* by medullary transection did not thus increase cortical facilitation, but neither did it prevent it. It can be said, therefore, that while cortical facilitation by hypothalamic stimulation is obtained almost exclusively from nuclear zones which are sympathetic in their autonomic function, such facilitation is independent of sympathetic activity as such.

The facilitatory effect is likewise not related to ipsilaterality of cortical stimulation, since with the hypothalamic and cortical electrodes contralateral to each other exactly similar results were obtained. Moreover, exploration of the cortex with the central electrodes activating a responsive hypothalamic point revealed that any cortical area productive of motor response was facilitated by hypothalamic stimulation. Another characteristic of this phenomenon is that "frequency differentiation" (production of differing motor responses by stimulation of a given cortical site with varying frequencies of impulse†) is preserved under these conditions.

It appears plausible that activation of the hypothalamus results in discharge of the thalamo-cortical system (dorso-medial nuclei of the thalamus to the cerebral cortex) discovered by Morison, Dempsey, and collab-

† Unpublished observations.

orators.[5,6] Similar efforts to confirm by electrocorticography the gross motor responses described are in process in this laboratory.

The implication of these findings in terms of normally operative physiological activity can, of course, only be conjectured. Observations of the effect of emotional stress on muscle strength, and clinical notes of movements of paralyzed limbs and production of ejaculatory speech in the hemiplegic aphasic[7,8] under conditions of excitement, anger, or joy may have their basis in hypothalamic-cortical facilitation.

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Carboxythiazole (2-Sulfanilamido-5-Carboxythiazole) in Blood, Urine and Feces After Oral Administration in Humans.

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Two general types of sulfonamide compounds have been used with some success in the treatment of certain enteric infections and in attempts to reduce the numbers of coliform and other bacteria in the intestinal contents in relation to surgical procedures. One type is represented by sulfaguanidine[1] which is fairly soluble in water, poorly absorbed from the gastro-intestinal tract, and, generally speaking, is about as active as sulfanilamide. The second type is one in which a substitution is made on the *p-amino* group of a more active sulfanilamide derivative, the resulting compound being totally inactive until the added group is released by hydrolysis which occurs within the intestinal tract. Glucose sulfapyridine,[2] succinylsulfathiazole,[3] and phthalylsulfathiazole[4] are examples of such compounds. They, too, are highly soluble, but only a small fraction of the active compound is released in the bowel and low concentrations of the active drug appear in the blood.

Carboxythiazole (2-sulfanilamido-5-carboxythiazole) is a third type of derivative in which a simple substitution is made on the thiazole ring of sulfathiazole.* This results in a compound which, though less active than the original sulfathiazole, is highly soluble and is poorly absorbed. In the present paper are presented the results of studies in human subjects on the occurrence of this drug in the blood, urine, and feces after single and repeated oral doses. The relevant findings in a small number of cases of enteric infections in which this drug was used are also summarized.

Materials and Methods. A single 5 g dose

1 Marshall, E. K., Jr., *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163.

2 Taylor, F. H. L., *et al.*, *J. Clin. Invest.*, 1940, **19**, 201; Lowell, F. C., Spring, W. C., Jr., and Finland, M., *ibid.*, 1940, **19**, 215.

3 Poth, E. J., and Knotts, F. L., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 129.

4 Mattis, P. A., Benson, W. M., and Koelle, E. S., *J. Pharm. Exp. Therap.*, 1944, **81**, 116.

* This compound was received from the American Cyanamid Co. with the following information: It has a melting point of 215.5°C; water solubility at 37°C and at pH 3.0 of 42.7 mg per 100 cc and a buffer solubility at pH 5.0 of 4920 mg per 100 cc. It is poorly absorbed from the intestinal tract, rapidly excreted from the blood stream, and practically non-toxic in mice, rats, rabbits, and dogs. Experimentally, its antibacterial activity is about equal to that of sulfaguanidine. (Personal communication from Dr. Harold J. White.)