

asked to urinate in both of the bottles before eating, drinking or smoking. The workers brought the bottles with them to work where they were immediately collected (7.0 a.m.) and cooled. Every worker gave the following information: age, smoker or non-smoker, how many years smoked, and any medication during the last few days. The urinary 5-HIAA concentration was determined according to HANSON and SERIN<sup>5</sup> as  $\mu\text{M/l}$ .

In the analysis of the material collected, it appeared that there were acceptable urinary samples from 72 non-smokers and 154 from smokers. All cases were discarded in which smoking was very small (less than 10 cigarettes per day) as well as those in which smoking had continued for less than 5 years or where any medication was involved. The Figure presents the distribution of the individual measurements. It appears that no clear differences can be seen between smokers and non-smokers. The mean in the non-smoker group was  $4.51 \mu\text{M/l}$  and in the smoker group  $4.57 \mu\text{M/l}$ . The mean age of the non-smokers was lower but it does not affect the result since no age-dependent change could be demonstrated in either group. As can be seen in the Figure the range of the amount of urinary 5-HIAA is wide, being of the same great order as

that found by SCHIEVELBEIN et al.<sup>2</sup> and is partly due to the fact that no dietary limitations were required. It seems, however, reasonable to assume that the dietary habits (no data on this matter were collected) are about equal in both groups of workers, even while differences exist between individual workers. This assumption is taken to be valid in relation to the quality of food eaten as well as the amount of urine excreted (only the concentration of 5-HIAA was measured). Consequently the present result is taken to mean that there is no difference in the concentration or amount of 5-HIAA excreted in the urine by habitual smokers and non-smokers.

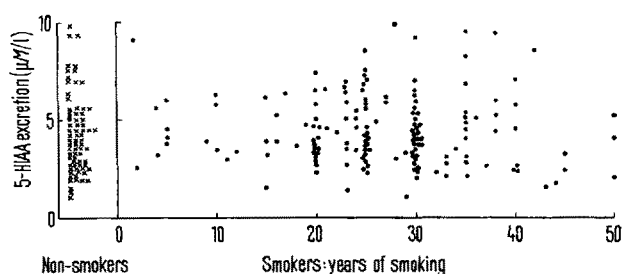
This result demonstrates that the habitual smokers studied have fully adapted to the nicotine effect so far as excretion of 5-HIAA is concerned. Our results do not confirm those presented by SCHIEVELBEIN et al.<sup>2</sup> in the case of habitual smokers, but are in full agreement with those of DEGWITZ<sup>4</sup>. As to the effects of inhaled nicotine on the tryptophan metabolism through the serotonin pathway, it seems that at least this metabolic pathway is not deranged.

**Zusammenfassung.** Die Ausscheidung von 5-Hydroxy-indoleessigsäure im Harn von Rauchern und Nichtraucher wurde untersucht. Die individuellen Ausscheidungswerte variieren sehr erheblich in beiden Gruppen, doch konnte keine Differenz zwischen den Mittelwerten der beiden Gruppen gefunden werden.

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<sup>5</sup> A. HANSON and F. SERIN, *Lancet* 1955 ii, 1359.



## The Release of Dopamine from the Putamen

The neostriatum contains the highest concentration of dopamine of any region of the mammalian brain<sup>1,2</sup>, and inasmuch as its metabolic product noradrenalin is present only in much smaller amount, the suggestion has been made that dopamine itself may be of importance to the functions of the nuclei concerned<sup>3</sup>.

Although its concentration there is very much less, the substantia nigra also contains appreciable amounts of dopamine<sup>1,2</sup>. Basing his conclusion on these facts, HORNYKIEWICZ<sup>2</sup> has argued for the existence in the extrapyramidal motor pathways of neurones liberating dopamine as a synaptic transmitter substance. ANDÉN et al.<sup>4</sup> and BERTLER et al.<sup>5</sup> have provided evidence for dopamine-containing neurones whose cell bodies lie in the pars compacta of the substantia nigra and whose axons form bundles in the crus cerebri and run in the internal capsule to reach the neostriatum.

McLENNAN<sup>6</sup> demonstrated an increased output of dopamine from the caudate nucleus in response to stimulation of nucleus centralis centralis (centromedianus) of the thalamus. Using a similar method it has now been shown that stimulation of the substantia nigra brings

about a marked increase in dopamine output from the putamen.

**Methods.** A push-pull cannula<sup>7</sup>, the outer tube being No. 22 S.W.G., was placed stereotactically in the putamen of cats lightly anaesthetized with pentobarbital. The region at the tip of the cannula was irrigated with Locke's solution modified by the omission of bicarbonate. Fluid was forced through the cannula by a motor-driven syringe at a rate of 0.1–0.15 ml/min, and the outflows collected in cooled tubes each containing a drop of 0.5N acetic acid. Samples were collected over 15 min periods, and 5–10 min were allowed between successive samples.

<sup>1</sup> Å. BERTLER, *Acta physiol. scand.* 51, 97 (1961).

<sup>2</sup> O. HORNYKIEWICZ, *Arch. exp. Path. Pharmacol.* 247, 304 (1964).

<sup>3</sup> P. HOLTZ, *Psychiat. Neurol.*, Basel 140, 175 (1960).

<sup>4</sup> N.-E. ANDÉN, A. CARLSSON, A. DAHLSTRÖM, K. FUXE, N.-Å. HILLARP, and K. LARSSON, *Life Sci.* 3, 523 (1964).

<sup>5</sup> Å. BERTLER, B. FALCK, C. G. GOTTFRIES, L. LJUNGGREN, and E. ROSENGREN, *Acta pharmacol. toxicol.* 27, 283 (1964).

<sup>6</sup> H. McLENNAN, *J. Physiol.* 174, 152 (1964).

<sup>7</sup> J. H. GADDUM, *J. Physiol.* 155, 1P (1961).

The dopamine contained in the effluent fluids was determined spectrophotofluorimetrically<sup>6,8</sup>.

Bipolar electrodes were directed to the substantia nigra and to nucleus centralis centralis, and square-wave stimuli of 0.1 msec duration delivered to them. The strength of the stimulus was such as to give a maximal evoked potential in the putamen (see below), using the outer tube of the cannula, which was insulated except at the tip, as a monopolar recording electrode.

At the conclusion of the experiments, the brains were removed and examined to verify cannula and electrode placements. All of the methods have earlier been described in greater detail<sup>6</sup>.

**Results and discussion.** The Table sets forth the results which have been obtained. The resting output of dopamine from the putamen was rather variable, averaging 380 pg/min, somewhat less than previously reported from the caudate<sup>6</sup>. Stimulation of nucleus centralis centralis, which had caused consistently an increased output of dopamine from the caudate, had little effect upon that from the putamen, although a projection from this nucleus to the putamen is known<sup>9</sup>. On the other hand, stimulation of the substantia nigra at 4–8 pulses/sec in every experiment increased the dopamine output, to an average of 720 pg/min. When individual experiments

were considered, the average increase was about three-fold. It has not been determined whether this range of frequency of stimulation is optimal. The Table also shows, however, that when trains of pulses giving about the same average frequency (0.5 sec of 20/sec, repeated every 2 sec) were used, a much less marked enhancement of dopamine output was found.

The evoked potentials recorded from the putamen in response to stimulation of the substantia nigra were complex. At higher intensities of stimulation, such as were used during the experiments discussed above, the response of longest latency indicated a maximum conduction in the pathway of 1.5–2 m/sec. ANDÉN et al.<sup>4</sup> have stated that the dopamine containing fibres are poorly myelinated, and therefore would be expected to have a slow conduction velocity. That the 2 m/sec group is that probably responsible for the extra liberation of dopamine from the putamen, is further indicated by the fact that reduction in the strength of the stimulating current to the point where the slowest response dropped out of the evoked potential record abolished the enhanced output.

The present results therefore appear to provide a neurochemical confirmation of the existence of the 'dopaminergic' pathway described on histochemical evidence by ANDÉN et al.<sup>4,10</sup>.

**Zusammenfassung.** Der Ruhertrag des Dopamins aus dem erregten Katzenputamen wurde bei genügender Niederfrequenzreizung der Substantia nigra mehr als verdoppelt. Mit dieser Beobachtung wird der histochemische Nachweis des nigro-neostriatalen dopaminergischen Weges gestützt.

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Department of Physiology, University of British Columbia, Vancouver (Canada), June 26, 1965.

<sup>8</sup> E. G. McGEER and P. L. McGEER, Can. J. Biochem. Physiol. 40, 1141 (1962).  
<sup>9</sup> T. P. S. POWELL and W. M. COWAN, Brain 79, 364 (1956).  
<sup>10</sup> This work was supported by the Medical Research Council of Canada. Thanks are due to R. WALKER for his excellent assistance.

Über die morphologischen Veränderungen am menschlichen Ovar unter Einwirkung eines hormonalen Antikonzeptivums

ERB et al.<sup>1,2</sup> haben festgestellt, dass während der ersten drei Behandlungscyclen mit einem hormonalen Antikonzeptivum (Lyndiol 2,5<sup>®</sup>: 2,5 mg Lynestrenol: 0,075 mg Mestranol<sup>1</sup>; Noracyclin<sup>®</sup>: 5 mg Lynestrenol + 0,15 mg Mestranol<sup>2</sup>) im Gegensatz zur allgemein verbreiteten Meinung<sup>3</sup> Corpora lutea gebildet werden, welche durch eine Hypoplasie oder Aplasie der Thecaluteinzellen charakterisiert sind. Weiterhin konnten diese Autoren nachweisen, dass die Theca interna auch in den Bläschenfollikeln und atretischen Follikeln unterentwickelt ist<sup>1,2</sup>. Wir hatten nun Gelegenheit, die Ovarien einer während zweier Cyclen mit einem weiteren hormonalen Antikon-

zeptivum (Anovlar<sup>®</sup>: 4 mg Norethisteronacetat + 0,05 mg 17 $\alpha$ -Äthinylöstradiol) behandelten Frau histologisch zu untersuchen<sup>4</sup>.

**Untersuchungsmaterial.** Für unsere Untersuchungen stand uns je eine Probeexcision aus jedem Ovar einer 32-jährigen Frau zur Verfügung. Die Frau war während zweier Cyclen mit Anovlar<sup>®</sup> behandelt worden und wurde

<sup>1</sup> H. ERB und K. S. LUDWIG, Exper. 21, 159 (1965).  
<sup>2</sup> M. MALL-HAEFELI, K. S. LUDWIG, M. KELLER und S. CLOEREN, Gynaecologia, im Druck.  
<sup>3</sup> G. PINCUS, The Control of Fertility (Academic Press, New York-London 1965).  
<sup>4</sup> Herrn Dr. H. AEPPLI, Chefarzt der Geburtshilflich-gynäkologischen Abteilung des Kantonsspitals Schaffhausen, möchten wir für die Übersendung des Materials unseren besten Dank aussprechen.