Aorta F^- and disease: CALL et al.[2] noted a significantly higher storage of bone F^- in cases with pyelonephritis, but no relationship of aorta F^- levels with the causes of death. In the present study, no correlation could be established between aorta F^- levels and the disease.

Discussion. As indicated in Table I, F^- levels in the aorta depend little, if at all, on the amount of Ca^{++} present. That F^- does not seem to be bound in appreciable amounts as calcium-fluoride (CaF_2), has been recognized by others, with respect to bones and teeth[15]. The erratic fluctuations of F^- levels in the aorta from person to person are noteworthy in this as well as in CALL's study. Some samples of aorta tissue contained virtually no F^-, and others up to 258 ppm. In a single organ such as the placenta[16] or in the skin of patients with various dermatological lesions[17] F^- levels vary widely in closely adjoining tissue areas.

Since the F^- content of the aorta does not parallel F^- levels in the skeleton, bone F^- cannot be considered a criterion of F^-'s presence elsewhere in the system nor can possible ill effects in the system be precluded on the basis of low F^- levels in bones.

Zusammenfassung. Fluor- und Kalziumwerte in verkalktem Aortengewebe wurden mit denen von makroskopisch normal erscheinendem Aortengewebe verglichen. Der Fluorgehalt der Aorta verschiedener Personen zeigte grosse individuelle Schwankungen, die unabhängig vom Kalziumgehalt waren. Eine direkte Korrelation des Aortenfluors mit dem Lebensalter wurde festgestellt. Die statistische Auswertung der Untersuchungen von CALL et al.[2] ergab, dass der Fluorgehalt der Aorta unabhängig von demjenigen des Skelettes ist.

G. L. WALDBOTT[18]

2930 W. Grand Boulevard, Detroit (Michigan 48202, USA), July 4, 1966.

[15] S. M. WEIDMANN, J. A. WEATHERALL, and R. G. WHITEHEAD, J. Path. Bact. *78*, 435 (1959).
[16] R. FELTMAN and G. KOSEL, Science *122*, 560 (1955).
[17] G. L. WALDBOTT, J. Asthma Res. *2*, 51 (1964).
[18] I appreciate the cooperation of Drs. E. BOOTH and J. R. MCDONALD, pathologists at Hutzel and Harper Hospitals respectively, for furnishing the aorta specimens; D. L. J. SAVAGE and Mr. J. M. LUCAS of the Department of Statistics at Yale University for their statistical interpretation of my data; Dr. R. A. KEMP HARPER, St. Bartholomew's Hospital, London, England, and Dr. G. NALBONE, Department of Industrial Medicine, University of Palermo, Italy, for furnishing the illustrations in Figures 1 and 2.

Site of Action of Dopamine and Apomorphine on Compulsive Gnawing Behaviour in Rats

According to early publications, injection of apomorphine into rodents results in gnawing behaviour, which effect is dependent on the presence of the corpus striatum[1]. Recently it has been shown that apomorphine shares this effect with DOPA (as a precursor of dopamine) and that the presence of a phenylethylamine configuration with OH-groups at the *para-* and *meta*-positions of the phenol ring is obligatory for provoking a compulsion to gnaw[2].

Injection of DOPA results in an accumulation of dopamine in the brain, especially in extrapyramidal structures[3]. It could be anticipated, therefore, that the site of action of dopamine and apomorphine would be situated within the extrapyramidal system. This report provides data supporting this assumption.

Experimental. Crystalline DOPA or apomorphine was tamped into a stainless steel cannula, which was introduced stereotaxically into the brain of male albino rats (140–160 g) under light ether anaesthesia. When the tip of the cannula had reached the desired position, the compound was delivered by pushing a stylet down the cannula. The amount of implanted material was about 100 µg. After implantation, the animals were placed in metal cages with a wire-mesh floor, on which the rats were able to gnaw, and their behaviour was observed for several hours.

Results. Implantation sites are shown in Figures 1–3. Effective implantations of DOPA resulted, after a delay of 1–2 h, in intense compulsive gnawing behaviour, lasting for 3 h and sometimes longer. After apomorphine implantation gnawing started within 30–40 min, lasting for about 2 h. Positive effects were observed with both compounds after implantation in the dorsal part of the cau-

[1] C. AMSLER, Naunyn-Schmiedenbergs Arch. exp. Path. Pharmak. *97*, 1 (1923).
[2] A. M. ERNST, Psychopharmacologia *7*, 391 (1965).
[3] A. BERTLER and E. ROSENGREN, Experientia *15*, 382 (1959).

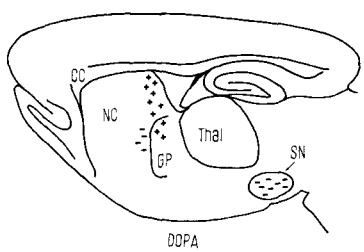


Fig. 1. Implantation sites of l-DOPA, shown in sagittal section of rat brain. + = evoking gnawing behaviour; − = ineffective.

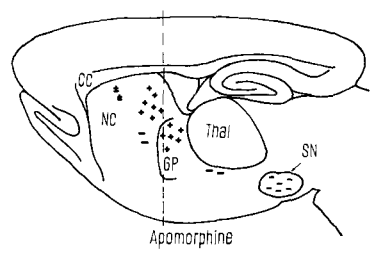


Fig. 2. Implantation sites of apomorphine, shown in sagittal section, at plane indicated in Figure 3 by broken line.

date nucleus and globus pallidum; negative results were obtained after implantation in the ventral part of the caudate nucleus, in the region medial to the caudate nucleus (N. lateralis septi), in subthalamic structures, and in the substantia nigra.

Sham implantations, made by introducing the empty cannula into the same sites, had no effect. Moreover, in the caudate nucleus of 8 animals *meta*-tyrosine was implanted; this drug has the same chemical structure as DOPA, but lacks a hydroxyl group at the *para*-position. *Meta*-tyrosine implantations did not provoke gnawing behaviour, which indicates the specificity of DOPA and apomorphine effects.

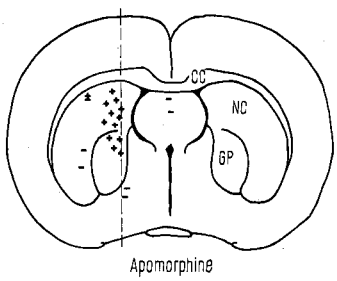


Fig. 3. Implantation sites of apomorphine, shown in frontal section, at plane indicated in Figure 2.

Conclusions. The site of action of DOPA as well as apomorphine appears to be located in the neostriatum. This indicates that accumulation of dopamine in this structure results in compulsive gnawing behaviour in rats, and that apomorphine, due to its structural relationship with dopamine, is capable of imitating this effect.

Zusammenfassung. Es wird die Relation von Struktur und Wirkung zwischen Dopamin und Apomorphin beim Zwangsnagen der Ratte, nach stereotaktischer Implantation der beiden Substanzen besprochen.

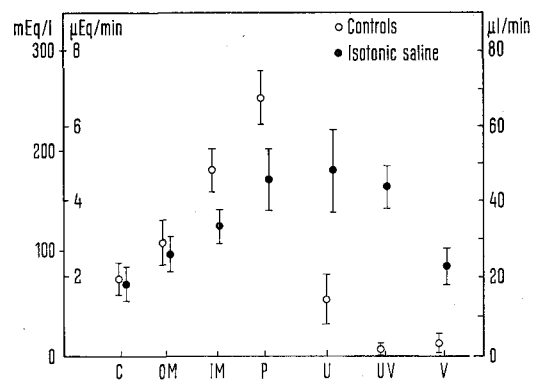
A. M. ERNST and P. G. SMELIK

Department of Pharmacology, Medical Faculty, University of Utrecht (The Netherlands),
May 22, 1966.

The Composition of the Renal Medulla During Natriuresis Accompanying Saline Loading in the Rat

The expansion of the extracellular fluid volume by isotonic saline infusion is accompanied by diuresis and natriuresis. This cannot be explained by an increase of the glomerular filtration rate, because even if it is experimentally decreased, these changes take place[1]. The mineralocorticoids[1] and antidiuretic hormone[2] are also not responsible for these changes. DIRKS, CIRKSENA, and BERLINER[3] proved in dogs and CORTNEY, MYLLE, and GOTTSCHALK[4] in rats by micropuncture technique that after isotonic saline infusion a decrease in the sodium reabsorption occurs in the proximal tubule. The mechanism by which this decrease takes place is not known; an unknown humoral factor other than aldosterone is considered to be the most logical explanation. This decrease in the sodium reabsorption, even if limited to the proximal tubule only, would be sufficient to explain natriuresis and diuresis after expansion of the extracellular volume. EARLEY and FRIEDLER[2], however, submitted another possible explanation of these changes. They demonstrated in experiments in dogs that after isotonic saline infusion the renal blood flow increases with a simultaneous decrease of the PAH extraction ratio; i.e. the noncortical blood flow increases and most probably therefore also the flow rate of blood through the renal medulla. This increased medullary blood flow could lead to a washout of sodium from the medullary interstitial tissue. Passive loss of water, which occurs in the descending limb of Henle's loop, whould thus – as a result of the decrease of the hypertonicity of the medullary intersticium – be decreased and the volume of the fluid flowing into the ascending limb, from where the sodium is transported, would be increased. In addition, the sodium concentration in this fluid would be decreased and, as a result of this, the net transport of sodium out of the ascending limb would decrease. If this idea is correct, the sodium concentration in the renal medulla in animals would have to be decreased during the isotonic expansion of the extracellular fluid volume.

In 38 rats, isotonic saline infusions were carried out at a rate of 0.22 ml/min for a period of 50–70 min. There was significant diuresis and natriuresis in comparison with the control group of 18 rats which did not receive an infusion (see Figure).



Values of sodium concentration in renal tissue (mEq/l of tissue water) and in urine (U: mEq/l) and of sodium excretion (UV: µEq/min) and of urine flow (µl/min) in control (o) and in isotonic saline infused rats (•). C = renal cortex, OM = outer medulla, IM = inner medulla, P = papilla.

[1] H. E. DE WARDENER, I. H. MILLS, W. F. CLAPHAM, and C. J. HAYTER, Clin. Sci. *21*, 249 (1961).
[2] L. E. EARLEY and R. M. FRIEDLER, J. clin. Invest. *44*, 929 (1965).
[3] J. H. DIRKS, W. J. CIRKSENA, and R. W. BERLINER, J. clin. Invest. *44*, 1160 (1965).
[4] M. A. CORTNEY, M. MYLLE, W. E. LASSITER, and C. W. GOTTSCHALK, Am. J. Physiol. *209*, 1199 (1965).