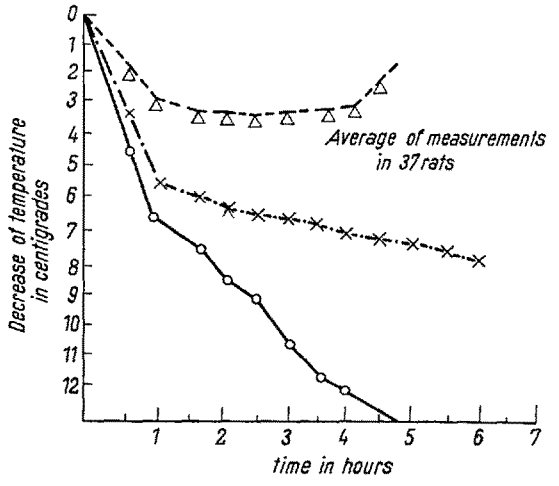
a few hours later the animals regained their original temperature and never died (Figure).

Changes in the rectal temperature of rats after injecting uraemic and control preparates



Key to the signs:

○—○—○ average of animals, died in 5 h
×—×—× average of animals, died in 24 h
△—△—△ average of control animals

Toxin obtained from the blood and cerebrospinal fluid of uraemic patients produced the same symptoms. Preparates obtained from healthy individuals, or of others suffering from any disease of non-renal origin, failed to produce these symptoms.

Since it is wellknown that hypothermy is one of the clinical symptoms of human uraemia[2], we tested whether this phenomenon was demonstrable in animals as well. After bilateral nephrectomy of 45 rats, we found that the temperature showed a gradual reduction between the operation and the death of the animals, reaching a level of about 25°C.

The preparate will become inactive if dyalized in flowing water in a cellophane bag suggesting that the toxin is a substance of small molecules. Since the native uraemic plasma has no toxic effect, but would become effective if dialyzed and prepared in the manner described above, we concluded that the toxin may circulate in the uraemic blood in the form bound to protein or to some other large molecule without being active in that state.

Incubated with pancreatic suspension or trypsine (Merck), the toxin would become inactive, suggesting that our substance may be a peptide.

Since, as a rule, the animals died after a severe drop in temperature, we tried to avert the action of toxin by the administration of a pyrogen agent. 1 h after receiving the toxin, the animals were injected intraperitoneally with 20 mg/kg body weight of Amphetamine. After this dose, the reduction in temperature discontinued, but the animals still died, even earlier than those treated only with the toxin.

Summarizing the results, it may be stated that we succeeded in demonstrating from blood samples of uraemic individuals and dogs, and from their cerebrospinal fluid, a substance as yet unknown as far as we know, which might play a role in the production of uraemic symptoms. Judging by the experiments carried out so far, the substance is considered to be a peptide of small molecules.

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Pathophysiological Institute and the Urological Clinic of the Medical University, Budapest (Hungary), May 3, 1958.

Zusammenfassung

Aus urämischem Menschen- und Hundeblut und Liquor isolierten wir eine uns bisher unbekannte Substanz, die unserer Ansicht nach für die Entstehung von urämischen Symptomen mitverantwortlich sein dürfte. Auf Grund unserer bisherigen Untersuchungen halten wir die Substanz für ein kleinmolekulares Peptid.

Acetylcholinesterase, Acid Phosphatase, and Succinic Dehydrogenase in the Hypothalamic Magnocellular Nuclei after Chlorpromazine Administration

Histochemical studies

Strong enzyme activity has been found to exist in the magnocellular nuclei of the hypothalamus, where neurosecretory material is formed[1]; the following enzymes have been demonstrated histochemically: acetylcholinesterase[2], acid phosphatase[3], and succinic dehydrogenase[4]. The influence of chlorpromazine upon the organism is primarily due to its depressive effect upon the central nervous system in the formatio reticularis of the brain stem and in the hypothalamus of the diencephalon[5]. We have previously investigated the influence of chlorpromazine upon the neurosecretory substance of the hypothalamic magnocellular nuclei and upon the secretion of antidiuretic hormone, and we found that chlorpromazine depresses the hypothalamus[6]. The purpose of the present study is to determine to what extent chlorpromazine affects the histochemically demonstrable acetylcholinesterase, acid phosphatase, and succinic dehydrogenase activity in the supraoptic and paraventricular nuclei of the hypothalamus.

Chlorpromazine (Largactil, May & Baker) was given subcutaneously, 25 mg/kg body weight, to six adult female albino rats for ten days. The control group consisted of an equal number of animals. The subjects were killed by rapid decapitation 4 h after the last injection. From their hypothalamus the acetylcholinesterase was determined according to Koelle's modification[7], the acid phosphatase according to Eränkö[8], and the succinic dehydrogenase according to Seligman and Rutenburg[9].

[2] E. Lauda, *Lehrbuch der inneren Medizin*, vol. 3 (Springer, Wien 1951), p. 223.

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[3] O. Eränkö, Acta physiol. scand. *24*, 1 (1951).

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[6] E. Kivalo, U. K. Rinne, and P. Marjanen, Ann. med. exp. biol. Fenn., in press (1958).

[7] G. B. Koelle, J. Pharmacol. *114*, 167 (1955).

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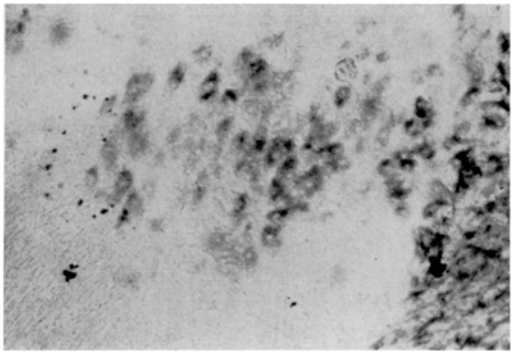
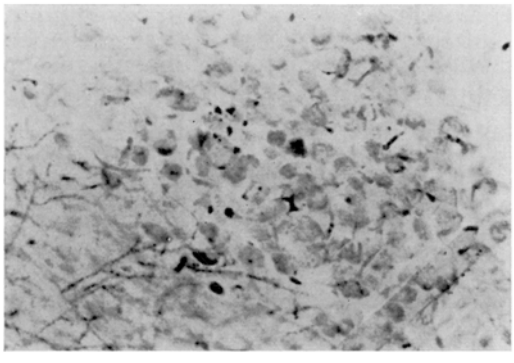
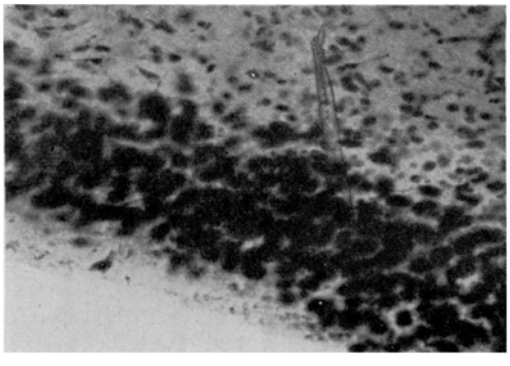
[9] A. M. Seligman and A. M. Rutenburg, Science *113*, 317 (1951).



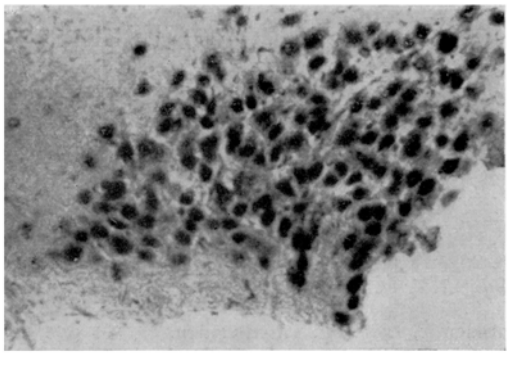
A



B



C



D

A Distribution of acetylcholinesterase in the nucleus supraopticus of control rat. *B* The same after administration of chlorpromazine. *C* Acid phosphatase activity in the nucleus supraopticus of control rat. *D* The same after chlorpromazine treatment. All 180×.

The normal acetylcholinesterase and acid phosphatase of the hypothalamic supraoptic and paraventricular nuclei were confirmed to be in accordance with earlier results, whereas the succinic dehydrogenase activity is slightly stronger in our opinion, than is shown by the earlier investigations. On comparison between the acetylcholinesterase, acid phosphatase and succinic dehydrogenase activities in the said nuclei of the animals under chlorpromazine administration and the controls, a moderate reduction in activity was observed for each enzyme with the animals that had been given chlorpromazine.

Our results are in agreement with our previous investigation, in which we showed that chlorpromazine lowers the discharge of antidiuretic hormone from the supraoptic nucleus and the paraventricular nucleus[6]. They are also in agreement with biochemical investigations, which have shown that chlorpromazine generally depressed the enzyme system in the brain[10]. It is further conceivable that the reduced activity of these various enzyme systems is connected with the sedative effects caused by chlorpromazine.

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Department of Anatomy, University of Turku (Finland), June 2, 1958.

Zusammenfassung

Der Einfluss des Chlorpromazins auf die Acetylcholinesterase, saure Phosphatase- und Bernsteinsäuredehydrogenaseaktivität des Nucleus supraopticus und Nucleus paraventricularis wurde histochemisch untersucht. Es wurde festgestellt, dass Chlorpromazin bei sämtlichen Enzymen eine mässige Herabsetzung der Aktivität bewirkt. Die Vermutung wird ausgesprochen, dass mit der Sedativwirkung des Chlorpromazins eine Verminderung der Enzymaktivität verknüpft ist.

[10] J. BERNSOHN, I. NAMAJUSKA, and B. BOSHES, J. Neurochemistry *1*, 145 (1956).

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Über das Glucosid von 1,2-Diphenyl-3,5-dioxo-4-*n*-butyl-pyrazolidin (Phenylbutazon)

Von einer Reihe therapeutisch wichtiger Glykoside, die schon lange unseren Arzneischatz bereichern, ist bekannt, dass das Aglykon allein eine zum Teil viel schwächere Wirkung als das Glykosid besitzt. Andererseits sind zum Beispiel von dem als Tuberkulostaticum bekannten Isonikotinsäurehydrazid Hydrazone mit Aldosen bekannt, die sich durch eine bessere Verträglichkeit, das heisst grössere therapeutische Breite auszeichnen[1]. Ausserdem ist es möglich, mit solchen Derivaten die Resorption zu verändern und so eventuell eine protrahierte Wirkung zu erzielen[2]. Da Phenylbutazon als β-Dicarbonylverbindung leicht enolisiert, erschien es uns interessant, das Enolglucosid darzustellen. Von BALLOU und LINK[3] sind eine

[1] H. LÜDHOF und E. KRÖGER, Klin. Wschr. *34*, 451 (1956). – G. BROUET, B. N. HALPERN, J. MARCHE und J. MALLET, Presse méd. *61*, 863 (1953). – J. KIMMIG, F. KRÜGER und J. MEYER-TOHN, Arzneimittelforsch. *7*, 157 (1957).

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