Tab. II. Urinary excretion of $C^{14}$-histamine and metabolites (expressed as counts/min) in anaesthetized cats. Comparison between ventricular perfusions of $C^{14}$-histamine during 40 min, and intravenous infusions of $C^{14}$-histamine during 40 min

| Experiment | Route of administration of $C^{14}$-histamine | Amount of $C^{14}$-histamine administered | | Minutes after start of administration of $C^{14}$-histamine 1–60 | 61–120 | 121–180 | 181–240 | 241–300 |
|---|---|---|---|---|---|---|---|---|
| 1 | Ventricular perfusion | 9 μg | Histamine | 16 | 5 | 32 | 9 | |
| | | | Methylimidazoleacetic acid | 40 | 136 | 120 | 96 | |
| 2 | Ventricular perfusion | 9 μg | Histamine | 11 | 3 | 0 | 12 | 0 |
| | | | Methylimidazoleacetic acid | 72 | 316 | 432 | | |
| 3 | Intravenously | 0.18 μg | Histamine | 23 | 5 | 5 | 0 | 0 |
| | | | Methylimidazoleacetic acid | 112 | 120 | 72 | 56 | 36 |
| 4 | Intravenously | 0.9 μg | Histamine | 72 | 10 | 3 | 5 | |
| 5 | Intravenously | 0.09 μg | Methylimidazoleacetic acid | 20 | 44 | 30 | | |

histamine, and only traces of $C^{14}$-methylimidazole-acetic acid.

In the following experiments (Table II), only $C^{14}$-histamine and $C^{14}$-methylimidazoleacetic acid were measured. Small amounts of $C^{14}$-histamine were excreted during and after the ventricular perfusions with $C^{14}$-histamine. Large amounts of $C^{14}$-methylimidazoleacetic acid were simultaneously excreted. Intravenous infusion of 0.18 μg $C^{14}$-histamine resulted in the urinary excretion of $C^{14}$-histamine and $C^{14}$-methylimidazoleacetic acid in amounts rather similar to those observed in the ventricular perfusions with 9 μg $C^{14}$-histamine. Correspondingly, 0.09 μg $C^{14}$-histamine intravenously gave less $C^{14}$-methylimidazoleacetic acid, and 0.9 μg intravenously gave more $C^{14}$-histamine, than 9 μg $C^{14}$-histamine perfused through the ventricles. This implies that roughly 2% of the $C^{14}$-histamine perfused through the ventricular system escaped into the blood stream. However, this conclusion may be somewhat uncertain since it is known that histamine catabolism *in vivo* can take place in the feline brain[3] and kidney[7,8]. The latter organ is probably similar to that of the dog, which has a considerable capacity to methylate histamine *in vivo*[9]. In the present experiments, also other organs may have contributed to the catabolism of administered histamine.

Using the gastric secretion as an index of the absorption of histamine into the blood stream, DRASKOCI et al.[2] obtained values indicating that 1–2% of the histamine perfused through the ventricles entered the blood stream. Thus, the estimates presented here agree fairly well with those obtained with doses of histamine several hundred times greater[2]. It remains to be established whether the histamine and its metabolites enter the blood stream directly from the ventricular fluid, or *via* the brain tissue.

*Zusammenfassung.* In narkotisierte Katzen wurde $C^{14}$-Histamin entweder durch Hirnventrikel perfundiert oder intravenös injiziert. Seine Ausscheidung und Metabolite in Urin wurde gleichzeitig bestimmt: Ca. 2% des durch die Hirnventrikel perfundierten $C^{14}$-Histamins wurde im Blutstrom resorbiert.

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## The Endecapeptide Eledoisin as Powerful Vasodilating and Hypotensive Agent in Man

Recently SANDRIN and BOISSONNAS have synthesized the endecapeptide 'Eledoisin'[1], the active principle of the posterior salivary glands of *Eledone moschata* and *Aldrovandi*. This principle has been recognized, isolated and purified by ERSPAMER[2]. It has a striking hypotensive effect in several animal species and particularly in the dog; the non-vascular smooth muscles are equally very sensitive to this peptide[3]. The effects of eledoisin have not yet been tested in man.

The present paper deals with information obtained experimentally on the effects of the synthetic eledoisin[4] on the arterial and spinal fluid pressure in man. This paper aims also at assessing some threshold effects comparing this substance with other vasoactive compounds with greater vasomotor power, namely Bradykinin and Histamine[4]. We wished to assess also whether hypertensive substances, such as Norepinephrine and Hypertensin[4], would antagonize the hypotensive effect

[1] E. SANDRIN and R. A. BOISSONNAS, Exper. *18*, 59 (1962).
[2] V. ERSPAMER, Exper. *5*, 79 (1949).
[3] V. ERSPAMER and A. ANASTASI, Exper. *18*, 58 (1962).
[4] We are grateful to Sandoz Co. of Basel for supplying synthetic eledoisin (ELD 950) and bradykinin (Br 640), to Roche Co. of Basel for histamine dihydrochloride (Imido), to Ciba Co. of Basel for Hypertensin, to Recordati Co. of Correggio (Italy) for norepinephrine (Nor-Adrec).

of eledoisin. The possible inactivating properties of plasma on eledoisin have been the object of our investigations.

*Technique.* (a) The arterial pressure was directly recorded through an indwelling needle placed in the femoral artery and connected to a Statham strain-gauge transducer. (b) The cerebro-spinal fluid pressure was recorded connecting the needle to the electromanometer as in (a). (c) Record of the respiration was obtained with a tachographic technique. (d) The drugs have been injected in the cubital vein (within 2–3 sec).

*Results.* (1) The injection of eledoisin constantly produces arterial hypotension, spinal fluid hypertension, increased rate of respiration, skin vasodilatation, particu-

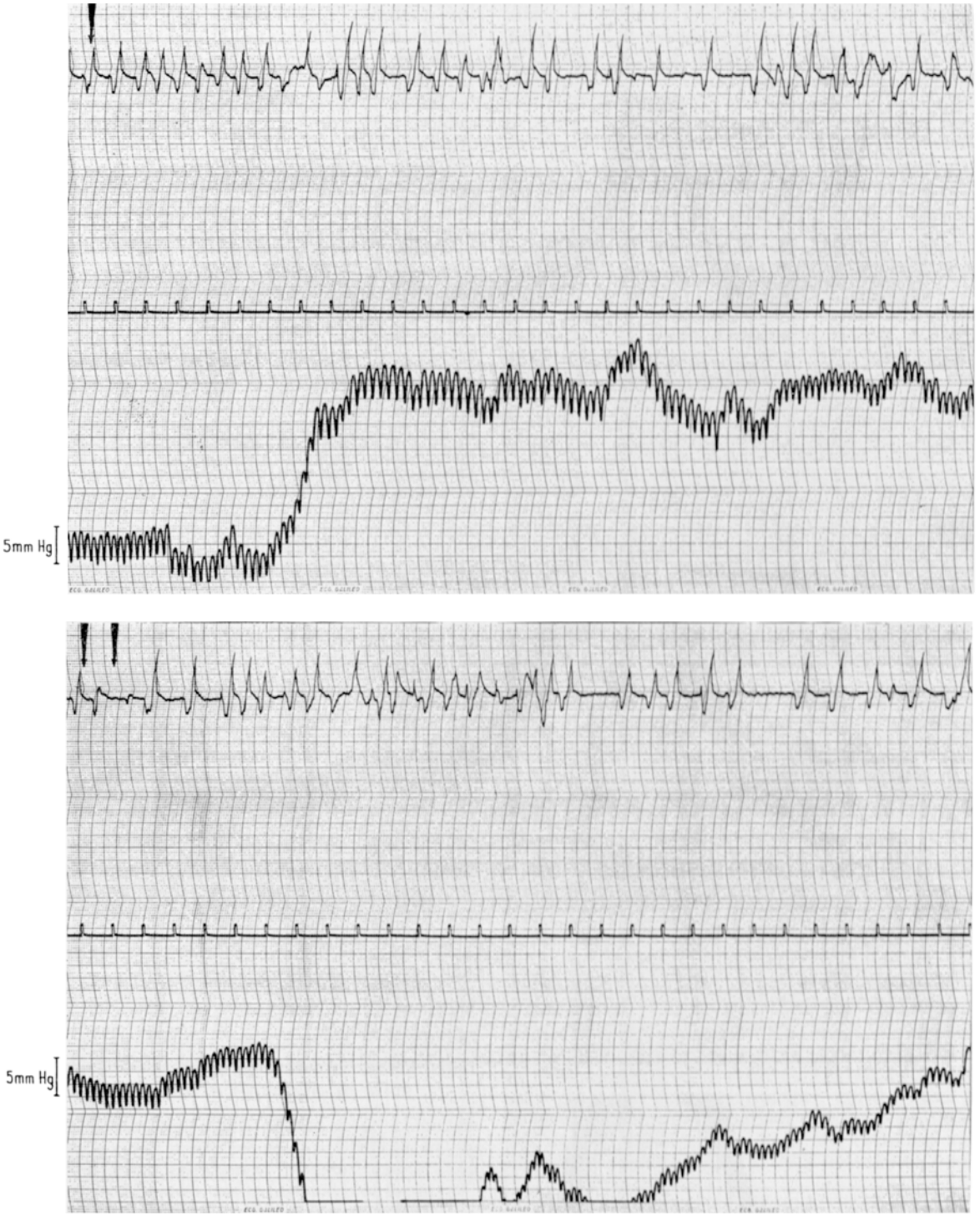
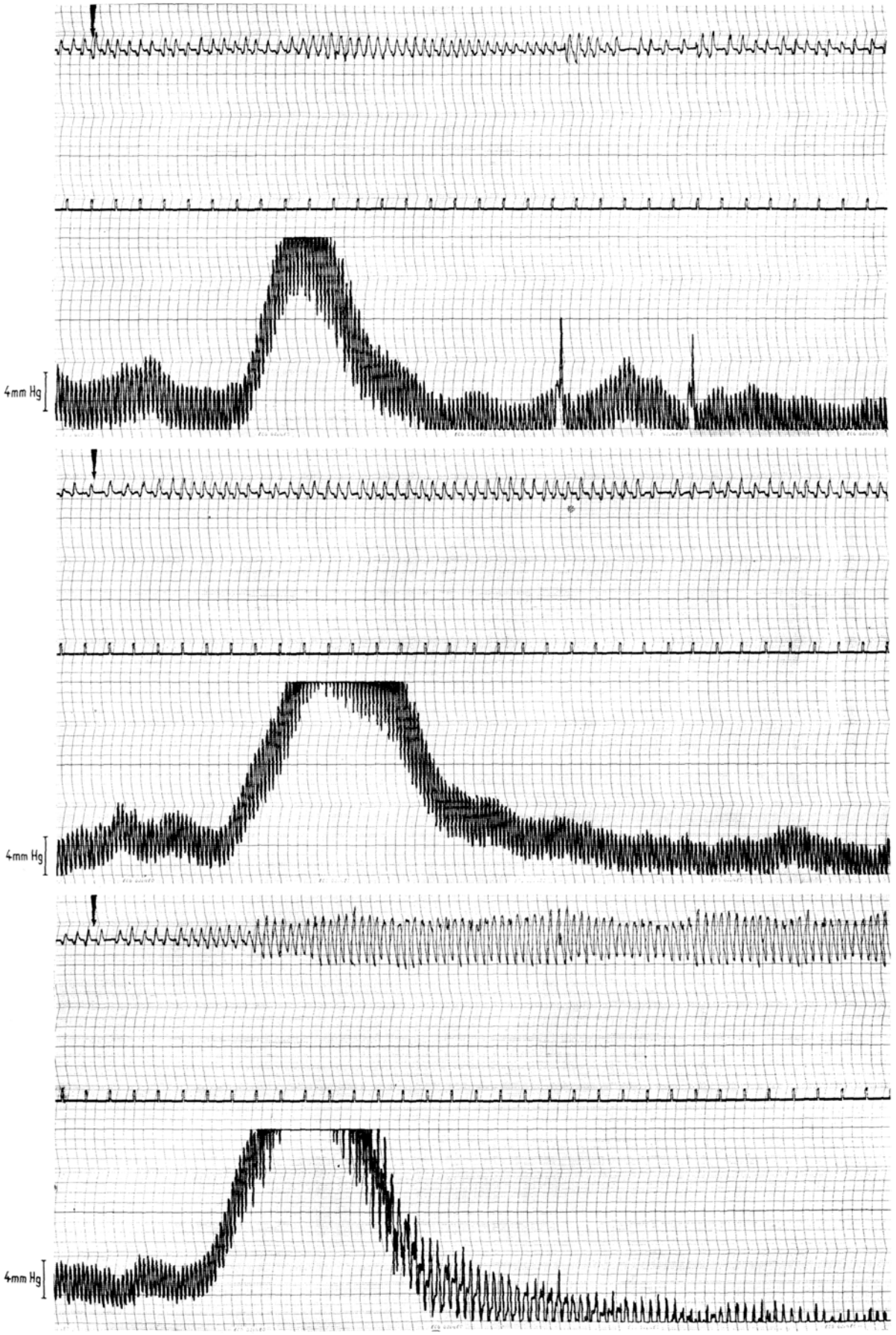



Fig. 1. Inversion of the effects of norepinephrine on blood pressure induced by Eledoisin injected intravenously. Top record: Norepinephrine 8 μg. Bottom record: Norepinephrine 8 μg (second arrow) injected 5 sec after 2 μg of Eledoisin. Each record inscribes tachographic tracing of the respiration, timer markings 5 sec apart and blood pressure tracing obtained electromanometrically using high sensitivity and filters.


4mm Hg
4mm Hg
4mm Hg

larly of the head, the minimal action being seen with doses of 1 to 2 μg (15 to 30 mμg/kg). (2) Definite arterial hypotension and spinal fluid hypertension have been produced in sensitive individuals with doses ranging between 1/10 and 1/5 of a μg (1,5 to 3 mμg/kg). (3) Intolerance may be shown when 15 to 30 μg (200 to 300mμg/kg) are injected. With such doses the subject will have hot flushes of the face, throbbing headache, palpitations, nausea, intestinal hyperperistalsis, intense polypnea, conjunctival redness, marked fall of the arterial blood pressure lasting between 10 and 20 min and spinal fluid hypertension. (4) Arterial hypertension induced by 3 to 5 μg of synthetic hypertensin or by 10 to 15 μg of norepinephrine is inhibited or reversed by 1 to 2 μg of eledoisin injected 5 sec previously (Figure 1). (5) The stimulation of eledoisin on the respiration is very intense and definitely greater than that elicited by serotonin, bradykinin, norepinephrine and hypertensin when used at equal doses as eledoisin. In some instances very small doses of of eledoisin (100 mμg) do not change the arterial blood pressure and pulse rate; in such cases a definite increase of the respiration rate would indicate the effect of the drug. (6) Hypertensive subjects are particularly prone to the hypotensive effect of eledoisin. A fall of the systolic blood pressure ranging between 80 and 100 mm of Hg and of the diastolic between 30 to 60 mm of Hg may be induced by 1 to 2 μg in these patients. However, with these doses, the blood pressure regains its normal levels within 5 to 10 min. (7) At comparable doses eledoisin is 3 to 5 times more active than histamine and 5 to 10 times more powerful than bradykinin when evaluated for 'threshold' effects on blood and spinal fluid pressure (Figure 2). Compared with these two substances hypotension from eledoisin is much more prolonged, the recovery time being 3 to 4 times longer with equal pressure changes. (8) Eledoisin incubated with human plasma (5 μg/ml) will partially lose its hypotensive effects depending on the time of incubation. In fact 2 h of incubation induce about a 20% decrease, 12 h a 50% decrease; after 24 h of incubation the hypotensive effect will be 70% of the original value. Comparatively synthetic bradykinin incubated with human plasma (20 μg/ml) will reduce its effects more than 50% after 30 min. The hypotensive effect of this drug is practically nil after 2 h of incubation. (9) No tachyphylaxis was found.

*Comment.* These first experiments of ours performed in man show that the synthetic endecapeptide 'Eledoisin' is the most powerful hypotensive agent ever tried, having effects many times greater than those of Histamine and Bradykinin. Remarkable is the longer hypotensive effect of eledoisin when compared with that of these two substances. The more intense and prolonged effect may be related to the fact that eledoisin is produced by an animal of quite different species to man. This raises the possibility that, when this organic compound is injected, no inactivation by a specific enzyme takes place as is conversely the case for histamine or bradykinin.

The vasodilating action of eledoisin seems to be greater and shows mainly in the upper part of the body, as indicated by the intense vasodilatation of the skin of the face, the conjunctival redness and the spinal fluid hypertension.

Particularly interesting is the intense stimulation of the respiration under eledoisin treatment. In fact, our first observations seem to show that this drug causes hyperpnea most likely with a direct action on the respiratory centre and does not depend solely on arterial hypotension. We may state that, starting with very low doses, hyperpnea appears first and precedes the hypotensive effect.

It is possible that eledoisin will find an important place in the clinical and therapeutical armamentarium once the marked hypotensive, vasodilating and hyperpneic properties have been thoroughly assessed.

*Riassunto.* Gli autori segnalano le prime osservazioni sugli effetti circolatori e respiratori della eledoisina nell'uomo. L'eledoisina, rappresenta il principio più potente in senso ipotensivo, vasodilatatorio e iperpneizzante.

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G. Franchi, and S. Michelacci

*Clinica Medica dell'Università di Firenze (Italy), August 7, 1962.*

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Fig. 2. In this Figure the effects of Eledoisin, Histamine and Bradykinin on the cerebral spinal fluid pressure are compared. Top record: Eledoisin 0.25 μg. Middle record: Histamine 5 μg. Bottom record: Bradykinin 80 μg. Each record in the figures inscribes tachographic tracing of the respiration, timer markings 5 sec apart and cerebral spinal fluid pressure which has been electromanometrically measured at high sensitivity and without dumping.

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## Influence of Previous Feeding with a High-Fat Diet on Liver Steatosis Produced by Acute Starvation or Growth Hormone in Mice

Acute starvation or a single dose of growth hormone (STH) in mice cause a marked fatty infiltration of the liver, which is a manifestation of enhanced mobilization of depot fat[1]. It is known that a high ratio of dietary fat leads to metabolic adaptation involving preferential fat utilization[2].

In female albino mice (H strain, 25–28 g body weight), fed for 12–22 days with a sufficiently supplemented high-fat diet[3] we investigated the occurrence of liver steatosis after a 25–36 h fast and/or the intravenous administration of STH (0.6 mg/animal). The results are summarized in the Table. Fasting, as well as STH, or a combination of both stimuli, lead to a substantial rise of liver fat in mice previously fed a control diet. On the other hand, in parallel groups fed a high-fat diet, liver steatosis does not develop either after a 24 h fast or in fed animals after STH administration. If 36 h fasting was combined

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