Male rats (Sprague–Dawley) weighing 135–155 g were separated at random into groups of 6 or 8 animals. The drugs were administered intramuscularly, 30 min before 10 μc/100 g of *dl*-7-H³-noradrenaline (13 μc/μg) was given intravenously. 2 h later the rats were killed by a blow on the head and the hearts were immediately removed, washed in water, and homogenized in 10 ml of ice-cold perchloric acid (0.4*N*). After centrifugation, the supernatant solution was assayed for H³-noradrenaline as previously described[3]. The following phenothiazine derivatives (Table) were tested: Promethazine (Phenergan), 10-(2-dimethylaminopropyl)phenothiazine HCl; promazine, 10-(3-dimethylaminopropyl)phenothiazine HCl; selenopromazine, 10-(3-dimethylaminopropyl) phenoselenazine maleate; chlorpromazine, 10-(3-dimethylaminopropyl) 2-chlorophenothiazine HCl. Dosage is expressed in mg of the free base.

Relation between ability to block uptake of H³-noradrenaline (NA) and other pharmacological effects

Drug	H³-NA in heart mμc/g[a]	Relative uptake (%)	Anti-histamine action	Anti-motor action	Anti-adrenaline action
None	575 ± 20	100			
Phenergan	576 ± 44	100	++++	0	+
Promazine	306 ± 26	53	+	+++	++++
Seleno-promazine	211 ± 43	37	++++	+	++++
Chlor-promazine	284 ± 32	49	++	++++	++++

[a] Mean ± S.E.M.

In one series of experiments the dose of chlorpromazine which gave about 50% inhibition of uptake of H³-noradrenaline in rat hearts was found to be 4 mg/kg. This dosage was then used throughout the study. The Table shows that all of the phenothiazine derivatives tested except Phenergan block the uptake of H³-noradrenaline. This effect on injected H³-noradrenaline is compared with other pharmacological actions. The antihistamine, antimotor (sedative) and antiadrenaline actions have been determined for each drug on the basis of work by GLASSMAN, SEIFTER et al.[4–8]. The gradation used in the Table was provided by Dr. J. SEIFTER.

The ability to lower the concentration of injected H³-noradrenaline does not seem to be related to antihistaminic properties since Phenergan, which has a pronounced antihistaminic action but little antimotor or antiadrenaline action, has no effect on the uptake of H³-noradrenaline. Furthermore, promazine has only a slight antihistaminic action, but reduced H³-noradrenaline concentration to about 50% of control value.

The antimotor actions of phenothiazine derivatives also seem to be unrelated to the ability to decrease the tissue concentration of H³-noradrenaline. Selenopromazine shows only a slight antimotor action but affects the concentration of H³-noradrenaline.

However, all of the drugs which have antiadrenaline properties (promazine, selenopromazine, chlorpromazine) had a pronounced effect on storage of H³-adrenaline. Phenergan, on the other hand, has only a slight antiadrenaline action and has no significant effect on H³-noradrenaline storage[9].

Zusammenfassung. Es wurden eine Reihe von Phenothiazin-Derivaten auf ihr Vermögen die H³-Noradrenalinaufnahme in das Rattenherz zu blockieren getestet. Dabei hat sich ergeben, dass dieses Blockierungsvermögen weniger mit den antimotorischen oder Antihistamineigenschaften der Substanzen gekoppelt zu sein scheint, sondern eher mit deren antiadrenergischen Wirkungskomponenten.

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Factor in Human Urine Inhibiting Lipid Metabolism

Adipokinetic activity has been found in the urine of humans[1] or experimental animals[2] during fasting or under other conditions leading to increased mobilization of depot fat. We have been able to detect such activity in extracts from the urine of rabbits during fasting[3] or on exposure to low temperatures[4]. However, attempts to demonstrate this activity in the urine of fasting human volunteers or cachectic patients gave variable results: occasionally the extracts proved adipokinetically active but in other experiments they depressed lipid mobilization. These results suggested a search for an additional factor or factors antagonizing the effect of the urinary adipokinetic factor.

Extracts were prepared from the pooled urine collected from (a) 20–80 healthy human volunteers during the last 16 h of a 36 h fast, (b) 3–5 cachectic patients suffering from malignant neoplasms, over the course of 2–3 weeks, (c) 20 healthy persons on a normal diet (control group). The extracts were obtained by adsorption on benzoic acid and further treatment following the procedure of CHALMERS et al.[1], except that carboxymethylcellulose rather

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Effect of urine extracts from fasting and cachectic humans, and humans on a normal diet (control group) on the ketone bodies, liver fat and blood sugar in mice 6 h after s.c. injection (mean ± S.E.; in parentheses the number of experimental animals in the test)

Material tested	Ketone bodies (mg%)	Liver fat (%)	Blood sugar (mg%)
Extract from urine			
1. Placebo[a]	6.40 ± 0.93 (8)	5.85 ± 0.26 (9)	81.2 ± 7.93 (8)
Control[b]	5.53 ± 0.62 (8)	5.22 ± 0.29 (9)	82.9 ± 4.60 (9)
Fasting[b]	2.33 ± 0.26 (9)[c]	4.92 ± 0.15 (9)[d]	90.1 ± 5.17 (8)
2. Control	4.75 ± 0.39 (9)	5.91 ± 0.20 (10)	83.6 ± 4.84 (9)
Fasting	2.89 ± 0.39 (10)[d]	5.18 ± 0.23 (10)[e]	86.2 ± 5.35 (10)
3. Control	4.62 ± 0.27 (11)	5.16 ± 0.16 (11)	—
Cachectic	1.40 ± 0.15 (10)[c]	4.45 ± 0.12 (10)[d]	—
'Fraction B' of extracts			
1. Placebo[a]	3.12 ± 0.27 (8)	5.76 ± 0.22 (8)	96.7 ± 5.40 (8)
Control	3.28 ± 0.54 (7)	5.62 ± 0.15 (7)	99.9 ± 5.97 (7)
2. Control	5.07 ± 0.44 (8)	5.55 ± 0.18 (12)	84.0 ± 7.27 (9)
Fasting	1.87 ± 0.27 (16)[c]	5.43 ± 0.09 (20)	92.8 ± 4.30 (18)
3. Control	5.25 ± 0.21 (10)	6.41 ± 0.43 (10)	72.0 ± 4.14 (10)
Cachectic	3.15 ± 0.24 (8)[c]	4.81 ± 0.19 (8)[d]	81.1 ± 3.95 (8)

[a] The same volume of solvent (0.5% Na_2CO_3 neutralized before injection). [b] Without adsorption on carboxymethylcellulose. [c] Statistically significant for $P < 0.001$; [d] for $P < 0.01$; [e] for $P < 0.05$.

than oxycellulose was used for adsorption in the final stage. A part of each extract was further fractionated on Sephadex G-25 in 0.1 *N* aqueous ammonia; the 'Fraction B' referred to below was obtained from the pooled eluates containing material with distribution coefficients[5], K_d, between about 0.05 and 0.25. The extracts and fractions were tested by subcutaneous injection into mice (H strain) in doses corresponding to 50–100 ml of the original urine; after 6 h the mice were exsanguinated and the blood sugar[6] and ketone bodies[7] as well as the liver fat content were determined.

The results collected in the Table show that the urine extracts from the fasting and cachectic groups, and the 'Fraction B' of such extracts, caused a marked drop in the ketone body blood level. In most cases this was accompanied by a significant decrease in liver fat and a slight, statistically not significant but nevertheless consistently repeated, increase in the blood sugar. These changes did not take place when the corresponding extracts, or their fractions, from the control groups on normal diet were given. It should be noted that in some experiments the inhibitory effect could be demonstrated in urine extracts even without adsorption on carboxymethylcellulose.

As an additional criterion, the *in vitro* release of fatty acids from rat epididymal fat pads was studied. Addition of the extracts of fractions active *in vivo* to the medium (0.5–1.0 mg per ml of Krebs–Ringer phosphate with 3% albumin, pH 7.4) caused a significant decrease, by 30–70%, of the release of free fatty acids, both in the presence of glucose (100–150 mg%) and its absence.

The results indicate that the urine of fasting or cachectic humans contains a mixture of substances with antagonistic effects on these parameters of lipid metabolism. In addition to a fraction of relatively low molecular weight with lipid mobilizing activity, we have found a fraction of higher molecular weight showing the opposite effect on lipid metabolism. The presence of this latter factor may be one of the reasons for the poor reproducibility of attempts to isolate the lipid mobilizing factor from the urine of diabetic[8] or fasting individuals. The physiological significance and chemical nature of these factors is being further examined.

Zusammenfassung. Ein im Urin hungernder oder kachektischer Personen vorhandener Faktor, führt bei Mäusen nach s.c. Injektion im Blut zur Senkung des Ketonkörperspiegels. Der Leberfettgehalt wird herabgesetzt und eine schwache, jedoch regelmässig auftretende Erhöhung des Blutzuckerspiegels herbeigeführt. Bei der Ratte hemmt der Faktor *in vitro* die Freisetzung von Fettsäuren aus dem epididymalen Fettgewebe. Er beeinflusst möglicherweise den im Harn hungernder Menschen vorhandenen 'lipid mobilizing factor' antagonistisch.

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Über die Wirkung von synthetischem ACTH (β^{1-24}Corticotropin) beim Menschen

Das von KAPPELER und SCHWYZER[1] synthetisierte β^{1-24}Corticotropin (CIBA 30920-Ba) besteht aus einer Kette von 24 Aminosäuren, die in gleicher Reihenfolge wie die ersten 24 Aminosäuren des natürlichen Corticotropins (mit 39 Aminosäuren) angeordnet sind[2]. Es ist bekannt, dass die Struktur des natürlichen Corticotropins nicht bei allen Tierarten gleich ist. Die Unterschiede bestehen in der Zusammensetzung und Anordnung der 25.

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