gegenüber dieser Verbindungsklasse empfindlicher ist als *T. congolense*.

Die bisher wirksamste Verbindung, das 4,4'-Bis(4-methylimidazolin-2-yl)-terephthalanilid (III) wurde in der Form seines Dimethansulfonates eingehend untersucht. Wir bevorzugten dieses Salz, da es besser wasserlöslich und wesentlich gewebsverträglicher war als z.B. das Dihydrochlorid oder die freie Base. Die Eliminierung von Trypanosomen aus dem peripheren Blut erfolgt mit diesem Präparat ausserordentlich rasch. So wird bei fortgeschrittener Trypanosomeninfektion (320000 Congolensetrypanosomen/mm³ Blut) nach einer einmaligen subkutanen Gabe von 3 mg/kg das Blut innerhalb von 24 h trypanosomenfrei. Um aber in diesem Versuch eine rezidivfreie Therapie zu erzielen, muss die einmalige Dosis auf 4–6 mg/kg erhöht werden.

Das Dimethansulfonat von III ist in physiologischem Milieu schlecht löslich, fällt daher nach subkutaner Injektion teilweise aus und bleibt längere Zeit liegen. Dieser Depotwirkung ist offenbar die gute prophylaktische Wirksamkeit dieser Verbindung zuzuschreiben. Bisherige Versuche mit 50 mg/kg s.c. ergaben eine 5monatige Prophylaxe gegenüber Bruceiinfektionen.

Summary. Compounds of the terephthalanilide series show, besides their antileukemic and bacteriostatic properties, considerable activity against *Trypanosoma brucei* and *T. congolense*.

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Fat-Mobilizing Substance in the Urine of Patients with Diabetes and with Pituitary Diseases and the Effect of Insulin on its Action

CHALMERS et al.[1,2] extracted a fat-mobilizing substance (FMS) from the urine of fasting persons, which causes weight loss, hypoglycaemia, elevation of lipids in serum and in liver of mice. Persons on normal diet do not excrete this material. The authors found this substance also in the urine of diabetic patients with ketosis. These results were confirmed in the present experiments.

The urine extract (prepared by CHALMER's method) of persons on restricted diet (1000 calories, 50 g carbohydrate daily, for four days) caused weight loss in mice when 0.3 ml of the extract was given every other day subcutaneously to groups of mice, each group having three animals. The mice were weighed every other day for nine days and the food ingested was weighed every day. The extract of urine of the persons on adequate diet (2000 calories and 200 g of carbohydrate per day) was administered similarly. The control animals received saline. In other experiments, 0.5 ml of urine extract was given subcutaneously to mice and 2–4 h later the total lipid content of liver and of serum was determined, while the controls received saline. Blood sugar determinations were carried out similarly, but only after 2 h. All these investigations were carried out on 13 persons without endocrine disease. All mice receiving saline gained in weight during nine days (mean + 3.13 ± 0.23 g). All but one animal receiving extracts of urine excreted on adequate diet also gained in weight (mean + 2.25 ± 0.35 g). All but two animals receiving extracts of urine excreted on restricted diet lost weight (mean – 1.93 ± 0.21 g); the weight of these two animals did not change. The food intake of all animals was the same, the weight loss was not due to decreased appetite. The treated animals, while loosing weight, were as lively as the controls; no toxic manifestation occurred. When giving the FMS intermittently, decrease and increase of body weight occurred in succession.

The serum lipid values in mice increased after injecting extracts of urine excreted on restricted diet (mean + 145.4 ± 11.53 mg%), whereas the urine extract excreted on adequate diet had very low activity (mean + 27.9 ± 12.11 mg% increase). Similarly the liver lipid

Table I. The effect of urine extract of acromegalic patients on adequate diet

	Change of:			
	Body-weight g%	Serum-fat mg%	Liver-fat g%	Blood-sugar mg%
Acromegaly	– 1.7	+ 235	+ 1.3	– 65
	+	+	+	+
	– 1.3	+ 180	+ 1.2	– 33
	+	+	+	+
Acromegaly + diabetes	– 3.0	– 105	– 0.7	– 10
	+	o	o	o

Table II. The inhibitory effect of different amounts of insulin on the action of FMS

	Liver-fat g%	Serum-fat mg%
Saline	6.30	325
FMS	7.65	505
FMS + 0.2 U insulin	6.20	345
FMS + 0.1 U insulin	7.05	440
FMS + 0.04 U insulin	7.35	560
0.2 U insulin	5.95	260
0.1 U insulin	6.15	340
0.04 U insulin	6.35	330

[1] T. M. CHALMERS, G. L. S. PAWAN, and A. KERKWICK, Lancet *1960 ii*, 6.

[2] T. M. CHALMERS, Extrait de *L'obésité* (Expansion Scientifique, Paris 1963).

content rose after the injection of extract of urine excreted on restricted diet (mean + 1.21 ± 0.056 g%; on adequate diet the mean value was + 0.34 ± 0.049 g%). The blood sugar decreased after administration of active extract (mean 38.5 mg%).

In the urine of a patient with Sheehan syndrome, no FMS activity could be detected on restricted diet. On the contrary, in two cases of acromegaly, the urine showed FMS activity on adequate diet. These findings suggest the pituitary origin of FMS[1]. A third patient with acromegaly had severe diabetes. The urine extract of this patient, while on adequate diet, caused weight loss in mice but had no effect on liver and serum lipids, similar to the effects of urine extracts of diabetics (Table I).

The urine extract of 16 out of 18 diabetic patients caused weight loss in mice in spite of adequate diet (mean − 1.34 ± 0.22 g) (Figure 1), but no increase of serum and liver lipid levels was found. The 16 positive cases were severe diabetics, with high blood and urine sugar levels, but without ketonuria. 15 patients received insulin, 1 carbutamide. After adequate control of the diabetic state, the weight-reducing effect of the urine disappeared. The two diabetics with negative results were well balanced cases. Particularly strong weight-reducing effect was found in the urine of a diabetic patient with complete pylorus-stenosis: one animal lost 7 g and two others 4–4 g during 9 days. In this case, the fat-mobilization was enhanced by two factors: by diabetes and by lack of food intake.

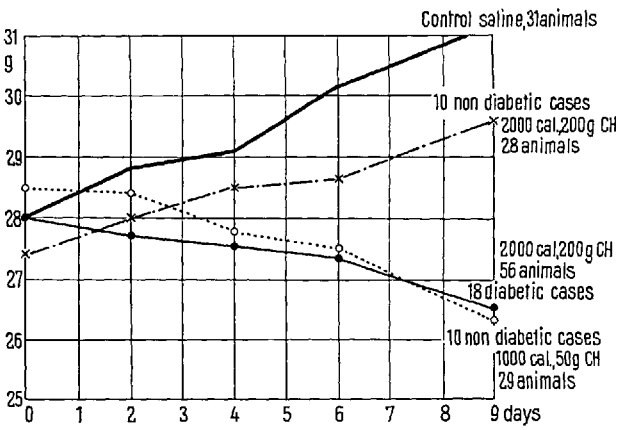

Fig. 1. The effect of different urine extracts on body-weight of mice.

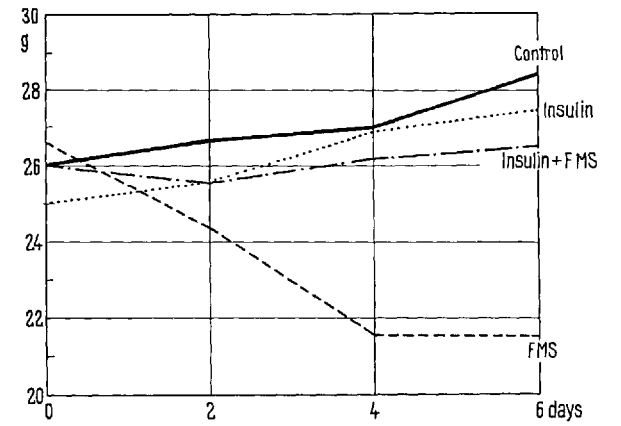

Fig. 2. Insulin inhibits the weight-reducing effect of FMS.

The disturbance of lipid metabolism is frequent in diabetes[3]. RANDLE[4,5] suggested the role of fat-mobilizing substances in the pathogenesis of diabetes. YOUNG[6] suggested the possible role of growth hormone in inducing diabetes; the fat-mobilizing activity of this hormone is well known.

Insulin decreases the serum lipid level in diabetes. The inhibitory effect of insulin on the action of FMS could be demonstrated in further experiments. The extract of urine of persons on restricted diet, which caused weight loss, increase of serum and of liver lipid level, did not exert these effects if the animals received simultaneously 0.2 U of insulin. The effect of insulin decreased in proportion to the decreasing amounts injected (Figures 2 and 3, Table II). In blood sugar examinations, a summarizing of the hypoglycaemic effect of FMS and of insulin was found.

The inhibitory effect of insulin on the fat-mobilizing action of FMS could be one factor in the serum-lipid decreasing and weight-gaining effect of insulin.

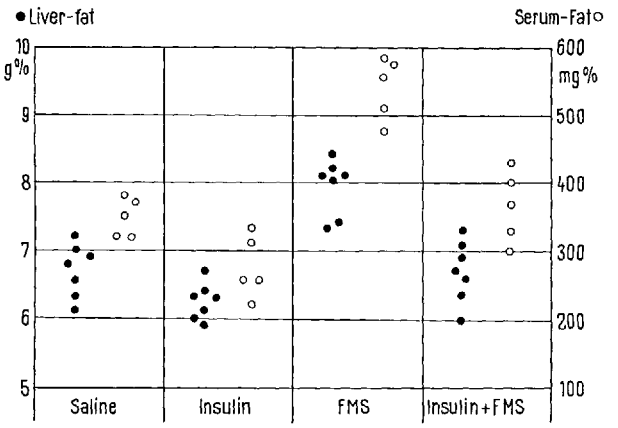

Fig. 3. Insulin inhibits the serum- and liver-lipid-increasing effect of FMS.

Zusammenfassung. Es wird gezeigt, dass beim Sheehan-Syndrom, trotz herabgesetzter Kalorienzufuhr, im Urin die fettmobilisierende Substanz (Chalmers) fehlt. Bei Akromegalie, teilweise auch beim Diabetes erwies sich der Urinextrakt bei normaler Diät als aktiv. Eine gleichzeitige Insulinzufuhr verhinderte die fettmobilisierende Wirkung.

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János Hospital, Budapest (Hungary),
November 23, 1964.

[3] W. SCHRADE, E. BOEHLE, R. BIEGLER, and E. HARMUTH, Lancet *1963 i*, 285.
[4] P. J. RANDLE, P. B. GARLAND, C. N. HALES, and E. A. NEWSHOLME, Lancet *1963 i*, 785.
[5] N. HALES and P. J. RANDLE, Lancet *1963 i*, 790.
[6] F. G. YOUNG, Brit. Med. J. *1961 ii*, 1449.