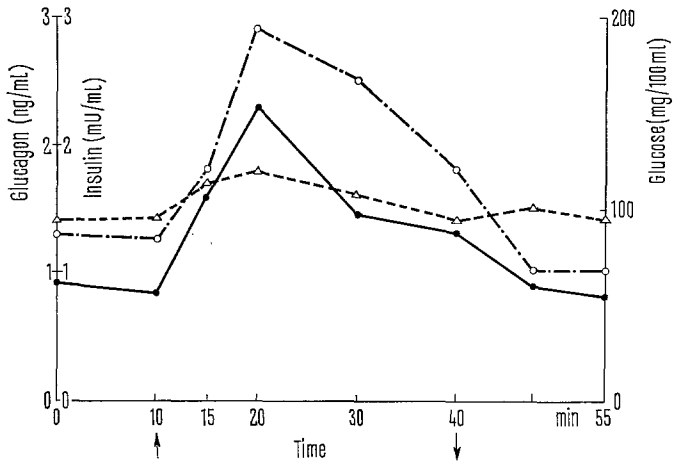
Effect of caerulein infusion on glucagon and insulin pancreatico-duodenal venous plasma concentration and on arterial glucose

	Glucagon (ng/ml)	Insulin (μU/ml plasma)	Glucose (mg/100 ml)
Physiological saline infusion	0.97 ± 0.62 $P < 0.05$ [a]	1450 ± 540 $P < 0.01$ [a]	95 ± 15 $P > 0.05$ [a]
Caerulein infusion (2 ng/kg/min)	3.30 ± 1.29	3700 ± 775	110 ± 20

[a] Student's t test. Figures are mean values at the maximum effect time.



Effects of infusion of caerulein at the rate of 2 ng/kg/min on glucagon (●—●) and insulin (○–·–○) concentration in the pancreaticoduodenal venous plasma and on arterial glucose (△– – –△). At the first arrow, infusion started, at the second arrow, infusion stopped.

the other hand, insulin and glucagon could well have counteracted reciprocally their effects on glycemia.

Present experiments do not contribute to the solution of the problem whether glucagon release is primary or secondary to the secretion of insulin. However, it may be observed that UNGER et al.[3] found that endoportal infusion of cholecystokinin (30 Ivy dog U/min/dog) produced a sharp increment in insulin (840%) as well as, although to a less extent, in glucagon (80%) and glucose concentration (60%); on the contrary, secretin infusion (10 U/min/dog) strongly enhanced (280%) insulin release but left unmodified pancreatico-duodenal venous glucagon and arterial glucose concentration. Also rapid endoportal injection of gastrin (60 μg/dog) increased insulin (400 to 1000%) but not glucagon and glucose concentration.

As stated above, in our present experiments caerulein infusion enhanced insulin (155%) as well as glucagon concentration (240%), with negligible changes in arterial glucose concentration (15% increase). This may signify that at least under our experimental conditions there is no relationship between the secretion of the two hormones. Thus, both cholecystokinin and much more caerulein are likely to possess a primary stimulant action both on the β and α cells of the pancreatic islets.

Riassunto. L'infusione di ceruleina (2 ng/kg/min) produce nel cane un significativo aumento della concentrazione del glucagone, oltre che della insulina, nella vena pancreatico-duodenale superiore, senza significative modificazioni della glicemia.

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Failure to Stimulate Significant Cortisol or Growth Hormone Secretion in Man by Ether Infusion

The tests for assessing pituitary ACTH reserve presently available for clinical use[1–3] are not completely satisfactory. The Metopirone test[1] endangers the patient with the possible crisis of hypocortisolism. Its principal failing is that it indicates the ability of the pituitary to secrete increased amounts of ACTH in response to a depression of blood cortisol levels but does not reflect the ability to increase ACTH secretion in response to stress. These 2 stimuli (decreased blood cortisol and stress) probably activate ACTH secretion by quite different mechanisms[4]. The Metopirone test has indicated a markedly depressed ACTH reserve in some patients who have subsequently responded to surgical stress with a normal increase in adrenal secretion[1]. Pyrogen[5] tests the ability of stress to increase ACTH secretion, but causes fever and other unpleasant side effects. Both tests are time-consuming and require hospitalization of the patient. Insulin-induced hypoglycemia[6] is potentially dangerous and is accompanied by disagreeable symptoms.

In a search for a more suitable diagnostic tool, we studied the effect of i.v. administered ether on the plasma 17-OHCS (17-hydroxy corticosteroids)[7]. Ether

was chosen as a stimulus since, in the rat, it apparently directly activates the hypothalamic median eminence to produce an increased release of ACTH from the pituitary[8]. It is thus probably similar to pyrogen and insulin hypoglycemia in activating ACTH secretion as a 'stress'. Surgery under ether anesthesia and ether anesthesia alone have also been shown to produce a pronounced rise in plasma cortisol levels and a marked increase in urinary 17-OHCS excretion[9]. Elevated levels of plasma ACTH[10] and growth hormone[11] after surgery and anesthesia have also been demonstrated. We therefore additionally assayed the blood samples in the volunteers for growth hormone[12].

Ether was given i.v.[13] to avoid the disagreeable effects of inhalation of this anesthetic on the respiratory tract and to provide a more easily standardized technique for calculating the dose. We infused the ether into the antecubital vein as a 5% solution in 0.9% NaCl. 2 healthy young male volunteers, premedicated only with 0.4 mg atropine, and 2 patients scheduled for corrective orthopedic surgery without obvious endocrine disease (premedicated with 0.4 mg atropine, 75 mg meperidine and 100 mg pentobarbital; or 10 mg morphine, 7 mg scopolamine, and 25 mg phenergan) were studied. In the volunteers, 200 ml of the ether-saline solution, and 300 ml in a repeat study of one of the subjects, were infused in less than 10 min. This induced unconsciousness of 2 to 3 min duration, followed by a quick recovery to normal mentation in less than 15 min. Neither of the volunteers reported unpleasant symptoms. The patients received 100 ml in 5 to 7 min. This markedly slowed and diminished their responses to touch, painful stimuli and calling their names.

Heparinized blood was sampled by i.v. catheter immediately before infusion and 10, 30, and 60 min thereafter. Additional samples were taken from the volunteers 120 and 210 min after the infusion. The volunteers were studied between 13.00 and 17.00 h to take advantage of the low plasma cortisol levels in the afternoon[14]. We felt a rise produced by ether would be easier to detect if there were a low basal level. The patients were studied between 9.00 and 13.00 h, since they were being prepared for surgery and could not be scheduled for later times. None of the subjects had eaten for at least 5 h before beginning the studies. Plasma cortisol was measured fluorimetrically[7] and growth hormone by radioimmunoassay[12]. Statistical comparison of the levels of plasma cortisol at the different time intervals was made by the NEWMAN-KEULS test[15].

Changes in plasma cortisol following infusion of 5% ether

Ether solution infused (ml)	Subject A 200	B 200	B 300	C 100	D 100
Minutes after beginning infusion					
0	22.6	17.8	18.9	17.0	14.5
10	16.9	17.2	21.9	13.5	11.0
30	13.7	14.4	27.5	11.5	11.0
60	17.9	14.2	19.2	9.5	18.0
120	21.2	15.7	20.6	–	–
210	26.0	29.6	22.4	–	–

A and B were normal volunteers. C and D were patients prepared for surgery. There was no statistically significant increase of plasma cortisol above the preinfusion level at any subsequent time interval ($p > 0.05$).

No striking rise in plasma 17-OHCS which gave promise this would be a useful provocative test was detected. Growth hormone levels were undetectable in all but one sample from all subjects. A value of 6.4 ng/ml was found at 210 min when subject 'B' was infused with 200 ml of ether solution. The method used readily detects HGH at concentrations of 1.0 ng/ml.

It is unlikely that the pentobarbital premedication to the patients inhibited the release of ACTH since HAMMOND et al.[9] found a rise in 17-OHCS serum levels following ether inhalation anesthesia in volunteers premedicated in a comparable fashion to our patients. It is possible that larger doses of ether, more than 10–15 ml per individual, would have caused increased 17-OHCS levels. However, larger doses were not tried since we hoped to find a rapid and inexpensive test of ACTH reserve. A more prolonged period of unconsciousness would be expected from larger quantities of ether. This would necessitate the presence of an anesthesiologist during the test and make it prohibitively expensive.

We report these negative findings in a very small series in order to save other investigators from a waste of effort in studying the usefulness of ether as a test for either ACTH or growth hormone 'reserve' unless a major modification of this technique is employed[16].

Zusammenfassung. Bei endokrin gesunden Menschen wurde die Wirkung einer intravenösen Äther-NaCl-Infusion auf den Gehalt an Cortisol im Plasma untersucht. Es erfolgte keine Stimulation von ACTH, respektive Cortisol oder Wachstumshormon.

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