diabetics, having reached a normal level of blood sugar with a given dose of insulin, tolerate a further supplementary dose before the slightest hypoglycaemic disturbance occurs. Fully in agreement with this, it was observed that latent diabetics also tolerated insulin, sometimes at even considerable doses, before showing symptoms of slightest hypoglycaemic disturbances. Thus, besides the normal glycaemic dose there is also a maximum tolerated dose. This did not represent a pharmacological phenomenon comparable with acquired tolerance, since prolonged administration of such a dose led to intolerance due to the appearance of a parallel phenomenon of remission of the diabetes. Moreover, this dose permitted the resolution of complications such as recovery of gangrene refractory to all treatment, and pregnancies brought to normal full term in diabetic and prediabetic subjects. Thus, it appears that the maximum tolerated dose, and not the normal glycaemic one, should be considered the therapeutic dose.

The effects of insulin and glucose on the translocation of rat epididymal adipose tissue hexokinase activity.

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Bound hexokinase activity was observed both in the mitochondria (25—40% of total) and in the microsomes (8—15%) of epididymal adipose tissue. The particles were obtained by differential centrifugation of the homogenate and identified by electron microscopy. In suspensions of mitochondria or microsomes, bound hexokinase was released in the presence of added glucose-6-phosphate. Subsequent addition of inorganic phosphate resulted in rebinding of the previously released enzyme. A larger amount of the total adipose tissue hexokinase activity was bound to subcellular particles in carbohydrate-fed rats (49 ± 3%) than in fasted rats (35 ± 2%).
Incubation of whole fat pads *in vitro* for 20 min at 37° C resulted in increased mitochondrial and microsomal hexokinase activity when insulin was present in the incubation medium (glucose absent). In the presence of glucose (insulin absent), mitochondrial hexokinase activity was increased while that of the microsomes was decreased. The addition of insulin (glucose present) stimulated such translocation of hexokinase activity by further increasing the mitochondrial hexokinase activity.
The results raise the question whether there is a relation between hexokinase translocation and the regulation of glucose metabolism.

Glucose tolerance, ACTH and insulin levels in adrenal insufficiency.

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Six patients with primary adrenocortical insufficiency, 5 patients with total adrenalectomy for Cushing's Syndrome (bilateral hyperplasia) and one patient with adrenogenital syndrome had i.v. glucose tolerance tests two hours after regular cortisol administration (KG I = 2.48 ± 1.63, $\bar{x} \pm s$) and after 18 to 24 h of cortisol withdrawal (KG II = 3.41 ± 1.83). Concomitantly with this increase in glucose tolerance, biological determination of plasma ACTH-levels (Klin. Wschr. 44, 1393, 1966) showed a marked elevation (0.44 ± 0.33 mU ACTH/ml of plasma) with low fasting insulin levels (IMI) being 13.6 ± 12.0 μU/ml). Thus the constellation of low 11-OHCS-values (fluorimetric assay), increased glucose tolerance and elevated ACTH-levels did not produce an elevation of insulin levels. No support was found from these data for the hypothesis that endogenous ACTH may show direct, extra-adrenal stimulation of insulin release.

The rate of disappearance of insulin from the plasma in patients with myxoedema and in normal subjects.

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Insulin tolerance tests, using standard doses of porcine insulin were performed on a group of normal subjects and on subjects with primary hypothyroidism. 99% of injected insulin disappeared from the plasma of normal subjects within 20—25 min, by which time the fall in blood sugar was complete.
In hypothyroidism, however, where blood sugar levels continue to fall for up to an hour, preliminary results indicate that the rate of disappearance of insulin from the plasma is slower.

Disturbing factors in studies on insulin-binding to rat diaphragm in vitro.

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Rat hemidiaphragms were incubated *in vitro*, and the disappearance of ^{131}I labelled and unlabelled insulin from the medium was determined by immunoassay and/or by measuring radioactivity.
Unlabelled insulin (100 μU/ml) was found to disappear rapidly, 40—50% of the initial concentration being recovered after 15 min of incubation. At later stages the disappearance progressed more slowly reaching values of 90% after 120 min. On addition of insulin-^{131}I (5—500 mC/mg) tissue-bound radioactivity amounted to 5—6% after 15 min of incubation, and a further rise to 10—15% was seen after 120 min. When, however, the disappearance of labelled insulin was measured simultaneously by immunoassay, values were obtained which closely approached those of unlabelled insulin. — Rapid disappearance of immunoreactive insulin also occurred in incubation media of diaphragms from which the tissue had been removed. A marked rise in TCA-soluble radioactivity was seen when labelled insulin was added under these conditions. — The results indicate that studies on the binding of insulin to diaphragm *in vitro* should be limited to a brief period of incubation not exceeding 15 min. Immunochemical procedures are required. When insulin-^{131}I is involved, direct counting of radioactivity cannot be used for this purpose due to rapid deiodination or degradation of the labelled hormone in the medium.

Biliary excretion of insulin in the rabbit.

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Intravenously injected bovine insulin is transferred to bile of normal and alloxan-treated rabbits. When ^{125}I-labelled bovine insulin was injected, about 1% of the radioactivity was recovered in bile within 2 h, but only a small proportion of this was precipitable with trichloracetic acid. The amount of immunoreactive insulin in bile represented about 0.1 per cent of an injected dose of insulin. Insulin and bromsulphthalein both appeared in bile within 10 min when they were injected together. The results of the experiments show that in spite of extensive degradation of the circulating hormone, significant amounts of intact insulin can be excreted in bile.

Assessment of depression in diabetics by Zung's self-rating depression scale.

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We have previously reported on the association of diabetes with depressive illness; furthermore, on the frequent