to subsequent estrogen stimulation and hence evoked no lactogen increase. In the second experiment on the other hand, the simultaneous administration of estrogen with thiouracil checked the depressing effect of the latter on the eosinophils and enabled the estrogen to evoke its normal increase of pituitary lactogen.

The increase in the pituitary weight following thiouracil treatment corroborates a similar report on thiourea-treated rats,[10] and is in line with the findings in thyroidectomized animals. The recognized ability of estrogen to increase pituitary size was evident both in the estrone and diethylstilbestrol-injected rats. However, the greatest augmentation of pituitary weight occurred in the rats which received the above estrogens in combination with thiouracil.

*Summary.* The administration of 0.1% thiouracil in the feed for 24 days to young female rats reduced the lactogenic hormone content of the pituitary below that in normal rats. The proven ability of estrogen to increase the lactogen content of the pituitary remained unimpaired in rats which were given the estrogen together with thiouracil for 21 days. However, when rats received thiouracil alone for a 2-week preliminary period, the subsequent administration of estrogen plus thiouracil for 10 days failed to maintain even the normal level of lactogenic hormone.

The pituitary and thyroid weights of the thiouracil as well as thiouracil plus estrogen-treated rats were increased above the normal controls. The thyroid hypertrophy in the rats which received estrogen and thiouracil for 10 days following a preliminary treatment of thiouracil alone for 2 weeks was less than in the rats which received only thiouracil for the same period.

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## A Brief Insulin Tolerance Test.*

G. J. KRONENBERG AND W. S. MCCULLOCH.†

*From Department of Psychiatry, University of Illinois College of Medicine, Chicago, Ill.*

Meduna *et al.*[1-3] by determining reducing substance (which is predominantly glucose) in venous blood at fasting and at 5, 10, 15, 20, 25, 30, 35, 45, 60, 90 and 120 minutes following the injection of 0.1 unit insulin per kg body weight, had found that the nadir was shallower and later in oneirophrenics than in normals, and had observed, in individual, normal records, a bump—*i.e.* a failure to fall or actual rise—before the nadir at which sympathetic counter-regulation initiates a rapid rise in blood-sugar peaking about the 45th minute. He had also found that throughout all of these changes the amount of reducing substances other than glucose was constant. The present work was begun in 1943 to increase the certainty of his separation and, by samples at the 12th and 17th minutes, to define the bump on the descending limb and finally, to construct a brief test for clinical use.

On the assumption that the effect of insulin in lowering the blood-sugar was proportional to its initial value, Meduna had expressed the observed decrease in percent of fasting value, and subsequent experience indicates that this is probably the best expression. He used colorimetric determination of alkaline ferricyanide reduced by tungstic acid filtrates from 0.1 ml of venous blood and this, by chance, gives mean fasting values of approximately 100 mg %, so that the mean

* Aided by a grant from The Josiah Macy, Jr., Foundation.

† The authors wish to express their indebtedness for technical assistance to Miss Genevieve Mack, Miss Edith Laslo, and Miss Ellen Ridley.

1 Meduna, L. J., and McCulloch, W. S., *The Medical Clinics of North America*, January, 1945.

2 Braceland, Captain F. J., Meduna, L. J., and Vaichulis, J. A., *Am. J. Psychiatry*, 1945, **102**, ....

3 Meduna, L. J., in press.

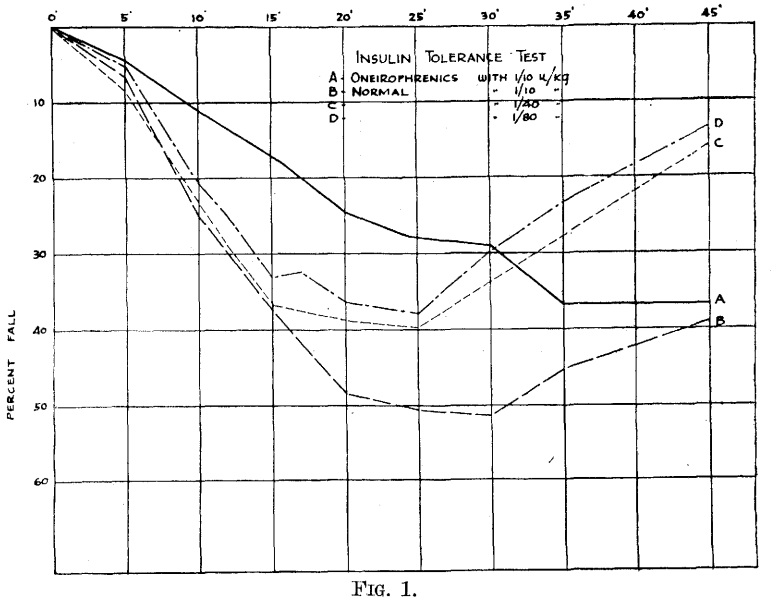


FIG. 1.

Insulin Tolerance Test in Oneirophrenics and Normals. Mean % fall of reducing substance of the blood in oneirophrenics (A) and in normals, showing early divergence and normal lack of dose sensitivity for the first 15 minutes, with doses of (B) 1/10, (C) 1/40, and (D) 1/80 u/kg.

TABLE I.

| | Subject | Dose | 15′ | | 20′ | | 25′ | | 30′ | |
|---|---|---|---|---|---|---|---|---|---|---|
| A | Oneirophrenic | 1/10 u/kg | 16.8 | σ 7.6 | 24.3 | σ 9.8 | 27.6 | σ 4.4 | 29.8 | σ 8.9 |
| B | Normals | 1/10 " | 37.6 | σ 10.1 | 48.4 | σ 9.5 | 50.6 | σ 8.8 | 51.7 | σ 9.2 |
| C | " | 1/40 " | 36.8 | σ 9.3 | 38.8 | σ 9.0 | 39.8 | σ 9.0 | 33.5 | σ 9.6 |
| D | " | 1/80 " | 33.0 | σ 7.0 | 36.3 | σ 7.8 | 37.8 | σ 7.6 | 29.0 | σ 6.9 |
| | | | t | P | t | P | t | P | t | P |
| AB | | Fisher's t | 7.75 | <.01 | 8.2 | <.01 | 7.0 | <.01 | 8.1 | <.01 |
| AC | | and prob. | 7.5 | <.01 | | | | | | |
| AD | | | 6.87 | <.01 | | | | | | |

fall in percent of fasting is approximately equal to the mean fall in mg %. The present data was obtained and charted by his methods.

The following curves are based on the first 20 to 25 cases in which the diagnosis of the patient was certain, the health of the control assured, the technic faultless and the data available for computation at the time this material was organized. Cursory examination of more than 300 records has indicated no important exceptions.

Fig. 1A is based on Meduna's data and shows the mean blood-sugar level at various times during the first 45 minutes after injection of 0.1 unit insulin per kg body weight in his first 21 reported tests of oneirophrenics. Fig. 1, B, C, and D are the same for healthy controls receiving that standard dose and ¼ and ⅛ of it respectively. These 3 normal curves are similar for the first 15 minutes and all fall far faster than the oneirophrenic at that time.

Table I gives the mean falls, the standard deviations, Fisher's "t" and the probability that the difference between the means is due to chance at the 15th, 20th, 25th and 30th minutes. From this it is clear that oneirophrenics differ significantly from normals through the 30th minute after which normals rise while some oneirophrenics continue to descend.

Table I also shows the lack of any reliable difference between the 3 groups of controls during the first 15 minutes, indicating that the rate of fall is independent of the dose

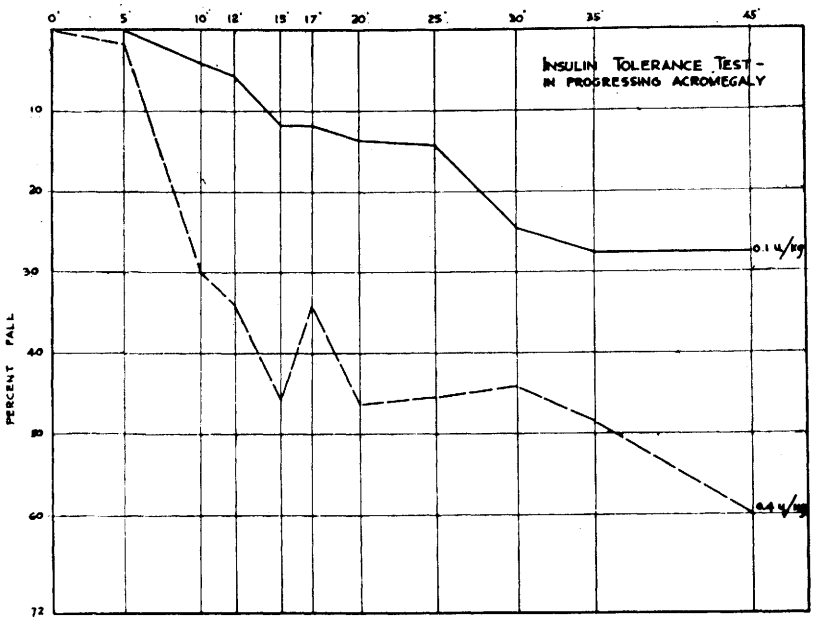


FIG. 2.
Dose Sensitivity in Acromegaly. Insulin tolerance curves in % fall of reducing substances of blood after 0.1 u/kg showing resistance but rapid fall and spike on descending limb after 0.4 u/kg.

which yet determines the nadir.

Finally, Table I shows that at the 15th minute the differences between oneirophrenics and normals receiving 1/8 as much insulin is still significant. In a few cases we have given 8 times the dose to oneirophrenics and found that, though it made the blood-sugar fall farther, it fell no faster. Obviously, therefore, in a clinical test one should use the early part of the test where a gross error in dose is insignificant.

Of many nondiabetic, medical and surgical conditions tested for increased resistance to insulin only one group of malignant hypertensives and the progressive acromegalic have shown resistance. The latter (Fig. 2) are interesting because the resistance can be exceeded by increasing the dose and then there may appear an exaggeration of the bump on the descending limb. Similar exaggerations have appeared following sundry operations on the brain.

The time at which this upward inflection occurs varies from the 12th to the 17th minute. A third of the bumps are actual spikes, a third are levels and a third are only decreased rates before the final, fast drop to the nadir. It is absent in less than one-tenth of normals and one-third of oneirophrenics, but it is frequently missed with 5-minute sampling and its temporal scatter averages it out in the mean curve except with the smallest dose. The mean value of the difference between the preceding and subsequent low and the mean highest value of the bump exceeds twice the mean error of the method and hence the probability that the bump is due to chance is negligible.

It is an increment in glucose. It is present in arterial blood. It occurs with all varieties of American insulin and with Danish insulin having no hyperglycemic factor. It is present in diabetis mellitus, Addison's disease, malignant hypertension, and after sundry insults to the brain. It is not prevented by terror or atropine, by sympathectomy or supradiaphragmatic vagotomy, by advanced disease of the liver or by splenectomy. It is not preceded or accompanied by any signs of autonomic change in EEG, EKG, blood pressure, respiration, pupillary diameter or dorsal skin potential. Presumably it is due to some as yet undiscovered mechanism counteracting some effect of insulin. Fortunately

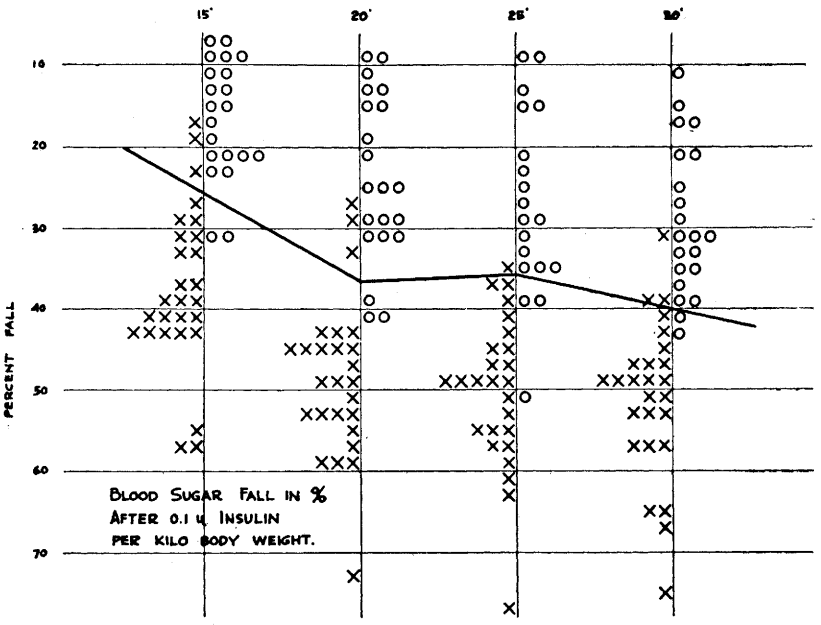


FIG. 3.
Scattergram for Use with Brief Insulin Tolerance Test. Scattergram of oneirophrenic, O, and normal, X, % fall from fasting of reducing substances of the blood.

it is not violent enough to prevent separation of oneirophrenics from normals.

Although in a given normal the blood-sugar may fall as fast and as far with an 80th as with a 10th unit insulin per kg body weight, the signs of so-called hypoglycemic shock—faintness, trembling, sweating, cardiac acceleration, and pupillary dilation—are minimal or absent. This would incline one to use the smaller dose, but as the law forbids sale of insulin at less than 20 units per cc one has to make up fresh sterile solutions for measurable doses, and many neurotics are resistant to it though they react normally to the regular dose. As the separation between oneirophrenics and normals is equally certain from the 15th through the 30th minute, only time is conserved by early sampling; but at the 15th minute the blood-sugar is falling 5 mg per minute in the normal which means that the timing must be accurate and venous return unobstructed. It is easier to note the exact time at which a sample is drawn than to draw it at a prescribed moment.

The following procedure, therefore, is recommended. The fasting sample is taken, then 0.1 unit insulin per kg body weight is injected intravenously. One or two samples are then taken between the 15th and 30th minutes and the time noted accurately. The patient may then be given sugar if desired. The total reducing substance is determined in each sample as noted above. If the fasting value differs significantly from 100 mg %, the falls are expressed in per cent of fasting; if not, they are left as mg %. Any such fall from fasting and the time after injection of insulin can then be compared with Fig. 3. This is a scattergram showing the distribution of oneirophrenics and normals on which is drawn one line running through those points at which a given value is as likely to be found in an oneirophrenic as in a normal. Inasmuch as the overlapping of the scattergrams is due to different mechanisms in the beginning and end of this interval, and no individual curves have been found to have more than one point across the line, 2 samples on either side of the line enhance the certainty of diagnosis. The chance of an erroneous diagnosis is, in fact, less than the product of chances for the 2 separately.

*Summary.* For the first 15 minutes the rate of fall in reducing substances in the blood

expressed in per cent of fasting value is not much affected by decreasing the size of the intravenous dose of insulin below 0.1 u/kg or by increasing it in oneirophrenics. At 15 minutes the separation is statistically valid despite a bump of unknown significance on this descending limb of the curve. Therefore, it is possible, in patients suspected of oneirophrenia, to estimate the resistance to insulin with a statistical validity as great as can be obtained from much longer tests.

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## Thiouracil in the Treatment of Leukemia.

O. C. HANSEN-PRUSS. (Introduced by W. A. Perlzweig.)

*From the Department of Medicine, Duke University Medical School.*

It has been observed that patients with leukemia may show many of the clinical features of hyperthyroidism, such as nervousness, tachycardia, decreased cholesterol in the blood, and increased metabolic rate. Temporary improvement may result from the rational use of Lugol's solution.[1-3]

During the past 15 years, 175 patients with various types of leukemia have been studied in this clinic. The disease remained stationary or progressed slowly as long as the cholesterol level was above 150 mg %, but progressed rapidly when the cholesterol values fell below 100 mg %.

The cholesterol levels appeared to be influenced by the absolute number of extremely immature forms and not by the total number of circulating leukocytes. The cholesterol levels decreased as the number of immature forms increased, but in one group of 15 patients who progressed rapidly to a fatal end, with extensive systemic and visceral myeloblastic proliferation, the total counts were slightly elevated, normal or reduced, and the absolute number of myeloblasts small, yet the cholesterol levels were constantly below 100 mg %.

In remissions induced by X-ray therapy, the serum cholesterol values were uniformly above 150 mg %, and as the patients became resistant to the X-ray, the cholesterol levels fell.

There was no constant relationship between the basal metabolic rate, the serum cholesterol values and the prognosis.

It seemed desirable to determine whether the administration of thiouracil would increase the serum cholesterol levels and improve the patient's symptoms.

*Case 1.* S.K., white female, age 29 years with chronic myelogenous leukemia. The disease was apparently in its second year when it was recognized in 1940. Between October 1940 and June 1945, she received several series of X-ray treatments. These were given by spray and locally over the spleen. (These treatments totalled 1100 R. by spray and 1950 R. over the spleen). She experienced several striking clinical and hematological remissions. The last X-ray treatment was on June 5, 1945. The subsequent events are summarized in Table I.

This patient received 1.5 g of thiouracil a day over a period of 60 days, or a total of 90 g. She tolerated the drug quite well. She had an irregular, intermittent fever which was present before the administration of thiouracil was begun and persisted thereafter. At first, she seemed clinically improved; she felt stronger and the hemoglobin and red cell levels rose temporarily. The circulating leucocyte count fell precipitately during the first 24 hours after the drug was given, but

[1] Friedgood, H. B., *Am. J. Med. Sc.*, 1932, **183**, 515.

[2] Williams, R. H., and Bissel, G. W., *New Eng. J. Med.*, 1943, **229**, 97.

[3] Atwood, E. B., *J. A. M. A.*, 1943, **122**, 78.