

shown by ORD and STOCKEN⁴. One of the largest accumulations is of deoxycytidine which has been shown by PARIZEK *et al.*⁵ to be excreted in urine in direct proportion to ionizing radiation.

The hormonal inhibition of mitosis by corticosteroids as a result of radiation suggests that cortisone is an adjuvant to radiation in achieving this end and exogenous cortisone used in treating the radiation syndrome should not detract from the therapeutic radiation effect.

Animals with intact adrenals tolerate radiation better as shown by many workers, but this study demonstrates considerably less nuclear degeneration in normal rats than in those adrenalectomised.

My thanks are due to Professor J. S. MITCHELL for advice and encouragement, to Dr. K. A. MUNDAY, University of Southampton for facilities and kindness during part of this work and to Miss N. BURR for histological assistance.

J. T. HEMINGWAY

Department of Radiotherapeutics, University of Cambridge, December 1, 1958.

Résumé

La vitesse de régénération du foie chez le rat surrénal-ectomisé, irradié, est comparée à celle du rat normal radio-protégé, afin d'établir si la sécrétion des corticostéroïdes est en partie responsable de l'inhibition de la mitose provoquée par la radiation.

Dans le présent travail, il est démontré que le rat surrénal-ectomisé possède une vitesse de mitose quatre fois supérieure à celle du rat normal, et ceci malgré d'importants dégâts causés au foie par la radiation.

⁴ M. G. ORD and L. A. STOCKEN, *Biochem. biophys. Acta* 29, 201 (1958).

⁵ J. PARIZEK, M. ARIENT, Z. DIENSTBIER, and J. SKODA, *Nature* 182, 721 (1958).

A Contribution on the Mode of Action of D 860

From many reports it is known that hypoglycaemic sulphonylurea compounds are ineffective in depancreatised dogs, rabbits, rats, toads and man, in rabbits and rats with severe alloxan diabetes, and in some severe forms of human diabetes. These facts support the hypothesis which explains the mechanism of the action of hypoglycaemic sulphonylurea compounds in terms of stimulating the beta cells of the islets of LANGERHANS to increased insulin secretion¹, or by enhancing the action of endogenous insulin^{2,3}. Diabetic animals, however, do differ from normal not only in the absence of beta-cells but also in a high glucose concentration in the extracellular fluid. In the present paper we are therefore concerned with the problem of the effect of D 860 on intact rats with hyperglycaemia induced by the exogenous administration of glucose.

Method. Wistar rats were used, weighing 200–300 g and fed on a standard diet, containing 25% protein, 20% fat and 55% carbohydrate (LARSEN's diet). Hyperglycaemia was induced by subcutaneous administration of

glucose, 180 mg/100 g of body weight, spaced over 20 min intervals, in three fractional doses. In order to avoid any uncontrollable loss of glucose in the urine, the ureters were ligated bilaterally under ether anaesthesia 1 h before the

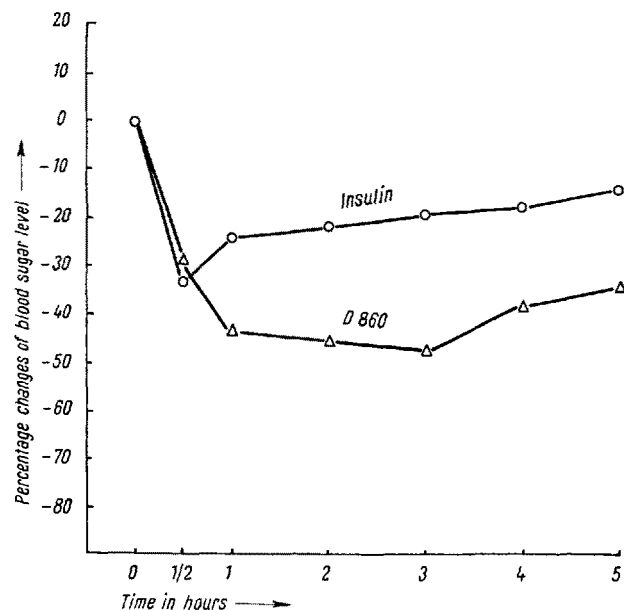


Fig. 1.—Percentage changes in blood sugar levels in rats with a normal initial value ($104.7 \pm 5.26^*$ and 103.4 ± 4.86 mg% after a single intravenous injection of 0.2 u. insulin, and an intravenous injection of 150 mg D 860/per kg body weight). * S.E. of mean.

experiment was begun. 2 h after the last dose of glucose, physiological saline was given intravenously to the first group (5 animals); to the second group (5 animals) 0.2 u. insulin (Novo)/kg of body weight was given; to the third group (6 animals) we administered 150 mg/kg D 860 (Artosin, Boehringer) as sodium salt intravenously. To the fourth group (6 animals), insulin 0.2 u. plus D 860 150 mg/kg of body weight was given intravenously. In two groups of intact rats (7 animals) with a normal blood sugar level, we tested the hypoglycaemic action of insulin and D 860. Blood sugar was estimated by a modification of the Somogyi-Nelson method (FRANK and KIRBERGER, 1950).

Results. Changes of the blood sugar level after a single dose of 0.2 u. insulin/kg body weight or 150 mg D 860 are shown in Figure 1. The maximum decrease in the blood sugar level after insulin occurs after half an hour, and subsequently it returns slowly to the initial level. After the administration of D 860 the blood sugar level decreases by 45%; the fall in blood sugar still being marked and statistically significant ($P < 0.001$) 5 h after injection. Figure 2 shows the percentage changes in blood sugar levels after a glucose load. In rats with a normal blood sugar, D 860 caused a drop in blood sugar of 45%. In animals with an initial hyperglycaemia, the same dose leads to a slowing down of the rate of return to normal values. 5 h after the administration of D 860, the blood sugar level is 108% higher than in the group after injection of physiological saline. A single dose of 0.2 u. insulin/kg body weight in animals with an initial hyperglycaemia leads to a more rapid return of the blood sugar to normal. The changes of the blood sugar level after the administration of insulin and D 860 is practically the same as after insulin alone. The blood sugar value after 5 h in the D 860 group was 357 ± 61.1 mg%; in the control group 164 ± 36.8 mg%; in the insulin group 127 ± 21.6 mg%;

¹ A. LOUBATIÈRES, *Ann. N. Y. Acad. Sci.* 71, 192 (1957).

² F. FRAWLEY, S. SEGAL, M. M. CAMUS, and J. FOLEY, *Ann. N. Y. Acad. Sci.* 71, 81 (1957).

³ A. MIRSKY, G. PERISUTI, and R. JINKS, *Proc. Soc. exp. Biol. Med.* 91, 475 (1956).

and in the group given insulin and D 860 134 ± 19.2 mg%. The difference of mean of the D 860 group as compared with other groups is statistically significant ($P = 0.02$, $P < 0.02$, $P < 0.01$).

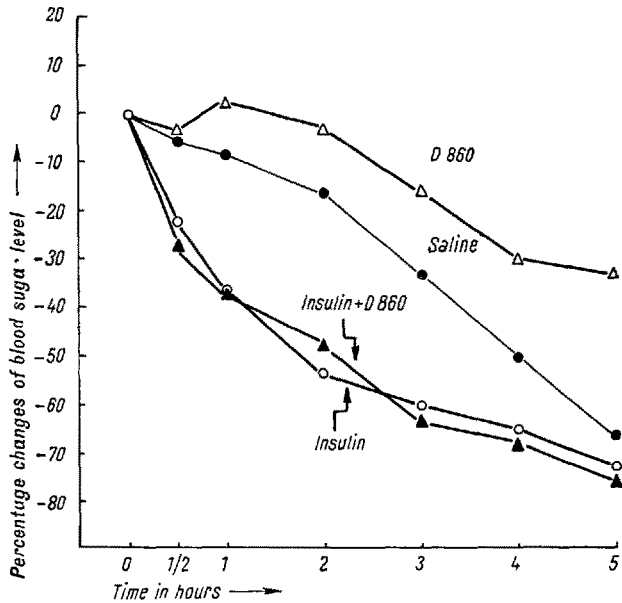


Fig. 2.—Percentage changes in blood sugar levels in rats after a glucose load with initial hyperglycaemia (480 ± 36.2 , 402 ± 29.7 , 504 ± 34.6 , 466 ± 30.1 mg%) and a single intravenous injection of physiological saline, 0.2 u. insulin, 150 mg D 860, 0.2 u. insulin plus 150 mg D 860 (per kg body weight).

Discussion. Hyperglycaemia caused by the administration of glucose leads to degranulation of the beta cells of the pancreas within 15 min⁴, which is generally regarded as an indication of increased activity. From our experiments, it is apparent that D 860 did not potentiate the effect of endogenous insulin. It is further obvious that under these experimental conditions no potentiation of the effect of exogenous insulin occurs. The 'paradoxical' effect of D 860 is marked in a single dose which cannot be regarded as toxic. The mechanism of this effect has so far not been elucidated and will be investigated in the future.

It appears, however, that the changes in carbohydrate metabolism after the administration of D 860 and related compounds depend to a great extent on the actual metabolic state of the organism and on the functional activity of peripheral tissues and the liver. From our experiments, it also appears that the ineffectiveness of oral antidiabetics in diabetic animals may be due to hyperglycaemia *per se*. Under these circumstances, we found the effect of insulin and D 860 distinctly different.

T. BRAUN, B. MOSINGER, and V. KUJALOVÁ

Institute of Human Nutrition, Physiological Department, Prague (Czechoslovakia), January 19, 1959.

Zusammenfassung

Es wird auf die Unwirksamkeit von D 860 bei Ratten hingewiesen, bei denen 2 h vor Verabreichung von D 860 Hyperglykaemie durch parenterale Verfütterung von Glukose hervorgerufen wurde. Die Hypothese wird ausgesprochen, dass Hyperglykaemie einer der Faktoren sein könnte, die die Unwirksamkeit des Sulphonylharnstoffes bewirken.

⁴ C. A. PETERSON, Proc. Soc. exp. Biol. Med. 70, 352 (1949).

Hormonale Beeinflussung des Stoffwechsels bei *Carcinus maenas*

Verschiedene Autoren stellten fest, dass bei Krebsen die Grösse des Sauerstoffverbrauches in den einzelnen Phasen des Häutungszyklus verschieden ist. Ergebnisse an einigen Krebsarten lassen darauf schliessen, dass in den neurosekretorisch tätigen Zellen des X-Organes der Augenstiele ein häutungsverhinderndes Hormon gebildet und in den Sinusdrüsen gespeichert wird. Nach Augenstielexstirpation zeigen sich vorzeitige Häutungen; in einigen Fällen wurde zugleich ein Anstieg des Sauerstoffverbrauches beobachtet. Die bisher gefundenen Resultate waren jedoch zum Teil recht unterschiedlich (DARCH¹, SCUDAMORE², BLISS^{3,4}, SCHEER und SCHEER⁵).

Die erwähnten Untersuchungen lassen nicht eindeutig erkennen, ob die Erhöhung des Sauerstoffverbrauches unmittelbar, das heisst durch die Augenstielexstirpation, oder durch einen Anstieg der Bewegungsaktivität während des Häutungsvorganges bedingt ist. Darum wurden an *Carcinus maenas*, an denen meines Wissens noch keine derartigen Untersuchungen durchgeführt wurden, zur Klärung der hormonalen Verhältnisse weitere Experimente gemacht.

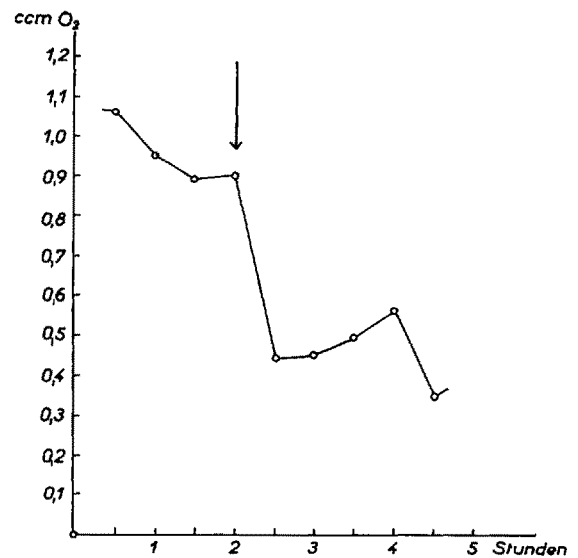


Abb. 1 Der Einfluss von Augenstielextrakten auf die Sauerstoffaufnahme von *Carcinus maenas* (Injektion ↓). Jeder Punkt der Kurve entspricht einer Messung.

Der Sauerstoffverbrauch der Versuchs- und Kontrolltiere wurde halbstündig nach der Methode von WINKLER bestimmt. Die Tiere wurden bei einer Temperatur von 12°C gehalten. Nach Feststellung der normalen Durchschnittswerte durch mehrere Messungen wurden die Versuchstiere mit Extrakten aus Augenstielen und die Kontrolltiere mit Seewasser injiziert. Ein Versuchsbeispiel bringt die folgende graphische Darstellung (Abb. 1). Wie hieraus ersichtlich ist, senkte die Injektion von Augenstielextrakten den Sauerstoffbedarf. Die zu gleicher Zeit mit Seewasser injizierten Kontrolltiere hingegen ver-

¹ P. DARCH, Biol. France Belg. 78, 40 (1944).

² H. H. SCUDAMORE, Physiol. Zool. 20, 187 (1947).

³ D. E. BLISS, Anat. Rec. 111, 502 (1951).

⁴ D. E. BLISS, Biol. Bull. 104, 275 (1953).

⁵ B. T. SCHEER und M. A. R. SCHEER, Pubbl. Staz. Zool. Napoli 25, 419 (1954).