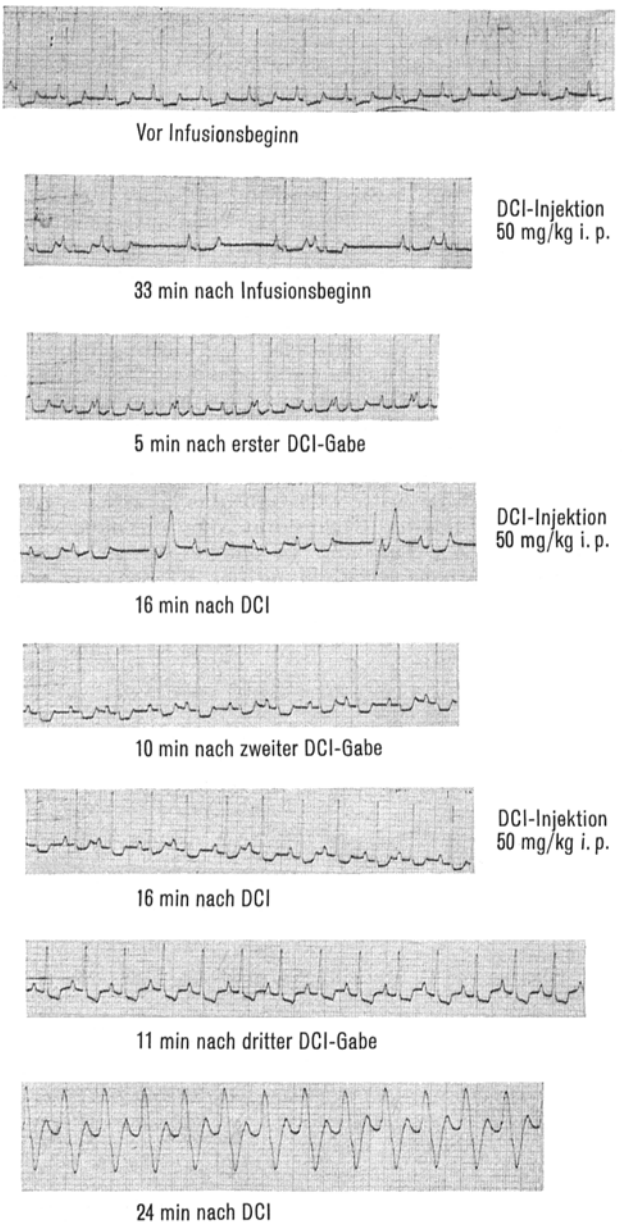
EKG-Veränderungen beim Meerschweinchen unter Infusion von g-Strophanthin $6 \cdot 10^{-5}$ g/ml und wiederholter intraperitonealer Injektion von Dichlorisoproterenol 50 mg/kg. (Versuch vom 4.6.1963, Ableitung II.)



schwache DCI-Einwirkung auf die pathologischen EKG-Zeichen beobachten.

DHE beeinflusste die Infusionstoxizität von g-Strophanthin nicht ($P > 0{,}2$). Ohne DHE ermittelten wir eine LD_{100} von 0,298 mg/kg ($n = 15$), mit DHE eine LD_{100} von 0,326 mg/kg ($n = 15$). In keinem Fall war eine deutliche EKG-Verbesserung festzustellen.

Diskussion. Unsere Befunde zeigen, dass auch bezüglich der Beeinflussbarkeit durch DCI Unterschiede zwischen den einzelnen Glykosiden bestehen. Eine Verminderung der Toxizität ist zum Beispiel bei Digoxin und Digitoxin nicht zu erzielen. Über die Ursache dafür lässt sich noch nichts aussagen[15]. Im Zusammenhang mit früheren Untersuchungen[16], in denen wir fanden, dass Calcium nicht bei allen Glykosiden den Digitaliseffekt potenziert, sehen wir in den Ergebnissen mit DCI eine weitere Bestätigung unserer Arbeitshypothese[17–20] von Unterschieden im Wirkungsmechanismus verschieden strukturierter Herzglykoside.

Des weiteren lassen sich durch unsere Befunde einige der Widersprüche in den Literaturangaben erklären: MORAN und PERKINS sahen in ihren Versuchen an Hunden, wie wir an Meerschweinchen, keinen sicheren Einfluss von DCI auf die Digoxinwirkung. Dagegen war in den Untersuchungen von TANZ, LUCCHESI und HARDMANN sowie MORAN et al. bei Verwendung von Ouabain ein DCI-Effekt nachweisbar[21].

Summary. In experiments of infusion made on guinea-pigs, Dichlorisoproterenol was injected after the appearance of the first symptoms of toxicity in the ECG. It reduced the toxicity of convallatoxol, g-strophanthin and lanatosid C, but it was not quite effective against digoxin and digitoxin.

W. SZIEGOLEIT und W. FÖRSTER

Pharmakologisches Institut der Medizinischen Akademie, Magdeburg (DDR), 23. September 1963.

[15] Während der Drucklegung durchgeführte Versuche mit Alderlin (3×70 mg/kg) führten auch bei Digitoxin zu einer signifikanten ($P = 0{,}02$) Abschwächung der letalen Wirkung.
[16] W. FÖRSTER und M. LINDENAU, Klin. Wschr. *41*, 339 (1963).
[17] W. FÖRSTER, Habilitationsschrift Medizinische Akademie Magdeburg (1961).
[18] W. FÖRSTER und W. SZIEGOLEIT, Exper. *18*, 573 (1962).
[19] W. FÖRSTER, Exper. *19*, 260 (1963).
[20] W. FÖRSTER, Arch. int. Pharmacodyn., im Druck.
[21] Wir danken Herrn P. KAPLANSKI für seine verständnisvolle Mitarbeit.

The Duration of Action of Certain Corticosteroids in the Acutely Adrenalectomized Rat as Estimated by Reference to their Protective Effect in Endotoxin Shock

The fact that corticosteroids are capable of affording protection against lethal shock produced by endotoxin has been demonstrated in different animal species by various investigators[1–7]. GASS and UMBERGER[3] have proposed survival time in endotoxin-treated rats as a response metameter for corticotropin and hydrocortisone bioassay; however, no report is known in which an 'all-or-nothing' reaction, i.e. survival following an otherwise lethal endotoxin dosage in animals treated prophylactically with corticoids, has been used as a means of measuring the duration of effect of the corticosteroids thus administered. The following is an account of experiments in which the protective effect of hydrocortisone and prednisolone was evaluated in adrenalectomized rats which were pretreated at varying times prior to being shocked at a fixed interval following adrenalectomy.

Methods and Materials. Male rats of a mean body weight of 170–210 g were adrenalectomized under light

ether anaesthesia using the dorsolateral approach; the operation was performed within less than 5 min, and the animals recovered from the anaesthesia within 10–15 min. Hydrocortisone and prednisolone (in the form of the water-soluble sodium hemitetrahydrophthalate) were injected intraperitoneally in varying amounts into groups of 10–20 animals per dose at intervals ranging from 7 to 24 h following adrenalectomy. Endotoxin (*Serratia marcescens* lipopolysaccharide[8]) was injected intravenously in an amount (100 μg/kg) which proved lethal in 100% (65 out of 65) of the untreated controls challenged 24 h after removal of the adrenals. Only animals still alive 40 h after administration of the endotoxin were recorded as having been protected from lethal endotoxin shock.

Results. The results are summarized in Figures 1 and 2. It is shown that prednisolone affords protection with as low a dosage as 1 mg/kg, the effect being almost identical regardless of whether the compound is administered 1 or 3 h before the endotoxin. With a dose of 3 mg/kg of prednisolone total or nearly total protection is obtained when the corticosteroid is given either simultaneously with, or 1 h before, the endotoxin; extending the interval to 3 h results in a survival rate of slightly more than 60%; after 17 h, 3 mg/kg prednisolone fails to display any protective activity at all. In order to obtain protection when the interval is 17 h, the dosage of prednisolone has to be increased to 30 mg/kg. Clearly, as the time elapsing between prednisolone treatment and endotoxin injection increases, larger amounts of the corticosteroid are needed to obtain comparable survival rates. Somewhat similar effects were observed when hydrocortisone was used instead of prednisolone, although there were two obvious differences: (a) with hydrocortisone the dose affording roughly 50% protection when administered simultaneously with, or 1 h before, endotoxin is some 5–10 times higher than that of prednisolone, and (b) protective activity subsides at a faster rate than with prednisolone.

Protective effect of prednisolone and hydrocortisone in the adrenalectomized rat.

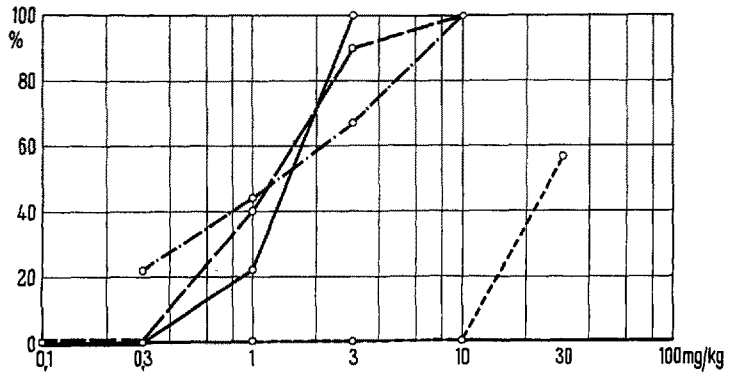


Fig. 1. Prednisolone.

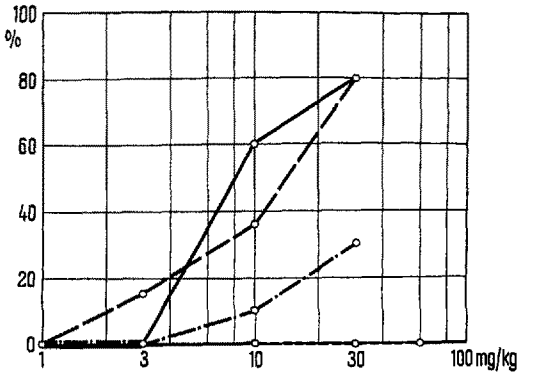


Fig. 2. Hydrocortisone.

Ordinate: Survival (%); each point represents the mean for 10–20 animals. – Abscissa: Dose of steroid (mg/kg, i.p.). – Interval between injection of steroid and challenge with endotoxin: o——o = 0 min, o– – –o = 60 min, o–·–·–o = 180 min, o·····o = 17 h.

Zusammenfassung. An der nebennierenlosen Ratte wurde die Dauer des Schutzeffektes von Prednisolon (P) und Hydrocortison (H) gegenüber letalem Endotoxinschock bestimmt. P war 5–10mal wirksamer als H; ebenso hielt der Schutzeffekt von P 5–10mal länger an als derjenige von H.

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Forschungslaboratorien der CIBA Aktiengesellschaft, Basel (Switzerland), January 17, 1964.

[1] H. J. Bein and R. Jaques, Exper. *16*, 24 (1960).
[2] M. S. Brooke, O. Hechter, and E. H. Kass, Endocrinology *69*, 867 (1961).
[3] G. H. Gass and E. J. Umberger, Proc. Soc. exp. Biol. Med. *100*, 127 (1959).
[4] R. D. Higginbotham, J. Allergy *33*, 35 (1962).
[5] H. Levitin, M. I. Kendrick, and E. H. Kass, Proc. Soc. exp. Biol. Med. *93*, 306 (1956).
[6] W. W. Spink and J. Vick, Circulat. Res. *9*, 184 (1961).
[7] M. H. Weil, Amer. Practit. *12*, 162 (1961).
[8] Kindly placed at our disposal by Dr. M. J. Shear, National Institutes of Health, Bethesda, Md.
[9] Present address: The J. Hillis Miller Health Center, Department of Microbiology, University of Florida, Gainesville (Florida, U.S.A.).

PRO EXPERIMENTIS

Measurement of Glass Microelectrodes

The necessity of using very sharp electrodes to study the electrical properties of the cellular membrane brought about extensive utilization of electrolyte-filled glass microcapillaries during the last twelve years. Ling and Gerard[1] and Nastuk and Hodgkin[2] reduced the diameter of the tip of the glass microelectrodes to about 0.5 μ to measure the cellular transmembrane potentials. Nastuk and Hodgkin[2] studying some of the physical properties of the glass microelectrodes, first used electron

[1] G. Ling and R. W. Gerard, J. cell. comp. Physiol. *34*, 383 (1949).
[2] W. L. Nastuk and A. L. Hodgkin, J. cell. comp. Physiol. *35*, 39 (1950).