maximalen Dicke von 800–1000 Å[9,18] lichtmikroskopisch nicht auflösbar; daraus resultiert ein vergleichsweise homogenes Bild der Fasern. Ordnen sich beim Übergang in den Sperrtonus oder bei pH 8,5 die dicken Filamente um und aggregieren teilweise miteinander, so entstehen scheinbar neue Einheiten, deren Durchmesser in der Grössenordnung des lichtmikroskopischen Auflösungsvermögens liegt und die als streifige Struktur in der Faser erkennbar werden. Diese Umordnung und Aggregation wird offenbar durch die mit 5-HT oder bei pH 8,5 bewirkte Erschlaffung wieder rückgängig gemacht, so dass das Aussehen der Faser homogen wird. Durch Aggregation dicker Paramyosinfilamente würde bei «Einschalten» des Sperrtonus ein hochgradig dehnungsresistentes System geschaffen, das Kontinuität über die ganze Faser besitzt und für den Serotonin- beziehungsweise pH-abhängigen hohen Dehnungswiderstand des gesperrten Muskels verantwortlich ist[7]. Für eine solche Interpretation spricht auch die Aggregation von gelöstem Paramyosin bei pH 6,5[19] und die analoge pH-Abhängigkeit des Dehnungswiderstandes von künstlichen Proteinfäden[11] aus Paramyosin[20].

Summary. Surviving muscle fibres of a molluscan smooth muscle (ABRM) in 'catch' exhibit a characteristic pattern of longitudinal stripes when examined with the NOMARSKI technique (Differential interference contrast). The pattern appears to be due to aggregated paramyosin-filaments; it disappears after abolishing the catch with 5-hydroxytryptamine or – in freeze-dried preparation – after raising the pH of the ATP-salt solution.

T. SCHUMACHER

Institut für Zellphysiologie
der Ruhr-Universität Bochum,
D-463 Bochum-Querenburg (Deutschland),
14. *November 1969.*

[18] J. HANSON und J. LOWY, Nature *184*, 286 (1959).
[19] W. H. JOHNSON, J. S. KAHN und A. G. SZENT GYÖRGYI, Science *130*, 160 (1959).
[20] Herrn Prof. Dr. J. C. RÜEGG schulde ich grossen Dank für die Anregung zu dieser Arbeit und für viele lehr- und hilfreiche Diskussionen.

Protective Effect of Ferric Dextran on the Embryopathic Action of Indium

The interaction of indium and ferric dextran in biological systems was first described by GABBIANI et al.[1]. They noted the remarkable protective effect of this iron compound on the severe hepatic damage induced in rats by indium. In addition, ferric dextran completely protected the animals from acute indium intoxication. Following the description of the profound embryocidal and site-specific teratogenic effects of indium nitrate on hamster embryos[2], further investigation of the interaction of indium and ferric dextran (Imferon) upon the developing mammalian embryo seemed desirable.

Materials and methods. These experiments utilizing ferric dextran were identical to previous studies utilizing lead, cadmium and arsenic in teratological investigations[3–5]. In essence, female hamsters in estrus were placed with breeding males overnight and separated the next morning. The day of separation was considered to be the first day of gestation. On the eighth day of gestation the pregnant animals were anesthetized with 6.5 mg/100 g body weight of sodium pentobarbital i.p. and then injected i.v. with varying amounts of indium nitrate (Table) made up so that the volume of the total dose of metal was 0.5 ml/100 g of body weight. Other groups, injected with identical amounts of indium nitrate i.v. under the same conditions, also received 50 mg of ferric dextran (Imferon) i.p. at the same time. The embryos were collected on either the 14th or 15th day of pregnancy. Resorption sites were counted at this time and all embryos were examined for gross external congenital malformations.

Results. It is apparent from the Table, as well as from previous data[3], that increasing the dosages of indium caused an increase in embryonic mortality. Likewise, the number of malformed limbs increased with higher levels of indium. Since all 4 limbs from each animal were possible teratogenic targets the percentage of malformed limbs was calculated on the basis of the total number of limbs in each group, i.e., the number of living embryos times 4.

The administration of 50 mg of ferric dextran at the time of the indium injection had a dramatic effect upon fetal survival as shown in the Table. The incidence of malformed limbs also dropped appreciably. Treatment with ferric dextran did not, however, affect the type or severity of malformation in those few malformations which did occur in that group. The malformations in both groups consisted principally of stunting of the digits or absence of one or more of the digits. There did not appear to be any preferential site of teratogenic action in relation to any particular digit or to upper or lower limbs. There was no apparent effect of the indium treatment on the mothers during the course of this experiment.

Indium (mg/kg)	No. of mothers treated	Living embryos	Resorption sites	No. of limbs malformed[a]
0.5	7	82	0 (0%)	31 (9.4%)
1.0	5	28	29 (51%)	9 (8.0%)
2.0	6	23	52 (69%)	15 (16.3%)
Indium–Imferon (mg/kg)				
0.5/50	4	42	1 (2%)	0 (0%)
1.0/50	21	238	14 (5%)	5 (0.5%)
2.0/50	12	139	3 (2%)	20 (3.6%)

[a] Percentages of malformed limbs calculated as the number of malformed limbs divided by number of living embryos times 4 (see text).

[1] G. GABBIANI, H. SELYE and B. TUCHWEBER, Br. J. Pharmac. *19*, 508 (1962).
[2] V. H. FERM and S. J. CARPENTER, Toxic. appl. Pharmac., in press.
[3] V. H. FERM and S. J. CARPENTER, J. exp. molec. Path. *7*, 208 (1967).
[4] V. H. FERM and S. J. CARPENTER, Lab. Invest. *18*, 429 (1968).
[5] V. H. FERM and S. J. CARPENTER, J. Repr. Fertil. *17*, 199 (1968).

Discussion. The experimental teratogenic effects of certain metals have been demonstrated in the golden hamster[3–5], and the toxic properties of indium have been studied in the rabbit[6] and rat[7]. The protective effect of ferric dextran on the hepatic lesions induced by indium alone led to the suggestion that ferric dextran stimulates the formation of a PAS-stainable material wherever ferric dextran is deposited in tissues[1]. This material might account for this protective effect against indium-caused liver damage. The teratogenic protection afforded by ferric dextran might be quite specific for it is the only agent out of several investigated, which protects against indium-induced liver damage[1].

The protective effect of certain substances against the known teratogenic activity of other substances has been documented previously. Thus, LANDAUER and CLARK[8] have shown that malformations in chicks produced by treatment with 6-aminonicotinamide can be prevented with the simultaneous administration of 3-acetylpyridine. As far as metals are concerned, zinc protects against the teratogenic action of cadmium in hamsters[4], and selenium protects against the teratogenic effects of both cadmium and arsenic[9]. These observations suggest that further intensive investigations concerning the interactions of various molecular teratogens will yield interesting and valuable information concerning the morphogenesis of congenital malformations[10].

Zusammenfassung. Nach Indiumnitratinjektion bei Goldhamstern mit 8-tägiger Schwangerschaft wird eine erhöhte Mortalität der Embryonen sowie Gliedmassenanomalie gefunden. Bei gleichzeitiger Verabreichung von Eisendextran (Imferon) werden die Embryonalschäden weitgehend unterdrückt.

V. H. FERM

Department of Anatomy,
Dartmouth Medical School,
Hanover (New Hampshire 03755, USA),
27 November 1969.

[6] C. P. MCCORD, S. F. MEEK, G. C. HARROLD and C. E. HEUSSNER, J. ind. Hyg. Toxicol. *24*, 243 (1942).
[7] E. AUVERGNE, F. CAUJOLLE, J. OUSTRIN and M. C. VOISIN, Annls. Biol. clin. *24*, 739 (1966).
[8] W. LANDAUER and E. M. CLARK, J. exp. Zool. *151*, 253 (1962).
[9] R. E. HOLMBERG and V. H. FERM, Arch. env. Health *18*, 873 (1969).
[10] This work was supported by USPHS Grants No. HD02616 and No. HD03298 as well as a grant from Easter Seal Research Foundation of the National Society for Crippled Children and Adults, Inc.

Dermal Toxicity of DDT[1]

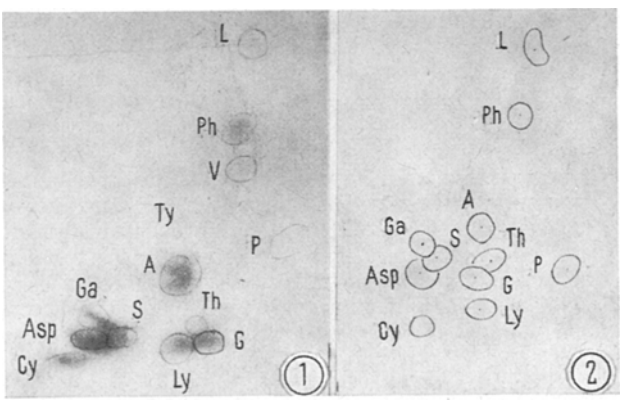
Various authors[2–9] in recent years have reported that the occupational poisoning by agricultural chemicals is more due to dermal absorption of the chemicals than to exposure by other routes. This indicates the degree of importance of the dermal toxicity studies and the amount of care and precautions needed in handling these chemicals. Among different insecticides, DDT perhaps ranks as the most extensively used and studied insecticide. Its application is diverse and well known. It is the best known, the cheapest and one of the most effective of the synthetic chlorinated hydrocarbon insecticides[10].

The present study has been made to show the biochemical alterations and the manner of damage that it may inflict on the cells of the skin tissue of guinea-pigs when applied dermally. There appears to be no literature on this point.

Materials and methods. ITRC bred guinea-pigs (body weight 350–400 g) were used throughout the experiment. The hair was removed on the latero-abdominal areas. DDT dissolved in absolute acetone was painted on those areas for a period of 3 weeks and 5 days in a week. The applied dosage of DDT ranged from 322 mg/kg to 400 mg/kg – a dosage 8–6 times less than the known acute dermal LD_{50} values for the female rats (Dermal LD_{50} values of DDT to female rats is 2,510 mg/kg). The animals of the control group received only the acetone painting for the same length of period. At the end of the experiment the animals were sacrificed and skin of the painted regions was removed and processed for the qualitative estimation of free amino acids according to the methods of AWAPARA[11]. Details of paper partition chromatography for the identification of free amino acids are reported elsewhere[12]. Histopathological observations of the skin tissue were also made with the help of paraffin sections, stained with iron haematoxylin and eosin.

Normal skin of female guinea-pigs contained the following free amino acids: alanine, aspartic acid, cysteic acid, glycine, glutamic acid, L/n-leucine, lysine, phenylalanine, proline, serine, threonine, tyrosine and valine. Of these, leucine, proline, serine, threonine, tyrosine and valine were present in 'trace' levels while the levels of the remaining amino acids were above normal. The significant changes in the relative concentration of the ninhydrin reacting constituents of the skin of the control and DDT-painted female guinea-pigs were very clearly detectable on the chromatograms (Figures 1 and 2). A tremendous decrease in the level of almost all amino acids of the skin was witnessed in the DDT-painted guinea-pigs.

WITTER and FARRIER[13] reported that DDT, when administered orally to albino rats, did not show any significant effect on levels of glutamic acid, alanine and



Figs. 1 and 2. Effect of DDT on free amino acids of guinea-pig skin; (1) control, (2) DDT-painted. A, alanine; Asp, aspartic acid; Cy, cysteic acid; G, glycine; Ga, glutamic acid; L, leucine; Ly, lysine; Ph, phenylalanine; P, proline; S, serine; Th, threonine; Ty, tyrosine; and V, valine.