These observations are significant in that inorganic lead ions are now known to cross the placental membranes of at least one mammalian species rapidly (within 15 min of i.v. injection) and in substantial amounts even at relatively low dosage levels (less than 3 mg/kg of maternal body weight in the group of animals receiving 20 μCi of $^{210}Pb(NO_3)_2$ only). Moreover, the demonstrated period of permeability to lead ions corresponded to the most critical stages of organogenesis in this species. These findings point up the hazard of even a low level of environmental contamination with inorganic lead since potentially even very small amounts of this metal entering the maternal blood stream can be transferred to the embryonic or fetal system. What constitutes a 'safe level' of lead in the blood plasma of mammalian species becomes even more of an equivocal question.

The exceptionally high levels of radioactivity observed in the membranes of the yolk sac placenta, particularly at the earlier postinjection intervals, suggests that in the hamster this is the route by which most lead ions are transferred from the maternal blood to the embryonic compartments. Only moderate levels of radioactivity were ever observed in the developing chorioallantoic placenta. This finding supports the contention of other investigators[21–23] regarding the preeminence of the yolk sac placenta in materno-embryonic transport during the early stages of gestation in many rodent species.

The generalized distribution of radioactive lead ions within the tissues of the exposed embryos was surprising in view of the highly specific teratogenic effect of this metal on the tail bud of this species[12–13]. In fact, lead is but one of several heavy metals[24] and numerous other chemical agents[25] that produce rather distinct patterns of developmental malformations in the embryos of hamsters treated during the teratogenically critical 8th day of gestation. The reason that lead ions exert a specific deleterious effect only on the developing tail bud tissues of the embryo and not to a detectable extent on the other rapidly developing organ systems to which they gain access during this period remains an interesting problem. It is possible that at this period of embryonic development this particular system has a special affinity and sensitivity to lead ions, i.e. there exists a specific organ: teratogen interaction. The suggestion[13] that lead ions interfere with a certain enzyme or enzyme system necessary for the normal development of the tail at this time merits further attention[26].

Zusammenfassung. Trächtigen Goldhamstern wurde am 7. und 8. Tag ^{210}Pb intravenös verabreicht. Von den Placentamembranen und vom Embryo wurde radioaktives Metallion stark aufgenommen und die Einlagerung autoradiographisch verfolgt.

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Palliative Effect of Gelatine in Benign Prostatic Hypertrophy

In the course of experimentation not relevant to the present report, it was observed that supplementation of the normal diet with a total daily amount of 25 g of gelatine (Knox Gelatine Inc., Johnstown, N.Y., 12095) given in 2–3 portions as a water suspension substantially relieves the distressing symptoms associated with benign prostatic hypertrophy. Burning and urgency disappear as the stream enlarges, and the frequency of micturition is reduced. Initially, these symptoms return promptly after the gelatine supplementation is discontinued. However, after gelatine is taken for 5–6 months, a few days discontinuation is no longer accompanied by as fast a return of the symptoms as in the beginning, and the daily dose may be reduced. The effects of gelatine are specific in that dietary supplementation with an equivalent amount of meat protein is without effect. Since these observations were peripheral to other objectives they were not followed up experimentally. The following is offered tentatively.

Ingestion of protein results in higher metabolic rate, an effect which is accompanied by increased body temperature and skin blood flow[1,6]. The specific dinamic action of protein is mainly due to a few amino acids, notably glycine, alanine, phenylalanine and tyrosine. Glycine, which constitutes about 25% of gelatine, induces a sustained increase of skin blood flow when taken orally[2]. It is not clear to what extent the increased skin perfusion induced by gelatine is due to the hydrolytically relesaed glycine. The effectiveness of gelatine in the treatment of split nails[3–6] appears to be linked to its circulatory effects.

The palliative effects of gelatine in prostatic hypertrophy are thought to be due to a reduction of prostatic edema, as this factor alone could account for the prompt amelioration of urinary distress. The benefits, if any, of prolonged improvement of drainage of prostatic acini remain to be determined.

Search of the literature revealed a report that a combination of glycine, alanine and glutamic acid is of value in the relief of urinary symptoms associated with benign prostatic hypertrophy[7]. Since relief was often associated with the disappearance of manifest edema, the authors concluded that disappearance of unirary distress and reduction in the size of the prostate were due to the diuretic action of their medication.

Our observations and conclusions are in line with those of Feinblatt and Gant[7], even though it remains to be demonstrated that the mechanism of action of the amino acid combination is identical with that of gelatine. Considerations of price, availability, palatability and

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improved physical fitness favor the latter as the agent of choice. The postulated reduction of edema points to a possible wider therapeutic usefulness of oral gelatine.

Another peripheral observation of dietary gelatine supplementation is that initially it is accompanied by a feeling of well being and greater physical stamina both of which seem unrelated to the amelioration of urinary distress. These subjective effects were observed by individuals who did not exhibit demonstrable protein or other dietary deficiency. The high glycine content of gelatine may be more readily linked to these effects since glycine may enter numerous synthetic pathways, including that of steroids. Feeding of gelatine has been reported to induce great physical output and work endurance, an effect attributed to a more rapid synthesis of creatine[8] and was believed to be beneficial in the management of patients suffering from muscular dystrophy[11]. However, glycine is not a precursor of creatine[9], even though its ingestion induces prompt creatinuria[9–11]. The report that feeding of gelatine does not increase muscular strength[12] does not necessarily negate the finding of decreased muscular fatigue and greater work output[8].

An interesting and possibly valuable clue regarding the mode of action of gelatine in benign prostatic hypertrophy is the observation that ingestion of this substance increased the work output of men by 37% to 240% above the control training level but was without effect in women[8].

Résumé. La consommation journalière de 25 g de gélatine soulage rapidement les symptomes urinaires accompagnant l'hypertrophie prostatique bénigne. La gélatine peut être trés utile dans le traitement de ce désordre.

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Selective Destruction of Adrenergic Nerve Terminals by Chemical Analogues of 6-Hydroxydopamine

After it had been shown that 6-hydroxydopamine (6-OHDA) selectively destroys adrenergic neurons (terminals only if given to adult animals, whole neurons if given to new-born animals), this drug became a widely used experimental tool for studying both peripheral and central adrenergic mechanisms (for references see[1]).

The synthesis of analogues of 6-OHDA was designed to discover even more effective compounds and to learn more about the possible mechanism of action by comparing the chemical structure and probable formation of reactive oxidation products with the effect on adrenergic neurons.

In a first series of experiments male Wistar rats, weighing 100–110 g, were injected i.v. with 2×0.25 mmoles of the various amines (Table) at an interval of 20 h. On account of a general high toxicity, the dosage of several amines had to be reduced to 2×0.125 mmoles. 4 h after the last injection the animals were killed, the heart and brain rapidly removed and homogenized in 0.4 *N* $HClO_4$. The norepinephrine (NE) content was determined according to previously described procedures[2,3]. Those analogues of 6-OHDA, which had produced a marked depletion of NE in the short-term experiments, were further investigated to evaluate their ability to produce a long-lasting NE depletion. The treatment was the same as in the short-term experiments but the animals were killed 7 days after the last dose. The determination of the NE content was extended to salivary gland, spleen and vas deferens, whereas that of the brain was omitted, since in the short-term experiments none of the compounds studied had produced a marked reduction of the brain NE content. Those compounds which produced a long-lasting NE depletion were also investigated for possible ultramorphological changes in the adrenergic nerve terminals. The treatment was the same as for the biochemical studies but the animals were killed 24 h after injecting the last dose of the drug. The processing of the tissue samples for electronmicroscopy was performed as described previously[4].

The following groups of compounds (synthetized by Dr. A. LANGEMANN and U. FISCHER, Chemical Research Department, F. Hoffmann-La Roche & Co. Ltd., Basel) were compared (Table): a) α-methyl-6-OHDA; b) analogues of 6-OHDA in which one of the phenolic OH-groups is replaced by $-OCH_3$, $-NO_2$ or $-NH_2$; c) analogues of 6-OHDA in which the H-atoms of the aromatic nucleus are replaced by either halogen or CH_3; d) analogues of 6-OHDA with the substitution pattern on the nucleus differing from the 2, 4, 5-type.

The introduction of an α-methyl group, rendering the amine resistant to metabolism by monoamine oxidase, did not markedly increase the potency of 6-OHDA. This is in agreement with the observation that in the periphery pretreatment with monoamine oxidase inhibitors does not increase the effect of 6-OHDA (unpublished results). However, in the brain the effect of intraventricularly injected 6-OHDA is markedly potentiated after inhibition of monoamine oxidase, particularly the effect on the dopaminergic neurons[5]. *O*-Methylated derivatives and diphenols (see Table, compounds Nos. 3 and 17) produced neither a short nor a long-lasting depletion of NE, most probably due to a lack of transport through the neuronal membrane of the adrenergic neuron. Of the 2 nitrodiphenols, only compound No. 5 produced a short-lasting depletion, whereas compound No. 6 was ineffective. This finding was rather unexpected, since at least a partial metabolic conversion into the corresponding amine-derivatives could be expected. These latter compounds (Nos. 7, 8, 9) were not only highly efficient depletors of

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