hydroxysteroids again demonstrates the reversibility of the Δ^5-3β-hydroxysteroid dehydrogenase-isomerase enzyme system[15,16]. The absence of significant label in the Δ^{16}-C_{19} steroid fraction of sweat was not surprising in view of the small incorporation into these steroids in urine[10].

Résumé. L'administration intraveineuse du prégnène-3β-ol-20-one[7α-^{3}H]-Δ^5 avec le progestérone[4-^{14}C] à un homme sain amena la sécrétion d'autant de radioactivité dans la sueur des aiselles que dans la plupart du reste du corps. Le prégnénolone-Δ^5, l'androstène-3,17-dione-Δ^4 et le déhydroépiandrostérone furent les principaux stéroïdes marqués identifiés comme partant des deux sources de sueur.

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Adrenocortical Lipoid Hyperplasia Induced in Rats by Aniline

While studying the toxic effects of various benzene derivatives we found that in rats treated with aniline (aminobenzene), the adrenal glands were markedly enlarged and bright yellow[1]. In order to verify this observation, a detailed morphological study of the adrenals of aniline-treated rats was undertaken.

The Table shows that aniline (J. T. Baker, Canlab, Montreal, Canada), given to female Sprague-Dawley rats (100 g) at a dose of 30 mg in 0.2 ml corn oil s.c. for 7 or 14 consecutive days, markedly increases the weight of the adrenal glands.

Histologically (Figure), the adrenal cortices were strikingly enlarged and the typical zonation became indistinct. The zona glomerulosa was almost indistinguishable except for small isolated areas where a few rows of swollen glomerulosa cells were still recognizable with some round PAS-positive hyaline droplets lying free in the extracellular spaces. The cortex consisted of cords of large polyhedral cells mainly of the fasciculata-type which, in several places, extended into the fibrous capsule. Lipoid droplets of various sizes filled the cytoplasm of these hypertrophied cells where some of them coalesced and became so large that they occupied almost the entire cytoplasm thus displacing the nucleus eccentrically and endowing the cell with a signet ring appearance. At some sites where cell membranes had ruptured, the lipoid droplets merged into cyst-like structures. Occasionally, empty needle-like formations were recognized. These obviously represented sites where cholesterol crystals had dissolved during the embedding process. Although lipoid accumulation was extensive throughout the cortex, it was more pronounced in the outer zona fasciculata where, in some places, the cells were markedly vacuolated. In other areas the cells were definitely swollen and had a granular, foamy and pale eosinophilic cytoplasm without being seriously vacuolated. The nuclei were usually dark, rich in chromatin and slightly pyknotic. As a result of marked cellular hypertrophy the sinusoids were compressed. Polymorphonuclear leukocytes and mononuclear cells were scattered throughout the cortex. This inflammatory reaction was mainly localized in the inner parts of the cortex but varied considerably in degree and extent from one animal to the other. In a few adrenal glands, small, sharply demarcated foci of necrosis were seen. Some of

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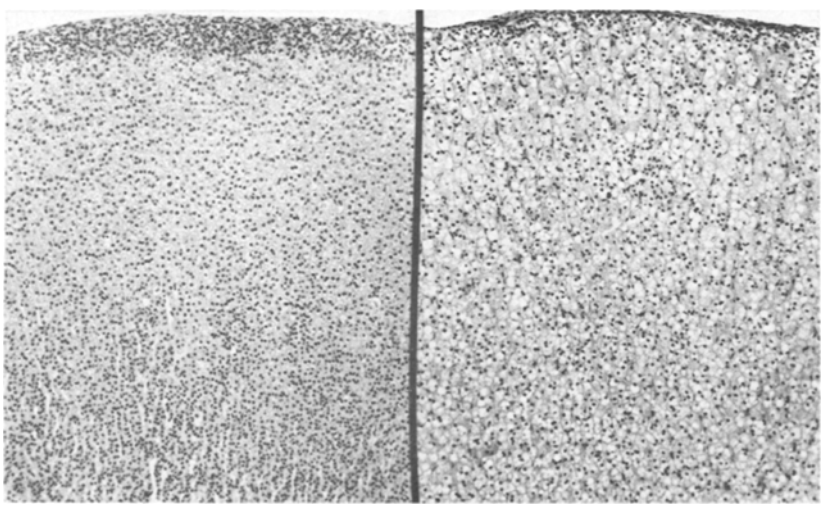

Left: Adrenal cortex of an untreated rat. Hematoxylin-Phloxine. × 120.

Right: Adrenal cortex of a rat treated for 14 days with aniline. Hematoxylin-Phloxine. × 120.

them were beginning to change into fibrous tissue and were occasionally calcified. Sections stained with Oil Red O and Sudan B black showed an increase in the positively staining lipoid material. No abnormalities were observed in the medullae.

The adrenal changes differed strikingly from those usually seen in the course of severe nonspecific stress. They closely resembled those which PRADER and GURTNER[2], and others[3], described as congenital-lipoid-adrenal hyperplasia in new-born infants, and were also similar to those found in humans and experimental animals following treatment with aminoglutethimide[4,5]. Under these conditions there is an inhibition of the enzymatic conversion of cholesterol to Δ^5-pregnenolone due to interference with 20-hydroxylation of the cholesterol side-chain and with the desmolase complex activity. As a result of these morphological similarities it can be supposed that a block also occurs in corticosteroidogenesis of aniline-treated rats. However, biochemical investigations are required to prove this hypothesis.

The aniline-induced adrenal changes can be prevented by simultaneous treatment with glucocorticoids which suggests that increased release of ACTH plays a decisive role in eliciting the adrenal lesion. This finding is compatible with the view that aniline, by inhibiting steroid synthesis, primarily affects the adrenal cortex, and the subsequent lack of circulating corticoids leads to a compensatory hypersecretion of ACTH. The importance of the local factor, however, cannot be neglected as the adrenal alterations elicited by aniline considerably differ from those due to the administration of ACTH.

Since aniline is metabolized to various substances mainly by the liver microsomes[6], the question arises whether aniline itself or one of its metabolites is responsible for the adrenal effect. There is no satisfactory answer at present to this question. However, it is worth mentioning that adrenal enlargement and lipoid accumulation in aniline-treated rats are not prevented by SKF 525-A, a potent inhibitor of a variety of microsomal enzymes[7].

It is interesting that both amphenone and aminoglutethimide, the well-known steroid synthesis inhibitors, contain aniline residues in their molecules. Further study is needed to verify whether aniline is the active principle in blocking steroidogenesis when these compounds are used[8].

Zusammenfassung. Subkutan injiziertes Anilin verursacht bei der Ratte eine Vergrösserung der Nebennierenrinde mit beachtlicher Ansammlung von Lipoiden. Morphologisch unterscheiden sich diese Veränderungen wesentlich von denen, die nach schwerer unspezifischer Stresswirkung entstehen, ähneln aber den durch Aminoglutethimid hervorgerufenen Läsionen. Es scheint, dass die Corticoidsynthese durch Anilin gestört wird und dass die Gewichtssteigerung der Nebennieren auf die ausgleichende Ausschüttung von ACTH zurückzuführen ist.

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Group	Duration of treatment	No. of rats	Final body weight (g)	Adrenal weight (mg/100 g body wt.)	
Control	–	10	106 ± 3.2[a]	33.3 ± 0.9	$p < 0.001$
Aniline	7 days	10	102 ± 2.7	56.2 ± 2.3	
Control	–	10	118 ± 1.6	27.3 ± 0.9	$p < 0.001$
Aniline	14 days	10	120 ± 4.1	64.3 ± 5.2	

[a] Mean ± S.E.

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In vivo Conversion of Corticosterone into Aldosterone in Rats Treated with ACTH or Submitted to Stress

The functional and morphological alterations of the adrenals in the resistance stage of the general adaptation syndrome (GAS) are generally attributed to an increased secretion of endogenous ACTH[1]. However, considerable differences in the pattern of adrenal cortical hormones have been demonstrated in rats treated with ACTH and rats injected with formaldehyde (a typical 'stressor' eliciting the GAS). After repeated administration of ACTH, the production of aldosterone was decreased; after formaldehyde treatment it was increased[2–5]. However, little is known of the biochemical background of this difference. The experiments described here were undertaken in order to obtain information on the in vivo conversion of corticosterone into aldosterone under different conditions.

Material and methods. Male white rats of 180–280 g body weight were anaesthetized with Nembutal (40 mg/kg i.p.). After i.v. injection of 1-2-H^3-corticosterone the adrenal venous blood was collected for 1.5 h according to the method described by VOGT[6]. The blood taken from the adrenal was permanently replaced by using an automatic device (for details see [7]).

The collected blood was haemolyzed and extracted with dichlormethane. The radioactive fractions of aldosterone and corticosterone were isolated by repeated chromatography and – in the case of corticosterone – by recrystallization (Figure 1). Their radioactivities were measured in a liquid scintillation spectrometer (Packard, type 3003).

To exclude an extra-adrenal conversion of corticosterone into aldosterone, blood samples of 7 adrenalectomized rats were collected from the femoral artery after the injection of 1-2-H^3-corticosterone. In all but one experiment, no radioactive aldosterone could be demonstrated in the femoral blood. In the 7th rat only a minimal amount of radioactive aldosterone (0.05% of the injected radioactivity/100) was obtained.