or turpentine granuloma). In the first stage, activation of cellular elements and mucopolysaccharides of the ground substance occurs—the apex of the desoxyribonucleic acid and hexosamine content in turpentine granuloma attained on the fifth day of the trial. The cellular component and the mucopolysaccharides form the basis for the development of connective tissue proteins. The second stage sets in—as shown by biochemical results—on the seventh day of the development of a turpentine granuloma when the levels of insoluble connective tissue proteins culminate. Finally in the third and last stage, the involved tissue is restored. The results show the turpentine granuloma to be a suitable model for the study of biological functions of the connective tissue in organism.

*Zusammenfassung.* Die Bildung eines Versuchsgranuloms, bei Ratten mittels subkutaner Injektion von Terpentinöl hervorgerufen, wurde verfolgt. Im Verlauf der Bildung des Granuloms erreichten die Spiegel der Desoxyribonukleinsäure und der Hexosamine am fünften und die Spiegel der unlöslichen Bindegewebeproteine am siebenten Tag des Versuches ihren Höhepunkt. Das Terpentinölgranulom zeigt sich als ein geeignetes Modell für das Studium der Bindegewebereaktivität.

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## Effect of X-Irradiation on Triglyceride Metabolism of the Rabbit

The exposure of various animals species to lethal X-irradiation results in significant alterations in plasma lipid and lipoprotein metabolism[1-3]. This is characterized in the rabbit by a pronounced hyperlipemia[4-5].

This study was undertaken to determine if radiation lipemia was due to an impairment in the removal rate of plasma triglycerides. In view of the intimate relationship between various plasma lipids, whereby an elevation in one results in concomitant increases in other lipids[6], the initial accumulation of plasma triglyceride could explain the rise in various other lipid fractions which characterizes radiation lipemia[2,7].

The intravascular removal rate of an injected $I^{131}$ labeled triolein emulsion was measured in normal and X-irradiated rabbits. The concentrations of plasma triglycerides and free fatty acids (FFA) and the extent of hepatic deposition of $I^{131}$ triolein were also determined.

*Methods.* Blood samples were obtained from the central ear artery of New Zealand Albino rabbits of either sex and weighing approximately 2.5 kg, prior to, and 16 h following sham-irradiation or exposure to 1000 r whole body X-irradiation. The X-ray unit was operated at 250 KVP, 15 ma with HVL of 2.0 mm Cu. The dose rate was 32 r/min at a mid-point distance of 70 cm, control and experimental rabbits were then fasted for 16 h. Plasma triglyceride[8] and free fatty acids[9] were determined. The $I^{131}$ labeled triolein emulsion was prepared as an anhydrous base[10] employing corn oil. The emulsion was administered intravenously 16 h after radiation exposure, as a 15% solution in the amount of 0.5 g of triglyceride/kg. The disappearance of the phospholipid and triglyceride components of this emulsion has been shown to be similar to that of homologous chylomicrons[10] and has been employed as a quantitative index of the intravascular removal rate of emulsified triglyceride[11].

Serial intracardiac blood samples were obtained from 2 to 30 min following the injection of the emulsion in unanesthetized rabbits and total radioactivity determined. The $I^{131}$ labeled lipid in whole blood was precipitated in the presence of carrier iodide by trichloroacetic acid[12] and counted in a scintillation counter. The data was analyzed according to the t-test for paired observations or employing a pooled variance.

*Discussion and Results.* In both control and irradiated groups the plasma FFA concentrations after 16 h of fasting were significantly higher than the initial values. Since no significant differences were noted between groups, the increased levels reflect the fasting state.

Plasma triglyceride concentrations in all control rabbits were significantly decreased below their initial values. In contrast, the plasma triglyceride concentrations in all the X-irradiated rabbits were significantly increased by a mean of 337% with increases ranging from 18 to 2140% above the pre-irradiation value.

A study of the plasma lipid alterations prior to and during the development of radiation lipemia indicated that plasma triglyceride, phospholipid and cholesterol

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Effect of X-irradiation on lipid metabolism of rabbits

| Group and No. | | Plasma FFA mEq/L 0 h | Plasma FFA mEq/L 16 h | Plasma Triglyceride mg% 0 h | Plasma Triglyceride mg% 16 h | $I^{131}$ Triolein t/2 min |
|---|---|---|---|---|---|---|
| Control | (6) | 0.430 ± 0.041 | 0.692 ± 0.078 | 70.7 ± 13.3 | 40.5 ± 6.1 | 3.8 ± 0.7 |
| 1000 r | (6) | 0.434 ± 0.063 | 0.754 ± 0.112 | 66.8 ± 17.8 | 291.9 ± 73.8 | 4.0 ± 0.6 |

Values are expressed as means ± standard error. The half-time (t/2) is equal to the time at which the amount of radioactivity present in blood is reduced to one-half its zero-time concentration. This is determined by plotting, semilogarithmically, the blood radioactivity against time.

fractions were all increased simultaneously, while no significant alteration occurred in the plasma FFA, making it unlikely that an initial disturbance in one lipid class was a causative factor in radiation lipemia[13].

Although a significant elevation in plasma triglyceride concentration occurred following radiation exposure, the intravascular removal rate of $I^{131}$ triolein in the X-irradiated rabbits was comparable to that obtained in the control group with the mean half-time being approximately 4 min. Although the disappearance rates of $I^{131}$ triolein and the chemically determined triglycerides of the emulsion were found to be identical, no correlation existed between the initial plasma triglyceride level and the removal rate of injected triglyceride.

The liver uptake of $I^{131}$ triolein was measured in an additional group of six control rabbits and six X-irradiated rabbits. 30 min after administration of the emulsion, the total $I^{131}$ activity of liver was 61.1 and 56.4% in the control and X-irradiated rabbits respectively. No difference in degree of deiodination (8%) was observed between the control and experimental group. Although it has been suggested that the deiodination of lipid might be correlated with the metabolic turnover of triglycerides, a limitation is suggested since $I^{131}$ lipids although possessing a similar tissue distribution as $C^{14}$ labeled fatty acids, do not have a similar incorporation into liver phospholipids[11].

The present data demonstrate a normal ability of X-irradiated rabbits to remove excess triglyceride from the circulation, and a normal rate of entry of the injected lipid into hepatic tissue. If the metabolic behavior of chylomicra and the $I^{131}$ triolein emulsion in the rabbit are comparable as reported in the dog[10], these findings indicate that the post-irradiation hyperlipemic state was not due to impairment in the removal rate of plasma triglyceride. The ability of X-irradiated rabbits to efficiently remove a lipid load sufficient to elevate plasma triglyceride levels 10–20 fold and yet manifest a post-irradiation hyperlipemia suggests the presence of abnormal lipoproteins of chylomicra which X-irradiated rabbits cannot efficiently metabolize[14].

*Zusammenfassung.* Nach letaler Röntgenbestrahlung wurde eine Zunahme der Triglyceride, aber keine Veränderung der freien Fettsäuren im Kaninchenplasma gefunden. Eine Belastungsprobe mit $I^{131}$ markierten Trioleins hat zu keiner Verhinderung der hepatischen Akkumulierung dieses Stoffes in den bestrahlten Tieren geführt. Der Befund weist darauf hin, dass nach Röntgenbestrahlung keine Störung des Fetttransportes aus dem Plasma resultiert, sondern dass die Lipämie eventuell durch abnorme Chylomicra zustande kommt.

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## Beitrag zur Wirkung des Hygroton®

Bei der Ödemgenese spielen die natriumretinierenden Corticosteroide, insbesondere das Aldosteron, eine entscheidende Rolle. Damit ergibt sich bei der Ödemtherapie mit Diuretica zwangsläufig eine wechselseitige Beeinflussung zwischen den natriumretinierenden Hormonen und den natriuretisch wirkenden, gleichfalls tubulär angreifenden Diuretica, wobei die Ausgangslage entscheidend ist für die Resultante beider Effekte. So kann an der intakten Ratte die durch Hygroton hervorgerufene Salurese durch Desoxycorticosteron-Glucosid abgeschwächt und die Kaliurese gesteigert werden (STENGER[1]). VEYRAT et al.[2,3] zeigten am Beispiel von Hygroton, dass das Versagen des Diureticums bei Patienten mit nachweisbarem Hyperaldosteronismus zumindest teilweise auf den erhöhten Aldosteronspiegel zurückgeführt werden kann.

Mit der Entwicklung der Spirolactone (CELLA et al.[4]; KAGAWA[5]; KAGAWA et al.[6]; LIDDLE[7]) wurde ein Verbindungstypus geschaffen, dessen Wirkungsmechanismus nach unseren heutigen Kenntnissen auf einer reversiblen kompetitiven Hemmung der Mineralocorticoide in den distalen Abschnitten des Nephrons beruht, woraus eine Natriurese bei gleichzeitiger Einschränkung der Kaliumelimination resultiert. Die Wirkung der Spirolactone ist an das Vorhandensein eines erhöhten Mineralocorticoid-Spiegels im Nierentubulus gebunden. Diese Mineralocorticoid-Antagonisten eignen sich somit zur Therapie jenes Ödemtypus, der allein oder vorwiegend durch einen erhöhten Aldosteronspiegel unterhalten wird.

In der vorliegenden Arbeit berichten wir über die Elektrolytelimination im Urin nach gleichzeitiger Applikation von Hygroton und Spironolacton an der Ratte.

*Methodik.* Die Untersuchungen erfolgten an männlichen weissen Ratten im Gewicht von 130–180 g (Trockenmischfutter; Wasser *ad libitum*). Verabreichung der Substanzen: allein oder gleichzeitig, 40 min vor Wasserstoss (50 ml/kg *per os*). Unmittelbar danach wurden die Tiere einzeln in Stoffwechselkäfige eingesetzt und die eliminierten Mengen

Elektrolytelimination im Urin während 5 h

| Substanz | Dosis mg/kg | Harn ml/h | $Na^+$ | $K^+$ m Aeq/h | $Cl^-$ | Tierzahl |
|---|---|---|---|---|---|---|
| Kontrolle | – | 1,32 | 0,032 | 0,063 | 0,051 | 303 |
| Hygroton® | 2,5 *per os* | 1,72 | 0,050 | 0,076 | 0,065 | 60 |
| | 5 *per os* | 1,83 | 0,067 | 0,085 | 0,100 | 175 |
| | 7,5 *per os* | 1,68 | 0,106 | 0,118 | 0,140 | 20 |
| | 5 subkutan | 1,86 | 0,096 | 0,095 | 0,127 | 60 |
| | 10 subkutan | 1,78 | 0,091 | 0,078 | 0,106 | 20 |
| Spirono- | 2,5 *per os* | 1,34 | 0,022 | 0,051 | 0,039 | 20 |
| lacton | 5 *per os* | 1,43 | 0,032 | 0,067 | 0,053 | 20 |
| | 10 *per os* | 1,56 | 0,025 | 0,057 | 0,039 | 20 |

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