reticulocytes. Also, data on hepatic and renal function (Table II) showed no appreciable variation at the end of the experiments.

Adriamycin causes a slight reduction in weight of the thymus, the spleen and the ovary: histologically, in a few subjects one observes, in modest form, dilatation of individual nephrons with some cells flaked off from the collector tubes, reduction of the splenic pulp, either red or white, hypoplasia of the bone marrow, degeneration of the duodenal epithelium with reduction of the number of mitoses, aspects of the degeneration during maturation, of the germinative tissue, either testicular or ovarian.

On the whole, therefore, adriamycin exerts an inhibiting effect on cellular reproduction which is particularly evident in the more actively proliferating tissues.

Table II. Adriamycin. Subchronic toxicity in rabbits

| Treatment | BUN mg/100 ml | Blood glucose mg/100 ml | Total protein g/100 ml | Albumin g/100 ml | Globulin g/100 ml α | β | γ | A/G ratio |
|---|---|---|---|---|---|---|---|---|
| Control | 27.2 | 136 | 6.31 | 3.50 | 0.90 | 1.40 | 0.51 | 1.27 |
| Adriamycin | 24.8 | 162 | 6.28 | 3.71 | 0.79 | 0.99 | 0.77 | 1.44 |

Mean values of blood chemistry determined on serum at the end of treatment.

*Riassunto.* Si è studiato sperimentalmente la tossicologia acuta e subacuta dell'adriamicina, un nuovo antibiotico antitumorale con struttura simile a quella della daunomicina, rilevandone l'attività depressiva sulla riproduzione cellulare.

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## Nitrous Oxide and Tissue Thiopental Levels in Rats

Previous reports on uptake and distribution of thiopental (pentothal) have been made in the absence of anesthetics[1-4]. Clinically thiopental is rarely administered alone, but most frequently used with nitrous oxide. We decided to determine whether nitrous oxide modifies tissue levels or the tissue distribution of thiopental. Such a possibility is suggested by the observation that diethylether alters both tissue distribution and metabolism of pentobarbital (Nembutal)[5].

*Methods.* Thiopental (25 mg/kg) was administered i.v. to 3 pairs of young male Sprague-Dawley rats (100–300 g). One rat of each pair was immediately placed in a 120-liter container pre-filled with 80% nitrous oxide in oxygen as determined by oximetry. Concentrations of nitrous oxide and oxygen were maintained by continuously flowing 4 l of nitrous oxide and 1 l of oxygen through the container. The paired control rat was exposed to room air. After 30 min both rats were simultaneously sacrificed by decapitation and duplicate measurements of tissue and plasma thiopental levels were made using the technic of BRODIE et al.[1]. Left ventricular blood was immediately obtained, heparinized, and centrifuged at 0 °C, 12,000 rpm for 5 min to obtain plasma. The following tissues were also immediately obtained for homogenization, always from the same site and in the same sequence: liver (including capsule); perirenal fat; and whole brain (sectioned at the lower brainstem). After blotting, up to 2 g of tissue were added to 5 ml of 0.1 *N* HCl and ground to an emulsion in a homogenizer. Samples of fat were emulsified in 0.1 *N* NaOH to extract thiopental into an aqueous phase. 1–2 ml of tissue homogenate or plasma were then added to an equal volume of 1.5 *N* $NaH_2PO_4$ and 30 ml of petroleum ether containing 1.5% isoamyl alcohol in a glass-stoppered bottle and shaken for 1 h. The supernatant (solvent) phase was transferred to a glass-stoppered bottle containing 5 ml of 2.5 *N* NaOH and, after shaking for an additional 2 min, was transferred to a test-tube, centrifuged, 3 ml of the aqueous phase then being removed and added to a cuvet and the optical density determined at 305 nm in a Beckman UV-spectrophotometer.

Reagent blanks and standards were carried through the same procedures. Both unknown and standard optical densities were determined at 305 and 330 nm. That tissue has a blank range which is not reproducible[1] was corrected on the basis that the optical density of tissue remains unchanged at both 305 and at 330 nm while the optical density of thiopental decreases by 90% between 305 and 330 nm. Thiopental, 50 µg, carried through the procedure as a standard produced an optical density of approximately 0.680. Thiopental added to plasma and tissue homogenates was recovered within 90 ± 3%.

Statistical significance of the results was determined by Student's *t*-test for differences between 2 sample means at 0.95 confidence levels ($p < 0.05$).

*Results.* The amount of thiopental in tissues of animals exposed to nitrous oxide was not significantly different than in animals exposed to room air (Table). The sum of the thiopental levels in plasma and tissues averaged 175.3 µg in rats exposed to room air, 169.2 µg in rats exposed to nitrous oxide. Nitrous oxide also did not alter the distribution of thiopental in tissues. Plasma: brain distribution coefficients, for example, averaged 1.84 in nitrous-oxide treated, 1.87 in control animals.

*Discussion.* The present data demonstrate that clinically effective concentrations of nitrous oxide have no significant effect on thiopental distribution 30 min after its i.v.

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administration. This indicates that the response to the combination of thiopental and nitrous oxide is not associated with altered concentrations of thiopental in an organ such as the brain.

Even as early as 30 min after administration of thiopental drug metabolism exerts a significant effect on blood and tissue thiopental levels[4]. In the present study the total amounts of thiopental recovered after 30 min were the same in both groups of animals. This suggests that within this period of time nitrous oxide had no significant effect on the rate of metabolism of thiopental. Further analysis of possible effects of nitrous oxide on thiopental metabolism would depend upon tissue levels determined over longer periods of time. An inhibitory effect of nitrous oxide on thiopental metabolism would appear unlikely, however.

We conclude that nitrous oxide does not contribute to the depressant action of thiopental by altering its tissue distribution or the rate at which it is metabolized[6].

Duplicate tissue concentration determinations (μg/g) of thiopental in paired rats exposed to room air or 80% nitrous oxide for 30 min following i.v. thiopental (25 mg/kg)

| | Room air | | Nitrous oxide | |
|---|---|---|---|---|
| Plasma | 22.6 | 20.1 | 20.3 | 17.7 |
| | 20.6 | 29.7 | 27.2 | 18.7 |
| | 22.8 | 23.7 | 21.9 | 21.3 |
| | Mean 23.3 ± 3.5[a] | | Mean 21.2 ± 3.3 | |
| Liver | 37.2 | 36.7 | 45.2 | 32.5 |
| | 43.5 | 32.5 | 41.5 | 47.2 |
| | 33.9 | 40.2 | 35.0 | 35.2 |
| | Mean 37.3 ± 4.1 | | Mean 39.4 ± 6.1 | |
| Fat | 134.3 | 128.5 | 99.5 | 77.5 |
| | 78.4 | 114.7 | 85.1 | 106.7 |
| | 78.8 | 79.0 | 91.3 | 127.2 |
| | Mean 102.3 ± 26.6 | | Mean 97.1 ± 16.1 | |
| Brain | 14.4 | 15.0 | 15.5 | 10.4 |
| | 11.7 | 9.7 | 9.3 | 12.5 |
| | 11.2 | | 9.9 | |
| | Mean 12.4 ± 2.2 | | Mean 11.5 ± 2.5 | |

[a] Standard deviation.

*Zusammenfassung.* Es wird gezeigt, dass sowohl Gewebemenge wie auch Pentotalverteilung im Rattengewebe von Lachgas nicht beeinflusst wird.

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## Die Degenerationsrate bei präimplantierten Ratteneiern

Viele Autoren widmeten sich dem Studium der Normalentwicklung präimplantierter Säugereier und verfolgten auch das Schicksal der unbefruchteten Keimzellen[1–3]. Die Ausfälle im Zusammenhang mit der Implantationsphase selbst waren Gegenstand zahlreicher experimenteller Untersuchungen[1,4,5] und andere. Während, dank der leichteren Gewinnungsmöglichkeit, über die Prozentsätze anormaler Spermien für viele Arten genaue Zahlen vorliegen, fehlen für fast alle Säuger mit Ausnahme des Opossums[6] Angaben über das Ausmass der physiologischen Degenerationsraten von Eiern in den verschiedenen Stadien der Präimplantationsperiode. In der Folge sollen die zu diesem Problem an Ratteneiern während der Segmentation gewonnenen Ergebnisse zusammengestellt und diskutiert werden.

*Material und Technik.* Für die Untersuchung standen uns 85 weibliche Ratten (Stamm Wistar und Ivanovas) zur Verfügung[7]. Sie erhielten standardisiertes Normalfutter und Salat. Gesamthaft wurden 941 Eier gewonnen, was einer durchschnittlichen Anzahl von 11,1 (Schwankungsbreite 2–18) Eiern pro Tier entspricht. Kriterien für die Degeneration waren: Vor der Teilung unregelmässige, mehr oder weniger aufgelöste Konturen. Nach der Teilung: Formverschiedenheiten der Blastomeren und exzentrische oder aufgelöste Kerne, scholliges Aussehen des Cytoplasmas nach DPHN-Nachweis, verursacht durch abwechselnd granulafreie und granuladichte Zonen[8].

Die Aussortierung der degenerierten Eier wurde manchmal gleich nach dem Ausspülen aus der Tube vorgenommen, meistens aber erst nach der DPNH-Nachweisreaktion. Weil sich auch unbefruchtete Eier ein- bis zweimal teilen können[3], ist die Möglichkeit, dass sich vereinzelt ein solches Ei im Material findet, nicht ganz auszuschliessen. Selbst den sogenannt normalen Eiern ist nicht mit Sicherheit anzusehen, ob sie nicht schon funktionelle Störungen in sich tragen.

*Befunde.* Die Entwicklungsphase, die das Ei in der Tube durchläuft, wurde für unsere Zwecke in 5 Stadien (I–V) aufgeteilt und die dazugehörigen Degenerationsraten errechnet (Tabelle I).

Zwischen der Anzahl ovulierter Eier pro Tier und dem Prozentsatz der davon degenerierten Eier war kein Zusammenhang nachzuweisen. Aus Tabelle I ist zu ersehen,

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[7] Den Firmen F. Hoffman-La Roche & Co., Basel, und CIBA AG, Basel, möchten wir für die Überlassung der Tiere sowie deren Pflege und Wartung unseren besten Dank aussprechen.
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