Cholecystokinin (CCK) in most cats increased the intestinal activity and relaxed the sphincter (Figure 1). Isoprenaline relaxed both sphincter and intestine, whereas terbutaline relaxed the sphincter with negligible effects on the intestine (Figures 1 and 2). These results support the conception of a choledochoduodenal junction operating independently of the intestine. The effect of terbutaline on the sphincter of Oddi, compared to its slight effect on the heart and the small intestine, indicates that these organs contain β-receptors that differ from those found in the sphincter of Oddi[10].

Zusammenfassung. Die β-Rezeptoren vom Sphinkter von Oddi werden durch Terbutalin selektiv stimuliert.

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Adriamycin: Toxicity Data

Adriamycin is a new antibiotic possessing both in vivo and in vitro antitumoral activity[1], obtained in these laboratories by cultivation of *Streptomyces peucetius var. caesius*; it has a structure similar to that of daunomycin being in fact 14-hydroxydaunomycin[2,3]. The initial clinical tests[4], which are now in progress, confirm the antitumoral activity in humans affected by leukemia or by malignant neoplasia of various types.

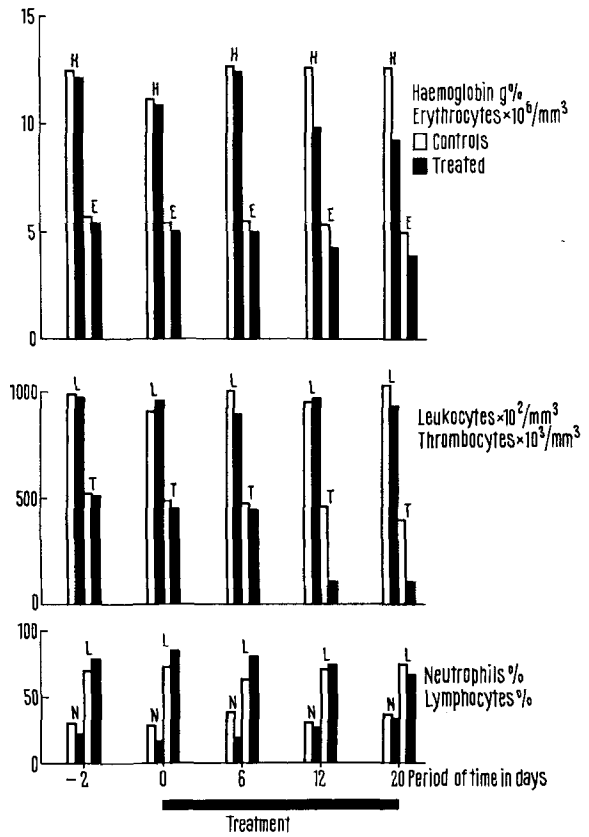
The acute toxicity has been determined in albino mice (Swiss strain) by means of i.v. injections of doses of adriamycin hydrochloride, increasing by a factor of 1.25, the doses being given to each of a group of 10 mice (5 males + 5 females).

The mortality rate, constant after 30 days from treatment, and the effect on body growth are reported in Table I; the statistical analysis of the death-rate, calculated by the method of the probits[5], gives a DL_{50} of 20.8 mg/kg. Mortality begins a few days after injection and is complete within 20 days; during this period the animals lose weight, show signs of anorexia and eventually of haematic diarrhea.

The subchronic toxicology has been studied in the rabbit; in a group of 6 animals (3 males + 3 females) adriamycin hydrochloride was administered i.v. at doses of 1 mg/kg (in 0.25 ml of physiological solution) every other day, for 3 weeks. Another 6 rabbits, kept as controls, were treated analogously with physiological solution only.

During the course of the tests there were no deaths, cases of haematic diarrhea nor any signs of clinical toxicity. Even the ECG does not reveal evident alterations in cardiac pattern; only the frequency is slightly higher (316 pulsations/min in treated rabbits compared with 235 in the controls). Only in the males is there a slight reduction in body weight increase.

Adriamycin provokes a slight normochromic anaemia with thrombocytopenia (Figure) without variation of prothrombin and coagulation time and of the number of



Adriamycin. Subcronic toxicity in rabbits. Mean haematological values before and during treatment.

Table I. Adriamycin. Acute toxicity in mice

Dose[a] mg/kg	No. of mice	No. of dead	LD_{50} mg/kg	Fiducial limits for $P = 0.05$	Body weight after days: 0	8	16	30
Controls	10	0	–	–	21.8	23.1	25.3	27.4
16	10	2	21.1	18.48–24.00	21.4	18.5	22.2	27.0
20	10	3			21.7	18.0	20.5	24.3
25	10	8			21.7	14.9	18.1	22.0

[a] Adriamycin was injected i.v. in 0.5 ml of distilled water, over 15 sec.

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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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