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**REPRINTS**

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Abstracts of the 1983 Annual Meeting

345 ASSESSMENT OF PRIMARY IRRITATION OF PARENTERAL DRUGS IN VITRO AND CORRELATION WITH IN VIVO TESTS. R.E. Bagdon, Robert Edward Bagdon, Inc., Livingston, NJ and H.N. Prince, Gibraltar Biological Labs., Fairfield, NJ.

Subthreshold cytotoxic conc. (CTC) of plastic extracts are nonirritating in the rabbit implant test (Rosenbluth et al., 1965). Chlorpromazine as Thorazine Injectable (T) was tested similarly. In vitro, the min. CTC (mg/ml,72 hr) to human fibroblasts: WI 38= 0.008; MRC-5= 0.016; human epithelial cells: Hep-2= 0.004. T was not cytotoxic after 4 hr but was irreversibly cytotoxic after 16-72 hr. The min. CTC to gram + microbes: staph. aureus= 0.05; bacillus subt. = 0.05; strep. pyogenes= 0.025; gram neg. microbes were resistant. The non CTC of T= 0.002 mg/ml. In vivo, T, 25 mg/ml, increased serum creatine phosphokinase (CPK) 4 fold in rats (0.4 ml/rat, im); 0.0025 mg/ml had no effect (NE). T, 25 mg/ml im to rabbits (1 ml): necrosis; 0.0025 mg/ml: NE. In the rabbit eye, T, 25 mg/ml (0.1 ml): severe conjunctival edema; 0.0025 mg/ml: NE. The conc. of T used clinically, 25 mg/ml, was cytotoxic or irritating in all tests. Cell culture, anti-microbial assays and serum CPK assays in rats are useful, quantitative tests for primary irritation evoked by injectable formulations.

**XXIVth CONGRESS OF THE**
**EUROPEAN SOCIETY OF TOXICOLOGY**
**Rome - 28th-30th March 1983**

**FORM "C"**
**ABSTRACT**

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TITLE (Capital letters)
ASSESSMENT OF PRIMARY IRRITATION OF PARENTERAL DRUGS IN VITRO

NAME(s) of AUTHOR(s) (Presenting author underlined), institution, city, country
R. E. Bagdon, Ph. D., Robert Edward Bagdon, Inc. Livingston, NJ, USA and H.N. Prince, Ph. D., Gibraltar Biological Laboratories, Inc., Fairfield, NJ, USA

ABSTRACT: Subthreshold cytotoxic conc. (CTC) of plastic extracts are nonirritating in the rabbit implant test (Rosenbluth et al., J. Pharm. Scien., 54, 156-159, 1965). Chlorpromazine as Thorazine Injectable (T), diazepam as Valium Injectable (V), verapamil as Calan Injectable (C) and hydrocortisone as an injectable suspension (HC) were tested similarly. In vitro, the min. inhib. conc. (MIC) to gram positive bacteria and the min. CTC to human cell lines are:

| | WI-38 fibroblasts | MRC-5 fibroblasts | Hep-2 epithelia | Staph. Aureus | Bacillus Subt. | Strep. Pyog. |
|---|---|---|---|---|---|---|
| | (mg/ml, 72 hrs) | | | (mcg/ml, 48 hrs) | | |
| T | 0.008 | 0.016 | 0.004 | 0.05 | 0.05 | 0.025 |
| V | 0.150 | 0.100 | 0.075 | 0.32 | 0.32 | 0.32 |
| C | - | 0.063 | - | - | - | - |
| HC | - | >2.5 | - | - | - | - |

The max. non CTC (mg/ml) to MRC-5 fibroblasts are: T=0.008; V=0.075; C=0.03; HC=>2.5. T was not cytotoxic to Hep-2 after 2-8 hrs but was irreversibly cytotoxic after 16-72 hrs; V was irreversibly cytotoxic only after 48-72 hrs. Gram neg. bacteria were resistant to T and V. The order of increasing cytotoxicity to human cells in culture is: HC<V≦C<T. In vivo, the conc. of T used clinically, 25 mg/ml, evoked severe necrosis when injected into the sacrospinalis m. of rabbits. T, 25 mg/ml, produced severe conjunctival edema when instilled (0.1 ml) into the rabbit eye. T, 25 mg/ml, administered im to the biceps femoralis m. of rats (0.4 ml/rat) increased serum creatine phosphokinase (CPK) 4 fold. However, a non CTC of T, 0.0025 mg/ml, was nonirritating in all 3 in vivo models. Cell culture and antibacterial assays are useful tests for primary irritation evoked by parenteral formulations. Cell culture is also useful as a quality control test for production lots of parenteral drugs. Advantages include a quantitative, precise, biological endpoint, a short term assay and good correlation with standard in vivo tests.

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333 8:45 **Carcinogenic Properties of Acrylamide in the Mouse Skin and Lung Adenoma Assays.** R.D Laurie, M Robinson, R J. Bull and D Cmehil, *Toxicol. and Microbiol. Div., HERL, U.S. EPA, Cincinnati, OH.*

334 9 00 **A Wide-range Method for Measuring Partition Coefficients for Weakly Ionizable Compounds.** A Jayaraj, A.O Obaseki and W R Porter, *School of Pharmacy, Univ. of Wisconsin, Madison, WI.* Sponsor R E. Peterson.

335 9 15 **Cardiotoxicity of 1-Isoproterenol in Cultured Myocytes: Prevention by 1-Ascorbic Acid and Sodium Bisulfite.** K. Ramos, A.B Combs and D. Acosta, *Dept. of Pharmacol./Toxicol., College of Pharmacy, Univ. of Texas, Austin, TX.*

336 9 30 **Studies on the Steady State Levels and Turnover Rates of Catecholamines in Rat Brain Following Chlordecone Treatment.** C.N. Aldous, C.S. Chetty and D. Desaiah, *Dept. of Neurol., Univ. of Mississippi Med. Ctr., Jackson, MS.*

337 9:45 **Biological Monitoring for Exposure to Synthetic Estrogens.** E.F Brennan and F.J Murray, *Syntex (U S.A.) Inc., Palo Alto, CA.*

338 10:00 **Diethyl Succinate Carboxylesterase Activity in Human Blood Serum.** R.E. Talcott, S M. Pond, C E. Becker and A Ketterman, *Northern California Occup. Health Ctr., Univ. of California, San Francisco, San Francisco, CA.*

339 10:15 **Experimental Sensitization to Formaldehyde.** M.H. Karol and K. Lee, *Dept. of Ind. Env. Health Sci., Grad. School of Pub. Health, Univ. of Pittsburgh, Pittsburgh, PA.*

340 10:30 **Effect of Estrogen Metabolites on PHA and MAF-Stimulated Cell Aggregation in Mouse Lymphocytes and Peritoneal Cells.** R.W. Pfeifer and M.I. Luster, *STB, NIEHS, Research Triangle Park, NC.* Sponsor: J. Goldstein.

341 10:45 **Evaluation of Citrinin Toxicity on the Immune System in Mice.** R.V. Reddy, M.J. Taylor and R.P. Sharma, *Toxicol. Program, Utah State Univ., Logan, UT*

342 11:00 **Regulation of Estrogen-induced Immunotoxicity.** M.I. Luster, G.A. Boorman, H.T. Hayes and R. Pfeifer, *Nat'l Inst. of Env. Health Sci., Research Triangle Park, NC.* Sponsor: J.A. Goldstein.

343 11:15 **B-Cell Immunosuppression Following Exposure to Benzopyrene.** J.H. Dean, L.D. Lauer and M.I. Luster, *Chem. Ind. Inst. of Toxicol., and Nat'l Inst. of Env. Health Sci., Research Triangle Park, NC.* Sponsor: J.E. Gibson.

344 11:30 **Immunotoxicologic Evaluation of Rubratoxin B in Male CD-1 Mice.** M.J. Taylor, R.V. Reddy and R.P. Sharma, *Toxicol. Program, Utah State Univ., Logan, UT.*

345 11.45 **Assessment of Primary Irritation of Parenteral Drugs *In Vitro* and Correlation with *In Vivo* Tests.** R E Bagdon, *Robert Edward Bagdon, Inc., Livingston, NJ;* H.N. Prince, *Gibraltar Biological Labs, Fairfield, NJ.*