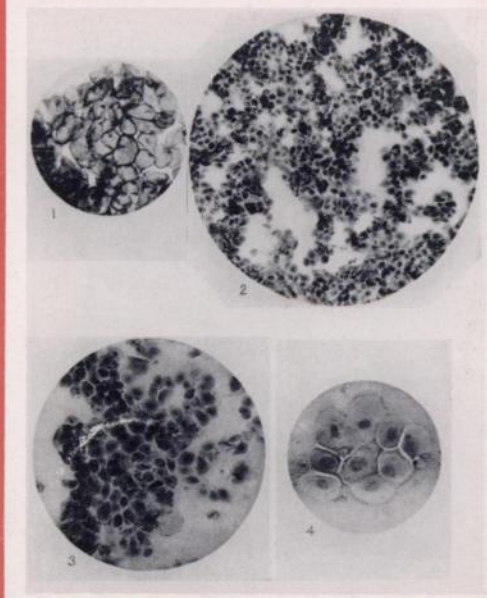
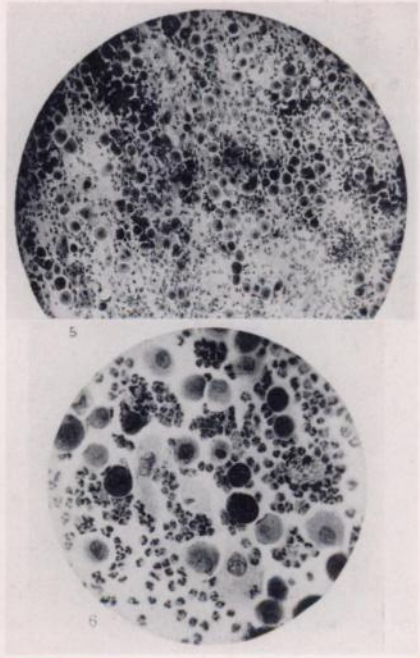
AMERICAN ASSOCIATION FOR CANCER RESEARCH
Ut Cancrum Vincamus
1907

Cancer Research

VOLUME 46 • NO. 2 CNREA 8 • PP 461-1013
February 1986





AN IMPORTANT MESSAGE TREATING CANCER

Clinical studies indicate that Ativan® (lorazepam) Injection can play a significant role in enhancing patient tolerance for and acceptance of chemotherapy.[1-5] In studies comparing Ativan Injection to other adjunctive agents, patients expressed a strong preference for the regimen including Ativan Injection because of its anxiolytic, amnesic and sedative effects.[2,4]

The reduction of recall following administration of Ativan Injection was considered by most patients to be not only acceptable, but also desirable.[1-5] Furthermore, due to its anxiolytic action, Ativan Injection was helpful in relieving the anxiety associated with the stresses of chemotherapy.[3,4]

NEW ADJUNCTIVE AGENTS NEEDED

A study of 52 mastectomy patients on regimens of cyclophosphamide, methotrexate and 5-FU (CMF) revealed that over one fourth of patients failed to even complete a treatment course of 12 to 18 months, mostly because of the side effects associated with these agents.[6] A recent survey of 56 oncology centers found up to 10% of patients refused further chemotherapy because of actual or feared side effects.[7] Statistics such as these have spurred researchers to seek new adjunctive agents or combinations of existing agents that would increase the tolerability of chemotherapy.

ATIVAN® INJECTION: A SUPPORTIVE ADJUNCT

In a study involving 18 patients receiving 36 courses of *cis*-platinum therapy, Ativan Injection was administered prior to therapy. Lack of recall for the chemotherapy infusion, and for the subsequent 8 hours, was reported in 33 of 36 courses of therapy studied. Furthermore, amnesia for the day of chemotherapy was reported in 29 courses. All 18 patients believed the lack of recall was highly desirable.[5]

Dr. John Laszlo and colleagues from Duke Comprehensive Cancer Center, Durham, NC, and Memorial Sloan-Kettering Institute, New York, reported a pilot study involving 32 patients receiving cisplatin with or without other cytotoxic chemotherapy and adjunctive use of Ativan Injection.[3] Thirty patients were evaluated over 45 courses of treatment (two were eliminated for protocol violations).

Dr. Laszlo observed that following lorazepam, recall of the day's events was reduced for most patients. Post-treatment anxiety was also reduced. Almost all of the patients in the study requested lorazepam (Ativan Injection) pretreatment again for subsequent chemotherapy courses, regardless of incidence or intensity of emetic episodes. From this study, Dr. Laszlo concluded that lorazepam can be an effective agent for these patients.

FOR PHYSICIANS
PATIENTS

A SIGNIFICANT ROLE IN ENHANCING COMPLIANCE IN CHEMOTHERAPY

Clearly, Ativan® (lorazepam) Injection represents an important supportive adjunct in chemotherapy. Patients' ability to tolerate the experience is usually enhanced. Their acceptance of a regimen incorporating Ativan Injection has been excellent. Thus, it is felt that many patients who might otherwise abandon treatment may now be more willing to proceed with Ativan Injection as an adjunct in their chemotherapy regimen.

If outpatients are treated with lorazepam injection, care must be taken on the day of treatment to prevent their undertaking any activity requiring full awareness or coordination.

REFERENCES:

1. Maher J: Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy (letter to the editor). Lancet *1*:91-92, 1981.
2. Gagen M, Gochnour D, Young D, et al: A randomized trial of metoclopramide and a combination of dexamethasone and lorazepam for prevention of chemotherapy-induced vomiting. J Clin Oncol 2:696-701, 1984.
3. Laszlo J, Clark RA, Hanson DC, et al: Lorazepam in patients treated with cisplatin: A drug having antiemetic, amnesic and anxiolytic effects. Presented at the meeting of the ASCO, San Diego, CA, May 23, 1983.
4. Bowcock SJ, Stockdale AD, Bolton JAR, et al: Antiemetic prophylaxis with high dose metoclopramide or lorazepam in vomiting induced by chemotherapy. Br Med J *288*:1879, 1984.
5. Semrad NF, Leuchter RS, Townsend DE, et al: A pilot study of lorazepam-induced amnesia with *cis*-platinum-containing chemotherapy. Gynecol Oncol *17*:277-280, 1984.
6. Wilcox PM, Fetting JH, Nettesheim KM, et al: Anticipatory vomiting in women receiving cyclophosphamide, methotrexate, and 5-FU (CMF) adjuvant chemotherapy for breast carcinoma. Cancer Treat Rep *66*:1601-1604, 1982.
7. Maule WF, Perry MC: Management of chemotherapy-induced nausea and emesis. Am Fam Physician *27*:226-234, 1983.

Please see important information on the following page.

ATIVAN® (LORAZEPAM) ℞
INJECTION I.V.

Wyeth Laboratories
Philadelphia, PA 19101

ATIVAN® (LORAZEPAM) Ⓒ IV
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

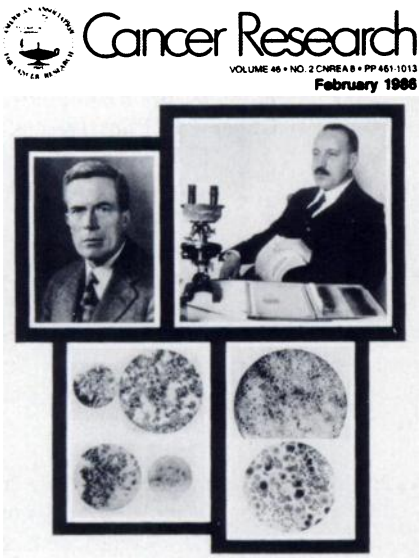
Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101

CI3117-1 7/31/80

COVER LEGEND



The importance of the "Pap smear" in the clinical detection of cervical carcinoma has obscured the basic investigations that preceded its practical applications.

In 1917, Stockard and Papanicolaou (Am. J. Anat., *22:* 225, 1917) described the cyclic changes in the vaginal cell population of guinea pigs and correlated the changes to changes in the reproductive system that indicated estrus. The observations were reiterated in the rat (Long and Evans, Mem. Univ. Calif., *6:* 1922) and the mouse (Allen and Doisy, J. Am. Med. Assoc., *81:* 819, 1923). The cyclic changes were aborted by ovariectomy and restored by ovarian extracts. These studies provided the essential bioassay method that facilitated the isolation and characterization of estrogenic hormones as well as the identification of vitamin E (see Corner, Hormones in Human Reproduction. Princeton, NJ: Princeton University Press, 1942).

Later, in 1933, Papanicolaou reported his definitive study on vaginal cytology which clearly defined the sexual cycle in the human female (Am. J. Anat., *52:* 519, 1933). This work provided to the gynecologist and the clinical endocrinologist a physiologically based, highly useful, and simple technique for the clinical evaluation of ovarian and other endocrine disorders and for the evaluation of drugs affecting the reproductive system.

Charles Rupert Stockard (1879–1939) was born in Mississippi and obtained his Ph.D. degree from Columbia University in 1906, continuing his academic career there until becoming professor of anatomy at Cornell Medical College in 1911. His many contributions were primarily in anatomy, endocrinology, and structural development.

George Nicholas Papanicolaou (1883–1962) was born in Greece, where he obtained his M.D. degree; he received his Ph.D. degree from the University of Munich. He emigrated to the United States and became a member of the Cornell faculty under Stockard. After retirement he headed the Papanicolaou Cancer Research Institute in Miami, FL. It is generally accepted that the vaginal cytology observations of the Stockard-Papanicolaou 1917 report were the contribution of Papanicolaou (see Carmichael, The Pap Smear. Springfield, IL: Charles C Thomas, Publisher, 1973).

Pictured are C. R. Stockard (*left*) (from Am. J. Anat., *64:* 378, 1929) and G. N. Papanicolaou (*right*) and two plates of vaginal smear cells (from Am. J. Anat., *22:* 225, 1917).

We are indebted to Dr. Nicholas L. Petrakis for suggesting the theme and supplying materials and to Dr. Julius Schultz for the photograph of Papanicolaou taken circa 1920 in New York.

M. B. S.

INTERNATIONAL CONFERENCE

ON

THEORIES OF CARCINOGENESIS

Facts, fashion or fiction?

A new type of conference arranged in Oslo, Norway, August 16–20 1986 in connection with the 14th International Cancer Congress in Budapest, Hungary, August 21–27 1986.

Current paradigms seem to have a heavy impact on research. We have an innate tendency to design experiments that confirm existing beliefs, rather than ones that test, and may disprove, the validity of our concepts. There is an urgent need for those interested in mechanisms of carcinogenesis to discuss among themselves the strengths and weaknesses of presently fashionable paradigms.

SCIENTIFIC PROGRAMME: The philosophy of science and the impact of paradigms on science. Theories involving oncogenes, chromosomal damage, DNA repair mechanisms, mutations. Theories related to the two-stage theory, initiation and promotion. Theories involving ageing, endogenous production of electrophiles, reactive oxygen species, anti-oxidants. Phenotypic cellular changes and evidence from liver carcinogenesis. Growth control, cell proliferation and differentiation, and hormonal carcinogenesis. Immune deficiency theories. Herpes virus, AIDS, leukemias and lymphomas.

More than 25 internationally recognized cancer research workers and a professor of philosophy have agreed to speak.

For further information, contact: The Secretariat, The Norwegian Cancer Society, Huitfeldtsgt. 49, 0253 OSLO 2, Norway.