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ANNUAL REPORT
UNIVERSITY OF ROCHESTER
BIOMEDICAL LABORATORY
BRIEF DESCRIPTION OF RESEARCH PAPERS
ACCEPTED FOR PUBLICATION DURING
1978

UNIVERSITY OF ROCHESTER
BIOMEDICAL LABORATORY
ROCHESTER, NEW YORK

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Prepared by: *Dorris B. Nash, Editorial Assistant*

Submitted by: *Paul L. La Celle, Director*

Date of Issue: *May 24, 1979*

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TITLE: Purification and characterization of the 45,000 dalton fragment from tryptic digestion of $(\text{Ca}^{2+} + \text{Mg}^{2+})$ -adenosine triphosphatase of sarcoplasmic reticulum (UR-3490-1338)

AUTHORS: J. J. Abramson and A. E. Shamoo

PUBLICATION: J. Memb. Biol., (in press)

SUMMARY: Tryptic digestion of $\text{Ca}^{2+} + \text{Mg}^{2+}$ -ATPase from sarcoplasmic reticulum of rabbit skeletal muscle has previously been shown to cleave the enzyme initially into a 55,000 dalton fragment and a 45,000 dalton fragment. In the present study, the two fragments are solubilized in sodium dodecyl sulfate (SDS) and separated by preparative polyacrylamide gel electrophoresis. The 45,000 dalton fragment is found to be a relatively nonselective, divalent cation-dependent ionophore when incorporated into an oxidized cholesterol membrane (BLM). Ionophoric activity of this fragment is inhibited by low concentrations of LaCl_3 , HgCl_2 and various reducing agents. There appears to be a relatively inaccessible disulfide bond in the 45,000 dalton fragment that is essential for transport. Addition of reducing agents inhibit the ionophoric activity of the succinylated undigested enzyme and the 45,000 dalton fragment but has no effect on the 55,000 dalton fragment. These experiments imply that the 45,000 dalton fragment and the 55,000 dalton fragment are in a series arrangement in the membrane.

TITLE: An extracorporeal complexing hemodialysis system for the treatment of methylmercury poisoning. III. Clinical applications (UR-3490-1363)

AUTHORS: A. H. Al-Abbasi, P. J. Kostyniak and T. W. Clarkson

PUBLICATION: J. Pharmacol. Exptl. Therap., 207: 249-254 (1978)

SUMMARY: Observations on experimental animals have established that extracorporeal complexing hemodialysis was a highly effective and safe procedure for removing methylmercury from the body. The procedure makes use of a commercially available artificial kidney (Travenol RSP 145 twin coil hemodialyzer) in which arterial blood is allowed to equilibrate across a semipermeable membrane with physiological saline. A small molecular weight complexing agent (L-cysteine) is infused into the arterial blood entering the dialyzer to convert methylmercury into a diffusible form. Within the coil, both free cysteine and the methylmercury-cysteine complex formed in the blood diffuse across the membrane into the dialysate according to their chemical potentials. The blood returning to the patient carries reduced concentrations of both methylmercury and free complexing agent. This report describes the application of this procedure to two patients having elevated blood concentrations of methylmercury. The clinical picture in two patients before treatment showed progressively worsening signs of methylmercury poisoning. Treatment of the patients with this procedure resulted in a reduction of concentrations of mercury in blood. Calculations of methylmercury removal from the blood compartment during treatment indicated that removal of methylmercury from extravascular body compartments had occurred. The clinical status of one patient followed over a 2-year period after treatment revealed considerable improvement. It was difficult to tell what degree of improvement was a result of the treatment procedure which was enacted rather late after the onset of poisoning. No adverse effects of the treatment procedure were encountered.

7 **TITLE:** Prenatal methylmercury poisoning: clinical observations over five years (UR-3490-1300)

AUTHORS: L. Amin-Zaki, M. A. Majeed, S. B. Elhassani, T. W. Clarkson, M. R. Greenwood and R. A. Doherty

PUBLICATION: *Am. J. Diseases Child.*, (in press)

SUMMARY: Thirty-two infants prenatally exposed to methylmercury and their mothers were examined over a five-year period following the Iraq methylmercury epidemic. Severity of poisoning was related in the mothers to the peak mercury concentration in hair and in the infants to the maximum concentration in maternal hair during pregnancy. In nine cases of cerebral palsy, methylmercury exposure was only during the last trimester. All except three infants (two orphaned soon after birth and one bottle fed) were exposed postnatally via sucking. Whereas the mother usually improved, the damage to the fetal nervous system appears to be permanent. Milder cases previously not identified in other studies are described. The syndrome consists of varying degrees of developmental retardation in addition to exaggerated tendon reflexes and the pathologic extensor plantar reflex (Babinski positive).

4 **TITLE:** Operant behavior of rats exposed before or after weaning to low levels of lead (UR-3490-1533)

AUTHOR: N. F. Angell (Supervised by B. Weiss)

PUBLICATION: *Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)*

ABSTRACT OF THESIS: Millions of children are exposed to lead at levels which do not cause overt signs or symptoms of plumbism. This asymptomatic lead exposure may not be benign; clinical reports have linked elevated lead levels with adverse effects on behavior of children. Comparisons of clinical reports with the experimental literature are difficult because the doses used in most studies of the behavioral toxicity of lead were sufficient to cause weight loss, neurological impairment or death. The present study was designed to investigate behavioral effects of lead in animals which showed no overt signs of toxicity.

Rats were exposed to lead under one of three conditions. One group received lead by suckling dams who had their drinking water replaced with a solution of 0.2% lead acetate (1090 ppm lead). A second group was placed on the same concentration of lead-treated drinking water at weaning. A third group received both preweaning and postweaning treatments. Controls were never exposed to lead above background levels.

Behavioral testing was begun on day 58. Rats were trained to press a bar and then were placed on a multiple fixed-ratio, time out, fixed-interval, time out schedule of reinforcement. In addition to the basic schedule, two extinction probes were run. A parametric manipulation of ratio size was also done in which ratio size was varied between FR20 and FR100 while the other schedule components were held constant. Blood lead concentrations were measured at various times in the experiment and brain lead concentrations were measured in sacrificed rats.

The median blood lead concentration at weaning was 100 μg percent. On day 133, the blood lead concentrations of the two groups exposed postweaning were 65 μg percent while the preweaning group had dropped to 9 μg percent. Median blood lead concentrations in controls were 2 μg percent or below at all measurement points. The only overt signs of lead exposure occurred in the group

exposed both preweaning and postweaning. This group showed a slight retardation of growth between weaning and day 54 of life.

These low levels of lead exposure produced subtle alterations in behavior. The two groups exposed postweaning showed a statistically significant lengthening of the median interresponse time (lowered response rate) in both the ratio and interval schedules. These effects were most pronounced during the first 15 sessions on the multiple schedule. In contrast, the group exposed only preweaning showed a shortening of the median IRT (increased response rate) on both schedules. The effect in this group approached statistical significance. In the ratio size manipulation, the control group showed an approximately linear trend when ratio size was plotted against time to the first response in the ratio. No such trend was evident in the lead-exposed groups. Instead, the exposed groups showed wide variability in their response to the manipulation and no trend was evident.

The results of this study, and two others in the literature which report effects of lead on response rates under operant schedules, lead to the speculation that the concentration-effect function for lead has an inverted U-shape. That is, low blood lead concentrations produce increases in response rate, while higher blood lead concentrations result in lowered response rates. Behavioral, neuropathological, and neurochemical evidence is consistent with the hypothesis that lead produces behavioral effects by interfering with dopaminergic neurotransmission.

The effects observed in this experiment occurred in rats which showed no overt signs of plumbism. The blood lead concentrations were slightly higher, but comparable, to concentrations currently accepted as safe for children. The results indicate that current standards for 40 μg percent for children may be too high. Such lead concentrations could produce behavioral damage with serious, long-term consequences.

5 TITLE: Two classes of β pleated-sheet conformation in poly(L-tyrosine): a model for tertiary structure in native proteins (UR-3490-1310)

AUTHORS: H. E. Auer and R. P. McKnight

PUBLICATION: *Biochem.*, 17: 2798-2805 (1978)

SUMMARY: Poly(L-tyrosine) generates the antiparallel β -sheet conformation at low ionization in aqueous solution. In this work the properties of three samples of $(\text{Tyr})_n$, numbered 1 - 3 in order of increasing degree of polymerization, were investigated at solute concentrations low enough to form only intramolecular (i.e., nonaggregated) β structures. It was concluded that two classes of β structure are formed by $(\text{Tyr})_n$ in solution, with samples 1 and 2 comprising class I and sample 3 representing class II. This finding is based on distinctions observed in the sedimentation coefficient and in the far-ultraviolet circular dichroism spectra, ascribed to the side-chain chromophore. Furthermore, distinctions in the entropy change for the β -disordered chain transition, the breadth of the transition, and the electrostatic potential in the ordered state, based on spectrophotometric-potentiometric titrations on samples 1 and 3, have already been reported [McKnight, R. P., and Auer, H. E. (1976), *Macromolecules* 9, 939-944]. A comparison of the experimental frictional ratios with values calculated from a variety of model ellipsoids of revolution reveals that the hydrodynamic properties of samples 1 and 2 are consistent only with very anisotropic model particles; it is likely that they have only a few polypeptide

chain segments folded into long, open-sheet β structures. The properties of sample 3, on the other hand, suggest that it adopts a more compact shape, and it is proposed that the β sheet in this particle is folded over onto itself to generate a double-layered structure. If so this may represent the first instance of prototypical tertiary structure generated in a system as simple as a β -forming homopoly-(amino acid). The distinctions observed for all other properties studied are consistent with these proposed hydrodynamic models. When sample 3 is transferred from sodium buffer, in which the properties summarized above are observed, to tetramethylammonium buffer, its behavior changes to that characteristic of the low-DP class. Dialysis back to sodium medium largely restores the original properties. This shows that the development of the folded β structure in $(\text{Tyr})_n$ is readily modulated by varying experimentally accessible parameters.

4 **TITLE:** Actinomycin D—deoxynucleotide interactions: binding isotherms at the benzenoid and quinoid portions of the drug (UR-3490-1389)

AUTHORS: H. E. Auer and T. N. Thompson

PUBLICATION: *Proc. Natl. Acad. Sci. USA*, 75: 4729-4733 (1978)

SUMMARY: Titrations of actinomycin D (AMD) with dG and with dG-dC were monitored by circular dichroism at 380 nm and 470 nm. These wavelengths are sensitive predominantly to nucleotide binding processes at the benzenoid and quinoid portions, respectively, of the phenoxazone ring of the drug chromophore [Auer, H. E., Pawlowski-Konopnicki, B. E., Chiao, Y. C. C. & Krugh, T. R. (1978), *Biopolymers*, 17, 1891-1911.]. The temperature dependence of these isotherms was analyzed by the van't Hoff equation to obtain values for the enthalpy and entropy changes. For dG these are about $-11 \text{ kcal mol}^{-1}$ and $-20 \text{ cal mol}^{-1} \text{ deg}^{-1}$, respectively, for complex formation at both the benzenoid and quinoid sites ($1 \text{ cal} = 4.184 \text{ J}$). The enthalpy and entropy changes for complex formation with dG-dC remain unchanged at the benzenoid site, but both values are more negative at the quinoid site. These results indicate that the additional process of binding C in the intercalated $\text{AMD}-(\text{dG-dC})_2$ complex, with respect to the simply stacked AMD-dG_2 complex, has distinctive properties at the two sites, reflecting their structural differences. The ability to resolve binding processes at the two sites by circular dichroism has permitted us to suggest assignments for the two ^{31}P magnetic resonance lines from the phosphodiester groups observed in the $\text{AMD}-(\text{pdG-dC})_2$ complex [Patel, D. J. (1976) *Biochim. Biophys. Acta* 442, 98-108].

^ **TITLE:** Characterization of the pH-dependent dimer-to-protomer transformation of cytochrome c oxidase at alkaline pH (UR-3490-1420)

- **AUTHORS:** H. E. Auer, M. Sun and M. Greulick

PUBLICATION: *Physiol. Chem. Phys.*, (in press)

SUMMARY: The pH-induced dissociation of cytochrome c oxidase from dimer to protomer has been studied in the pH range 7 to 11. The heme A:copper ratio is 1.0 at both pH 7.4 and 10.6. The relative enzymatic activity is preserved at all pH values at which the dimer or protomer are found. The fraction of protomer, determined from sedimentation velocity profiles, increases from 0 to 1 as the pH is raised. The absorption and circular dichroism spectra in the Soret region change

in ways indicating that the contributions of cytochrome *a* in the typical cytochrome *aa₃* spectral patterns are progressively lost as the pH increases. At pH values more alkaline than the above denaturation occurs. The fraction of protomer and certain parameters which are defined to quantitate the changes in spectral form exhibit similar pH profiles for a given preparation, but these concerted changes occur over different pH ranges with different preparations. Nevertheless, the optical parameters are linearly correlated with the fraction of protomer for each preparation. It is concluded that the spectral properties of the dimer and the protomer are intrinsic attributes of each species, respectively, and are not directly affected by changes in ambient pH.

§ *TITLE:* The determination of ^{210}Po and ^{210}Bi in human urine by direct extraction on nickel (UR-3490-1088)

AUTHORS: W. F. Bale, R. W. Helmkamp and V. Hrynyszyn

PUBLICATION: Intern. J. Appl. Radiation Isotopes, (in press)

SUMMARY: Added ^{210}Po and ^{210}Bi in hydrochloric acid and in acidified urine were determined by extracting the solutions with 4.5 X 11 cm nickel foils for three to four hours at 90° to 100° C or for 48 hours at room temperature. Quantitative recoveries of ^{210}Po were obtained from 900 to 2000 ml of 0.25 N HCl at 90° to 100° C and from 1800 ml of 0.1 to 0.5 N HCl at room temperature. Extraction of ^{210}Po from 2 X 1335 to 2 X 1700 ml of acidified urine was likewise quantitative at 90° to 100° C. Average recovery from similar volumes of urine at room temperature was 92.7%.

Silver foils also extracted ^{210}Po quantitatively at 90° to 100° C from 900 to 2000 ml of 0.25 N HCl. However, extraction from HCl at room temperature and from urine at both 90° to 100° C and room temperature was less efficient than on nickel.

The recovery of ^{210}Bi on nickel from spiked solutions was determined from the ingrowth of ^{210}Po on decay of the deposited ^{210}Bi . Quantitative recoveries were obtained from 1700 and 1800 ml of 0.1 to 0.5 N HCl at both 90° to 100° C and room temperature. From a 1700 ml specimen of spiked human urine, acidified by addition of 0.5 mole of HCl/l of solution, recovery at 90° to 100° C was 94.7%.

When gamma-emitting ^{207}Bi was substituted for ^{210}Bi , average recovery at 90° to 100° C and at room temperature from 1700 ml of 0.05 to 0.5 N HCl was 93%, and from the same volume of human urine, acidified by addition of 0.25 mole of HCl/l of solution, 91.6%. When the spiked urine was acidified with 0.5 mole of HCl/l of solution, recovery of ^{210}Bi was substantially lower. A very significant decrease in the average recoveries of ^{210}Bi and ^{207}Bi occurred when the foils were rinsed on removal from the extracted solutions.

If detection efficiency was 50%, the calculated average ^{210}Po content of three different pools of normal human urine on excretion was 0.03 pCi/l and that of ^{210}Bi 0.87 pCi/l.

9 **TITLE:** The cleavage and adsorption of parathyroid hormone at high dilution. Implications for receptor binding studies (UR-3490-911)

AUTHORS: P. Q. Barrett and W. F. Neuman

PUBLICATION: *Biochim. Biophys. Acta*, 541: 223-233 (1978)

SUMMARY: Like other polypeptide hormones, purified intact parathyroid hormone (1-84) parathyroid hormone is notoriously unstable and is subject to large adsorptive losses in routine laboratory manipulation. The present studies were undertaken with ^{125}I -labeled hormone to quantitate the problem and to develop preventive measures, particularly with concentrations of physiological interest, $1 \cdot 10^{-10}$ M.

It was found that spontaneous cleavage of the hormone takes place upon its incubation in air or oxygen. This can be prevented by the presence of mercaptoethanol or by plasma levels of cysteine and ascorbate.

Under noncleavage conditions, adsorption was found to be extensive on all materials tested. This adsorption increased with time up to two hours, was independent of ionic strength, increased with increasing temperature and was presumed to involve hydrophobic interactions. Under given conditions, adsorption was proportional to concentration (constant percentage). However, at very high concentration, $1 \cdot 10^{-6}$ M, adsorption was markedly reduced.

Adsorption was minimized at low pH (2). Bovine serum albumin reduced adsorption under all conditions when present at concentrations of 2 mg/ml or more. Coating laboratory ware with cetyl alcohol also was helpful. Using optimal conditions, cleavage is prevented and losses are less than 5% at neutral pH, and under 2% and pH 2.

10 **TITLE:** The heterogeneity of radioiodinated parathyroid hormone in rat plasma (UR-3490-1269)

AUTHORS: P. Q. Barrett, A. P. Teitelbaum and W. F. Neuman

PUBLICATION: *Metabolic Bone Disease and Related Research*, (in press)

SUMMARY: Parathyroid hormone has been reported to occur in plasma as a mixture of intact hormone and fragments most of which exhibit a molecular weight around 6000 daltons. The present studies were undertaken to clarify the origins of these fragments. Labeled hormone was found to generate the 6000 molecular weight fragment(s) presumably by peripheral proteolytic degradation. The metabolite(s) derived from bioinactive hormone (iodinated by chloramine-T) was cleared less rapidly from the circulation of the rat than was the metabolite(s) derived from biologically active hormone (iodinated electrolytically). However, in neither case did the 6000 molecular weight fragment exceed the concentration of intact hormone in the circulation of the rat.

It was found that a widely used chromatographic system (nondenaturing) underestimates the proportion of intact hormone present in plasma samples.

11 **TITLE:** Studies on a mutant regulatory protein synthesized by gene 45 of bacteriophage T4D: differential functional stabilization and suppression of temperature-sensitive characteristics (UR/3490/LCP-10)

AUTHOR: B. R. Baser (Supervised by J. S. Wiberg)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: Bacteriophage T4 diverts host cell metabolism from bacterial to viral functions after infection. The pattern is one of total, rapid, and irreversible host genome inactivation and degradation and involves time-ordered sequences of gene expression generated by both transcriptional and posttranscriptional regulation.

E. coli B infected with wild-type T4 at 37° C synthesizes "early" proteins until about 12 minutes postinfection (mpi); this is called the S1 shutoff. When DNA synthesis is blocked by mutation, early protein synthesis continues to roughly 22 mpi; this shutoff (S2) is controlled in *regA* function. Infections which are (DNA⁺, *regA*⁻), with the exception of maturation-defective (MD) mutations coupled to *regA*⁻, have an S1 shutoff. Neither (DNA⁻, *regA*⁻) nor (MD, *regA*⁻) infections show an S2 shutoff, resulting in considerable overproduction of many early proteins.

Protein 45 (P45), another regulatory protein of T4, is obligatory both for synthesis of T4 DNA, as a component of the replication complex, and for late transcription, where it is found in association with T4-modified RNA polymerase. Late transcription is coupled to DNA synthesis for T4, quite possibly through this dual function of P45. The pattern of P45 synthesis is also unusual among the primarily catalytic early proteins, not only because S1 and S2 are coincident for P45 at about 8 mpi, but also because it constitutes 2% of total phage protein synthesized 5 to 7 mpi. An understanding of the controls operating on and through P45 to regulate DNA synthesis and late transcription is therefore central to the understanding of late protein production and viral maturation.

This thesis examines the regulation of P45 synthesis by a double mutant (*ts45,regA1*) producing a temperature-sensitive P45 at 40.8° C, a temperature barely permissive for the single *ts45* mutant, and explores the effect of a thermolabile P45 on DNA synthesis and late transcription. The mutant (*ts45,regA1*), compared to (*ts45*), synthesizes considerably more DNA and slightly more late RNA at 40.8° C because of a delay in the S1 shutoff which allows extended synthesis of thermolabile P45. This extended synthesis of P45 was visualized through SDS-polyacrylamide gel electrophoresis of ¹⁴C-amino acid pulse-labeled phage proteins. The delay in S1 is attributable, either directly or indirectly, to relatively defective late transcription by (*ts45,regA1*) at 40.8° C.

The separability of P45 functions was exploited in the isolation and characterization of a spontaneous triple mutant (*ts45,regA1,S16*), arising from (*ts45,regA1*), with respect to DNA, late RNA, protein, and phage production. A derivative double mutant (*ts45,S16*) was also characterized. The dominant mutation S16 suppresses the temperature sensitivity of the thermolabile P45 at 40.8° C to different extents in the presence or absence of *regA* function: for (*ts45,S16*), both DNA and late RNA synthesis are 50% to 60% that of T4⁺ for at least one hour; for (*ts45,regA1,S16*), DNA synthesis is 100% that of T4⁺ over an hour, and does not depend on extended synthesis of P45, while the amount of late RNA synthesis (initially about the same at (*ts45,S16*)) becomes negligible by 40 mpi. These results suggest a possible role for *regA* in DNA and RNA synthesis. We have not yet been able to isolate

S16 as a single mutant but have been able to determine that it lies either in g45 or just outside g45 (i.e., in g44 or between genes 45 and 44).

In the course of these studies, a discrepancy in the literature regarding the role of g55 (MD) mutants in the shutoff of early RNA synthesis was examined (g45 mutants display both MD and DNA⁻ phenotypes under appropriate conditions). These results fully support the evidence indicating g55 is partially responsible for the shutoff of early mRNA synthesis.

2
TITLE: Lymphadenopathy without lymphocytosis (UR-3490-1085)

AUTHORS: J. M. Bennett and M. A. Lichtman

PUBLICATION: Chapt. 10 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 195-222 (1978)

SUMMARY: This chapter presents a diagnostic approach to the chronic problem of lymph node enlargement.

3
TITLE: Book review of "Radiation Effects. ESR and ENDOR Analysis" by H. C. Box. Academic Press, New York, 280 pp., 1977 (UR-3490-1470)

AUTHOR: W. A. Bernhard

PUBLICATION: *Radiation Res.*, (in press)

SUMMARY: This book focuses on the free radical mechanisms of radiation-induced alterations in biomolecules. The author uses Part I of the book to introduce ESR theory and techniques, setting the stage for Part II where information gained mainly from ESR and ENDOR is used to discuss the current understanding of how various biochemicals are modified by radiation.

4
TITLE: Effects of fast neutrons on rabbits. II. Comparison of pathologic effects of fractionated neutron and photon exposures of the lung and spinal cord (UR-3490-1388)

AUTHORS: E. W. Bradley, B. C. Zook, G. W. Casarett, K. L. Mossmann and C. C. Rogers

PUBLICATION: *Intern. J. Radiation Oncol., Biol. and Phys.*, (in press)

SUMMARY: Young adult rabbits were irradiated at high intensity twice weekly for six weeks to the cervical and thoracic spinal cord region (> 50% of lungs included in field) with photons (4 MeV) to four cumulative doses (from 4,800 to 19,200 rad) or fast neutrons (15 MeV) to four cumulative doses (from 1,680 to 6,720 rad), with photon doses 2.86 times as large (assumed relative biological effectiveness) as corresponding neutron doses. The rabbits were observed especially for pulmonary and neurologic signs and when paralyzed or moribund were sacrificed for histopathologic study. Paraplegia occurred only after 6,720 rad of photons or after neutron doses of 2,520 rad or greater. Only in these rabbits were spinal cord lesions observed; they varied from occasional swollen axons to extensive necrosis and myelin loss and were much more severe in the white than in the gray matter. Malignant bone tumors were found only in the irradiated field in two of the three rabbits receiving 2,520 rad of neutrons. Radiation-induced lung changes were found in all irradiated rabbits with the character of the lesions depending upon dose and time after irradiation. Signs of severe respiratory diseases were seldom observed until just before death.

5 TITLE: Purpura, thrombocytopenia, and thrombocythemia: hemorrhage as a result of defects in primary hemostasis (UR-3490-1218)

AUTHORS: R. T. Breckenridge and M. A. Lichtman

PUBLICATION: Chapt. 13 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 277-295 (1978)

SUMMARY: This chapter describes the diagnosis and management of patients who have hemorrhage from a defect in primary hemostasis which includes platelet and vascular factors.

6 TITLE: Studies on the mechanisms underlying the transfer of calcium and phosphate from bone to blood (UR-3490-1468)

AUTHOR: R. J. Brommage, Jr. (Supervised by W. F. Neuman)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The skeleton is recognized as a crucial organ in the minute-to-minute regulation of the blood levels of calcium and phosphate. The fluxes of calcium and phosphate to and from bone greatly exceed the entry and exit of these ions occurring in the intestine and kidneys. Parathyroid hormone, calcitonin and 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) are known to influence the transfer of calcium and phosphate from bone to blood.

Three mechanisms have been proposed to explain the hormonal control of the calcium and phosphate effluxes from bone. The concept of a "bone membrane" maintaining a distinct bone extracellular fluid composition has led to the "pump" and "pH gradient" theories. Under these proposals, calcium and phosphate are either actively transported from bone to blood or dissolved from the bone mineral crystal surface by the action of a decreased pH in the bone extracellular fluid. An alternate "solubilizer" theory proposes that bone cells secrete a substance which increases the solubility of the bone mineral.

The "bone membrane" concept was originally proposed to explain the presence of the apparent anomalously high concentrations of potassium in the bone extracellular fluid. These elevated potassium levels were found to result, in part, from the zeta potential-induced concentration of polarizable ions. Nonvital chick calvaria were shown to concentrate the sodium and potassium in bone water by a factor of approximately two over the buffer levels of these ions. At the present time, estimates of the volume of skeletal water occupied by cells are sufficiently imprecise to preclude the proper assignment of skeletal potassium between cellular and extracellular compartments. Thus, the available evidence does not allow an unambiguous decision concerning the presence of a bone membrane.

Incubated calvaria from neonatal mice previously injected with 1,25-(OH)₂D₃ were used to explore the mechanism of action of this hormone. Calvarial lactate production was unaltered by 1,25-(OH)₂D₃ treatment and consequently 1,25-(OH)₂D₃ does not appear to promote the mobilization of bone mineral through a lactate-mediated "pH gradient" mechanism. 1,25-(OH)₂D₃ did increase the solubility of nonvital bone, clearly demonstrating that the "solubilizer" mechanism is at least partially responsible for the mobilization of bone mineral and the regulation of blood levels of calcium and phosphate.

Studies were undertaken to develop a system of vitamin D-deficient bone suitable for *in vitro* examinations of the skeletal actions of various vitamin D metabolites. Vitamin D-deficient female rats fed a 0.2% calcium, 0.4% phosphorous diet and supplemented with daily injections of 0.75 pmole of 1,25-(OH)₂D₃ were shown to be capable of bearing young. When the injections of 1,25-(OH)₂D₃ were terminated at delivery, the dams and pups showed signs of vitamin D deficiency approximately one week later. Vitamin D-deficient rat pups were also produced by placing normal impregnated rats on a vitamin D-deficient diet soon after mating.

17 **TITLE:** Mechanism of the mobilization of bone mineral by 1,25-dihydroxyvitamin D₃ (UR-3490-1442)

AUTHORS: R. Brommage and W. F. Neuman

PUBLICATION: *Am. J. Physiol.*, (in press)

SUMMARY: Lactate production and mineral solubility of calvaria were studied in an *in vitro* incubation system. The calvaria were taken from four- to five-day-old mice, some of which were previously injected with 20 ng of 1,25-(OH)₂D₃, an active metabolite of vitamin D₃. In live bones, 1,25-(OH)₂D₃ induced bone mineral mobilization as evidenced by the increased release of both calcium and phosphate into the medium. No effect of 1,25-(OH)₂D₃ upon lactate production was observed. 1,25-(OH)₂D₃-treated calvaria also supported higher buffer levels of calcium and phosphate in the absence of cellular metabolism, indicating that 1,25-(OH)₂D₃ increased the solubility of bone mineral. The implications of these findings are discussed in terms of the existing theories of bone mineral mobilization.

18 **TITLE:** The passive accumulation of magnesium, sodium and potassium by chick calvaria (UR-3490-1487)

AUTHORS: R. Brommage and W. F. Neuman

PUBLICATION: *Calc. Tiss. Res.*, (in press)

SUMMARY: Four-day-old chick calvaria were used to determine the passive concentrations of magnesium, sodium and potassium in nonvital bone. When incubated in buffers containing the blood levels of sodium and magnesium, nonvital calvaria contained sodium and magnesium at the same concentrations found in freshly-dissected calvaria. Calvarial sodium and magnesium levels could be varied by altering the buffer concentrations of these cations. The potassium content of nonvital calvaria incubated in buffers containing 4 mM potassium was determined to be less than 20% of the content found in freshly-dissected calvaria. By systematically varying the buffer concentrations of sodium and potassium, nonvital calvaria were found to concentrate these cations by a factor of approximately two in the bone extracellular fluid. Presumably, the hydroxyapatite crystal zeta potential is responsible for this concentrative phenomenon. These results are discussed in terms of the control of the ionic content of the bone extracellular fluid by the postulated "bone membrane".

9
TITLE: Anion inhibitor-sensitive unidirectional sodium movements in the human erythrocyte (UR-3490-1123)

AUTHORS: T. J. Callahan and D. A. Goldstein

PUBLICATION: *J. Gen. Physiol.*, 72: 87-100 (1978)

SUMMARY: The increased unidirectional sodium influx found when human erythrocytes are suspended in isotonic salt solutions containing bicarbonate ions as a replacement for chloride ions was examined. The increased sodium movement appears to have the transport characteristics of anion movement. Inhibitors of anion transport such as furosemide, fluorodinitrobenzene (FDNB), and 4-acetamido-4'-isothiocyano-stilbene-2-2'-disulfonic acid (SITS) drastically inhibit these augmented sodium movements. An ion-pair mechanism appears to phenomenologically describe much of the data. A possible role for carbamino groups is considered. Such a model, however, requires additional assumptions to explain the selectivity and the anion inhibitor effects.

20
TITLE: Biochemical and morphological characterization of light and heavy sarcoplasmic reticulum vesicles (UR-3490-1504)

AUTHOR: K. P. Campbell (Supervised by A. E. Shamoo)

PUBLICATION: *Ph.D. Thesis, University of Rochester School of Medicine and Dentistry* (1978)

ABSTRACT OF THESIS: Light (30-32.5% sucrose) and heavy (38.5-42% sucrose) sarcoplasmic reticulum vesicles (LSR,HSR) have been isolated from rabbit leg muscle using a combination of differential centrifugation and isopycnic zonal ultracentrifugation. They were then diluted and washed with 0.25 M sucrose or 1.0 M KCl and referred to as sucrose or KCl washed vesicles. Thin-section electron microscopy of LSR vesicles reveals empty vesicles of various sizes and shapes whereas the HSR vesicles appear as rounded vesicles of uniform size filled with electron dense material similar to that seen in the terminal cisternae of the sarcoplasmic reticulum. The sucrose HSR vesicles have an additional morphological feature which appears as membrane projections that resemble the "SR feet". The freeze-fracture morphology of either type of SR reveals an asymmetric distribution of intramembraneous particles in the same orientation and distribution as the sarcoplasmic reticulum *in vivo*.

Sodium dodecyl sulfate gel electrophoresis of LSR vesicles shows that the LSR consists of predominantly $\text{Ca}^{++} + \text{Mg}^{++}$ ATPase (80-90%), a small amount of the high affinity Ca binding protein (5%) and a 5000 dalton proteolipid. The sucrose HSR vesicles contain the $\text{Ca}^{++} + \text{Mg}^{++}$ ATPase (50%), Calsequestrin (25%), high affinity Ca binding protein (5%), one extrinsic 34,000 dalton protein (3%), one intrinsic 30,000 dalton protein (3%), a 9000 dalton proteolipid and a 5000 dalton proteolipid. The sucrose-washed HSR vesicles contain greater than three times the calcium content of the sucrose-washed LSR vesicles (114 vs 34 nmoles Ca^{++} /mg of protein) where as the KCl-washed vesicles contain less than 15 nmoles Ca^{++} /mg of protein each. The rate of passive calcium efflux from the HSR vesicles is approximately twice that of the LSR vesicles. The first order rate constant for calcium efflux from the HSR-sucrose vesicles is 25% greater than that of the HSR-KCl vesicles while in the presence of 20 μM Na dantrolene their rate constants are approximately equal.

The light and heavy sarcoplasmic reticulum vesicles were both able to accumulate calcium in the presence of ATP to amounts greater than 100 nmoles Ca per mg of protein in less than one minute. Exchange of methanesulfonate for chloride resulted in the release of calcium from both the light and heavy SR vesicles. Due to the difference in permeability between methanesulfonate and chloride this change should result in a decreased positivity inside the vesicles with respect to the exterior. Sucrose (200 mM) causes a slight inhibition of chloride-induced calcium release from the heavy SR vesicles but it greatly reduces the release of calcium from the light SR vesicles. The amount of ^{14}C -sucrose or ^{22}Na that is released from the light SR vesicles is three to five times greater than that released from the heavy SR vesicles during a chloride-induced release of calcium. Na dantrolene (20 μM) has no effect on the release of calcium from the light SR vesicles but it inhibits the release of calcium from the heavy SR vesicles.

Our results indicate that the chloride-induced release of calcium may be acting by two mechanisms, osmotic swelling and depolarization and that the release of calcium from the light SR vesicles and heavy SR vesicles is probably predominantly due to osmotic swelling and depolarization, respectively.

HSR vesicles were phosphorylated at room temperature for 10 minutes in 5 mM MgCl_2 , 1 mM EGTA, 10 mM HEPES (pH 7.4) and 10 μM [γ - ^{32}P] ATP. ^{32}P -phosphoproteins were determined by SDS-gel electrophoresis and autoradiography. In the absence of EGTA there was little phosphorylation but when 1 mM EGTA was present phosphorylation of several proteins could be seen. The phosphorylation was c-AMP independent, hydroxylamine resistant and was seen without the addition of endogenous protein kinase. The molecular weights of the phosphorylated proteins not known to be involved in glycolysis were 64,000 (E-1), 42,000 (E-2) and 20,000 daltons (E-3). Band E-1 corresponds to the protein calsequestrin in mobility on the Laemmli slab gel while bands E-2 and E-3 have no corresponding bands on the stained gel. Na dantrolene (20 μM) caused the decrease of the phosphorylation of the band E-1. The band E-3 was found in both the light SR vesicles and the HSR vesicles whereas the bands E-1 and E-2 were found only in the HSR vesicles. Isolation of calsequestrin by gel electrophoresis or calcium precipitation reveals a low level of ^{32}P incorporation into calsequestrin.

The biochemical and morphological data indicate that the LSR is derived from the longitudinal sarcoplasmic reticulum and the HSR is derived from the terminal cisternae of the sarcoplasmic reticulum, contains junctional SR membrane and has three unique proteins (calsequestrin, an intrinsic 30,000 dalton protein and a 9000 dalton proteolipid).

TITLE: The role of the membrane potential in active intestinal sugar transport (UR/3490/LCP-9)

AUTHOR: C. A. Carter-Su (Supervised by G. A. Kimmich)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The contribution of the membrane potential to active Na^+ -dependent monosaccharide transport was studied in both isolated brush border membrane vesicles and ATP-depleted isolated intestinal epithelial cells.

Brush border membrane vesicles isolated from chicken intestine were shown to retain the cell's ability to transport D-glucose in a Na^+ -dependent, phlorizin-sensitive, substrate-specific fashion.

When a large NaSCN gradient was imposed across the membrane in such a way as to induce the development of a transitory inside negative diffusion potential, "active" D-glucose transport was observed in the form of a brief (peak within 15 seconds) 2.5 to 4-fold overshoot over subsequent steady state levels. Attempts were made to overcome the drawback of rapidly dissipating membrane potentials by incorporating cytochrome oxidase into the brush border membranes. Purified cytochrome oxidase incorporated into asolectin vesicles by a variety of techniques retains its ability to create and maintain an inside negative membrane potential in the presence of extravesicular electron donors (cytochrome *c* and ascorbate) and an intravesicular electron acceptor (O_2). Incorporation into brush border membranes was assessed by the ability of a hydrogen ionophore to increase the activity of cytochrome oxidase as measured with an O_2 electrode. Electrical coupling between a cytochrome oxidase-maintained membrane potential and an electrogenic D-glucose transport system was assessed by the ability of D-glucose to increase respiratory rates in the presence of Na^+ ions. Although numerous reconstitution procedures were attempted and several gave limited success, none was found that allowed reproducible incorporation of cytochrome oxidase into brush border membranes as judged by these assay procedures.

Energy-depleted isolated intestinal epithelial cells offered an alternative system for dealing with rapidly dissipating ion gradients and diffusion potentials. They permit a degree of experimental control over cellular ion composition and eliminate metabolic contributions to the membrane potential. Because of increased membrane integrity and larger size, imposed ion and solute gradients can be maintained for much longer intervals. Sustained solute overshoots are observed (peak at 10 to 20 minutes) and unidirectional flux rates can be determined easily.

Rotenone or dinitrophenol treatment was used to decrease cellular ATP levels by over 90% and produce a cell population in which no steady state accumulation of 3-O-methyl-glucose (3-OMG) against a concentration gradient was observed. The Na^+ -independent transport system which compromises the gradient-forming capability of the Na^+ -dependent system was inhibited with 200 μM phloretin. Imposed inward-directed anion or outward-directed cation gradients were used to create inside negative-induced diffusion potentials.

In the presence of a large inward-directed NaCl gradient, ATP-depleted cells actively accumulate 3-OMG to a 4.5-fold gradient which is sustained for ten minutes. The initial flux rate is 80% of control values and 24 times faster than the phlorizin-insensitive rate. The active accumulation and stimulated initial flux rate were diminished but still observed in the absence of a $[Na^+]$ gradient as long as conditions were appropriate for maintaining a membrane potential. 3OMG uptake in the presence of a given imposed Na-anion or anion gradient could be correlated with the magnitude of the diffusion potential as determined by the membrane permeability of the given anion ($SCH^- \succ Cl^- \succ Isethionate^- \succ SO_4^{=}$). The influx rates with imposed NaSCN or NaCl gradients are comparable in magnitude to those obtained in energized cells with a similar NaCl gradient. The slight difference (energized cells $\succ$ ATP-depleted cells) is diminished by the addition of ouabain, which suggests that an electrical potential difference (diffusion potential or rheogenic $Na^+ - K^+$ ATPase ion pump-generated potential) was responsible for the difference rather than a direct metabolic energy input. Although initial 3-OMG uptake rates into Na^+ -depleted normally energized cells also varied with the anion gradient, these differences disappeared with incubation time or when Na^+ was included in the preincubation medium.

Concentrative 3-OMG uptake can also be demonstrated with an outward-directed imposed K^+ gradient. Again, a large "overshoot" (up to 6-fold) occurs in the presence or absence of an imposed Na^+ concentration gradient which is markedly stimulated when K^+ membrane permeability is enhanced by valinomycin (up to a 9-fold overshoot). In cells with an imposed 20-fold outward $[K^+]$ gradient and no $[Na^+]$ gradient, valinomycin causes large increases (≈ 4 -fold) in maximal initial flux with very little change in the $[3\text{-OMG}]$ at which half maximal flux is observed (≈ 2 mM).

A similar stimulation of transport by diffusion potentials was observed when L-valine rather than 3-OMG was the transported solute. Initial fluxes were greater but overshoots were smaller than those seen with 3-OMG.

All of these experiments point to a very important role for the electrical membrane potential as a part of the thermodynamic driving force for Na^+ -dependent solute transport systems. While the mechanistic role for membrane potentials remains to be elucidated, it is clear that they exert a dramatic effect on carrier-mediated solute influxes and consequently on accumulation ratios.

TITLE: Marrow cell egress: specificity of the site of penetration into the sinus (UR-3490 1377)

AUTHORS: J. K. Chamberlain and M. A. Lichtman

PUBLICATION: *Blood*, 52: 959-968 (1978)

SUMMARY: Blood cells exit the marrow through the wall of the marrow sinuses. Using quantitative electron microscopy of mouse marrow, we addressed two questions regarding the anatomic process of egress: Do leukocytes and reticulocytes exit at specific sites on the sinus wall or do they exit at random loci? Do leukocytes and reticulocytes in egress use a preformed pore or do they make the pore as they exit? We confirmed that exiting leukocytes and reticulocytes do not pass through intercellular junctions; rather they penetrate endothelial cells. The distance of migrating cells from endothelial cell junctions ($1.4 \pm 0.1 \mu m$) was significantly less ($p < 0.001$) than the distance of endothelial cell junctions from points selected randomly along the sinus wall ($4.0 \pm 0.4 \mu m$). The initial stage of cell penetration is often associated with thinning and formation of pits in the endothelial cell. A close-fitting migration pore forms and allows passage of the cell to the sinus lumen. The migration pore of leukocytes reaches a maximum diameter as the middle third of the cell is in transit, whereas the migration pore of reticulocytes is maximal as the first third of the cell is in transit. In sinuses with leukocytes in transit, pores unassociated with migrating cells compose only 10%, whereas pores associated with migrating cells compose 90% of the 25 pore/mm of the sinus wall. In sinuses without cells in transit, pore frequency was only 2/mm. Pores without migrating cells were smaller and were sealed by abluminal adventitial cells. They may represent residues of recent transit. These studies provide quantitative support for a preferential migration site for cells at the parajunctional zone of the endothelial cell and support the concept that pores are made at the time of egress.

TITLE: Splenomegaly (UR-3490-1188)

AUTHORS: J. K. Chamberlain, A. W. Bauman and M. A. Lichtman

PUBLICATION: *Chapt. 11 in Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 223-245 (1978)

SUMMARY: This chapter describes the causes of splenic enlargement and emphasizes those

disorders associated with splenomegaly that have particular pertinence to hematologists.

24 **TITLE:** Properties of continuum source particle beams: II. Beams generated in capillary expansions (UR-3490-1423)

AUTHORS: Y. S. Cheng and R. F. Dahneke

PUBLICATION: *J. Chem. Phys.*, (in press)

SUMMARY: Choked capillary flow is described by an isothermal, locally developed flow model while flow in the supersonic free jet originating at the capillary exit is assumed isentropic in order to calculate volumetric gas flow through the capillary and the terminal velocity of particles suspended in the expanding gas. The results are compared to experimental data and found to agree within 2% to 3%. The principal cause of error is believed to be the failure of the capillary flow model near the capillary exit.

25 **TITLE:** Radioactive mercury distribution in biological fluids and excretion in human subjects after inhalation of mercury vapor (UR-3490-1220)

AUTHORS: M. G. Cherian, J. B. Hursh, T. W. Clarkson and J. Allen

PUBLICATION: *Arch. Environ. Health*, 33: 109-114 (1978)

SUMMARY: The distribution of mercury in red blood cells (RBCs) and plasma, and its excretion in urine and feces are described in five human subjects during the first seven days following inhalation of radioactive mercury vapor. A major portion (98%) of radioactive mercury in whole blood is initially accumulated in the RBCs and is transferred partly to the plasma compartment until the ratio of mercury in RBCs to plasma is about 2 within 20 hours. The cumulative urinary and fecal excretion of mercury for seven days is about 11.6% of the retained dose and is closely related to the percent decline in body burden of mercury. There is little correlation between either the urinary excretion and plasma radioactivity of mercury, or the specific activities of urine and plasma mercury, suggesting a mechanism other than a direct glomerular filtration involved in the urinary excretion of recently exposed mercury. These studies suggest that blood mercury levels can be used as an index of recent exposure, while urinary levels may be an index of renal concentration of mercury. However, there is no reliable index for mercury concentration in the brain.

26 **TITLE:** ESR and ENDOR study of 5'dCMP at 6 K (UR-3490-1421)

AUTHORS: D. M. Close and W. A. Bernhard

PUBLICATION: *J. Chem. Phys.*, (in press)

SUMMARY: The ESR spectra of single crystals of deoxycytidine 5'-phosphate-H₂O (5'dCMP), X-irradiated at 11 K and observed at 6 K, exhibit signals from three distinct free radicals. Analysis of the ENDOR spectra from two of these radicals indicates that these results from oxidation and reduction of the cytosine base. The reduced species exhibits hyperfine coupling to the C₆-H_α proton ($A_{\text{iso}}(\text{H}_6) = -1.392 \text{ mT}$). The oxidized species exhibits hyperfine couplings to the C₅-H_α proton ($A_{\text{iso}}(\text{H}_5) = -1.495 \text{ mT}$), N₁ and N₃, ($A_{\text{iso}}(\text{N}_1) \sim 0.5 \text{ mT}$), ($A_{\text{iso}}(\text{N}_3) \sim 0.25 \text{ mT}$) and to the

C₁'-H_β proton ($A_{\text{iso}}(\text{H}_\beta) = 1.483 \text{ mT}$). The third free radical has ESR spectra characteristic of an oxygen-centered defect and is thought to be a hole located primarily on the C₃'-O₃' oxygen, but shared with a neighboring HO-PO₃'-CH₂- group.

24
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TITLE: ESR and ENDOR study of X-irradiated single crystals of β-alanine at room temperature (UR-3490-1404)

AUTHORS: D. M. Close, G. W. Fouse, W. A. Bernhard and R. S. Andersen

PUBLICATION: *J. Chem. Phys.*, (in press)

SUMMARY: Three radicals have been identified in the room temperature ESR spectra of X-irradiated single crystals of β-alanine ($\text{N}^+\text{H}_3\text{CH}_2\text{-CH}_2\text{CO}_2^-$). ENDOR spectra from one radical exhibit hyperfine coupling to 1 α-proton ($A_{\text{xx}} = -33.12$, $A_{\text{yy}} = -20.68$, $A_{\text{zz}} = -10.50 \text{ G}$) and 2 β-protons ($A_{\text{iso}}(\text{H}_{\beta 1}) = 13.24 \text{ G}$, $A_{\text{iso}}(\text{H}_{\beta 2}) = 4.89 \text{ G}$). From the anisotropic nature of the α-proton coupling, it has been determined that these splittings arise from a $\text{N}^+\text{H}_3\text{CH}_2\dot{\text{C}}\text{HCO}_2^-$ radical. It has been shown that this radical is the decay product of the unstable low temperature oxidation product. A second room temperature radical, $\text{N}^+\text{H}_3\text{CH}_2\text{CH}_2\dot{\text{C}}=\text{O}$, has been shown to be a decay product of the primary reduction product. A minor room temperature product has been tentatively identified as a $\dot{\text{C}}\text{H}_2\text{-CH}_2\text{-R}$ radical.

24
TITLE: Polycythemia (UR-3490-1111)

AUTHORS: J. Cohen and M. A. Lichtman

PUBLICATION: *Chapt. 4 in Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 87-103 (1978)

SUMMARY: This chapter describes the diagnostic approach to patients who present to the physician with an elevated packed cell volume.

24
TITLE: Electron probe microanalysis and the cellular basis of intestinal calcium absorption (UR-3490-1353)

AUTHOR: J. R. Coleman

PUBLICATION: *Proc. 13th Ann. Conf. on Microbeam Analytical Soc.*, May 1978, Ann Arbor, Mich., pp. 25A-25E (1978)

SUMMARY: It was early recognized that the absorption of calcium by the intestine and the retention of calcium by the kidney were essential to the prevention and cure of the debilitating disease of rickets. The intestine and kidney, along with bone, formed the three elements of the complex mechanism which controls calcium metabolism, and maintains the concentration of calcium in blood between narrow and rigid limits. In addition to the effects of calcium on rickets, it has become increasingly evident in recent years that calcium plays an extremely important role in intracellular metabolism. That increased calcium concentration in muscle cells resulted in contraction has been clearly documented and current investigations center on the mechanisms that cyclically release and sequester calcium within the muscle cell. Other investigations have shown in

several different types of cells that calcium serves as a signal to increase or decrease the operation of several metabolic processes.

Microprobe methods offer distinct advantages for investigating such questions: microprobe analysis is sensitive to the very small amounts of calcium contained in a calcium-transporting cell; microprobe analysis is capable of sufficient spatial resolution that the location of calcium within a cell may be determined. Since individual cells may be analyzed, it is not necessary to deal with the uncertainties associated with measuring the average properties of a population of cells, some of which may be inactive or engaged in other processes. Consequently, in our studies of calcium absorption, we turned to microprobe analysis to obtain some greater insight into the cellular mechanisms involved.

h⁰ **TITLE:** X-ray analysis of biological samples (UR-3490-1341)

AUTHOR: J. R. Coleman

PUBLICATION: *Scanning Electron Microscopy, II: 911-926 (1978)*

SUMMARY: Electron probe X-ray microanalysis of biological samples involves samples with properties quite different from those usually encountered with geological, metallurgical and materials science specimens. In order to optimize conditions for analyzing biological samples, it is necessary to take into account the ways in which the biological materials interact with the electron beam and the X-rays generated by the electron beam. Range of electron penetration, beam spreading, X-ray-induced X-ray fluorescence, beam current, accelerating voltage, and electron source brightness influence analysis, and the effects of these parameters are examined. The physical density of the sample, its surface characteristics, and mean atomic number also affect analysis and the role of these parameters in analysis are outlined. Types of quantitative analysis are described and appropriate quantitative procedures for each type are presented and analyzed.

h¹ **TITLE:** Behavioral toxicity of chronic postweaning lead exposure in the rat (UR-3490-1365)

AUTHORS: D. A. Cory-Slechta and T. Thompson

PUBLICATION: *Toxicol. Appl. Pharmacol., (in press)*

SUMMARY: The behavioral effects of chronic lead acetate administration were assessed using the operant lever press maintained by a fixed interval 30 second food reinforcement schedule. On this schedule, the first response occurring at least 30 seconds after the preceding food presentation resulted in food delivery. To investigate the importance of exposure in post-weaning animals, 20- to 22-day-old rats were exposed to 50, 300, or 1000 ppm lead acetate or tap water drinking solutions. Exposure to 50 and 300 ppm lead acetate increased response rates and intersubject variability while time to initiation of responding in the interval (pausing) decreased. Response rates and initiation of responding times of subjects exposed to 50 ppm gradually returned to control levels once exposure ceased. Exposure to 1000 ppm initially decreased response rates and increased response initiation times. Time-dependent effects of either lead exposure or maturation were indicated by changes in response rates over sessions. Postweaning lead exposure in the rat, therefore, can produce changes in behavior as reflected by the fixed interval schedule.

32
TITLE: Properties of continuum source particle beams: I. Calculation methods and results (UR-3490-1400)

AUTHORS: B. E. Dahneke and Y. S. Cheng

PUBLICATION: *J. Aerosol Sci.*, (in press)

SUMMARY: The properties of continuum source particle beams, also called aerosol beams or seeded molecular beams, are investigated. Beams generated by expansions through converging cone nozzles are considered. Beam properties pertinent to the application of aerosol beams in the on-line measurement of particle size and composition distributions are emphasized. Methods for calculating the dependence of aerosol beam properties on particle size, shape and mass, source temperature and pressure and nozzle geometry are described and results are presented. The calculated results are compared to experimental data. A simple empirical method of modeling frictionless, isentropic transonic and supersonic flow in a free jet is described and used in the numerical experiments.

33
TITLE: Iron absorption in the thalassemia syndromes and its inhibition by tea (UR-3490-1494)

AUTHORS: P. A. de Alarcon, M-E. Donovan, G. B. Forbes, S. A. Landaw and J. A. Stockman, III

PUBLICATION: *New Engl. J. Med.*, (in press)

SUMMARY: To determine the hemoglobin concentration at which iron absorption is minimal, five subjects with thalassemia major and one with thalassemia intermedia underwent a series of iron-absorption studies. The effect of tea as an inhibitor of non-heme iron absorption was also tested. Iron absorption increased as the hemoglobin concentration decreased, although iron absorption was much higher at any given hemoglobin level in the subject with thalassemia intermedia. In the subjects with thalassemia major, iron absorption averaged 10% at hemoglobin concentrations between 9 and 10 and 2.7% between 11 and 13 g per deciliter. The percentage of iron absorbed could be accurately predicted from the nucleated red cell count ($r = 0.91$, $P < 0.001$). Tea produced a 41% to 95% inhibition of iron absorption.

Since patients with thalassemia intermedia may absorb a large percentage of dietary iron, inhibitors of iron absorption such as tea may be useful in the management.

34
TITLE: Granulocyte growth modulators elaborated by human cell lines (UR-3490-1351)

AUTHORS: J. F. DiPersio, J. K. Brennan and M. A. Lichtman

PUBLICATION: *In Hematopoietic Cell Differentiation*, Vol. 10, Ed. by D. W. Golde, M. J. Cline, D. Metcalf and C. F. Fox. (Proc. ICN-UCLA Symp. on Molecular and Cellular Biology, March 1978, Keystone, Colo.) Academic Press, New York, San Francisco, London, pp. 433-444 (1978)

SUMMARY: Two human monocyte-like cell lines have been established which produce colony stimulating activity (CSA) and colony inhibitory activity (CIA) for man and other species. Cell line CSA has been partially characterized and shown to be heterogeneous on Sephacryl S-200. Cell line CIA, a low molecular weight hydrophobic molecule has been partially purified and shown to inhibit not only CFU-C growth but the growth of various lymphoid cell lines.

35
TITLE: Methylmercury sexual dimorphism in the mouse (UR-3490-1308)

AUTHORS: R. A. Doherty, A. H. Gates, C. E. Sewell and C. Freer

PUBLICATION: *Experientia*, 34: 871 (1978)

SUMMARY: Five to eight days after a single nontoxic dose of radioactive methylmercury chloride adult male mouse kidneys contain twice as much radioactive mercury per unit wet weight as do kidneys of similarly dosed adult females.

36
TITLE: The affinity of antibody secreted by a single cell (UR/3490/LCP-12)

AUTHOR: D. M. Doran (Supervised by I. L. Spar)

PUBLICATION: *Ph.D. Thesis, University of Rochester School of Medicine and Dentistry* (1978)

ABSTRACT OF THESIS: It was the intention of this research to measure the affinity of antibody secreted by a single cell and to describe the spectrum of affinities displayed in response to antigenic stimulation.

The single cell secreting specific antibody was isolated by means of the hemolytic plaque assay. The amount of antibody secreted by the cell was to be measured through the use of a solid phase radioimmunoassay. The affinity of the antibody would be estimated by comparing the diameter of the plaque and the amount of antibody secreted with a mathematical theory of the formation of a plaque in agar.

As a test system, a solid phase radioimmunoassay was developed for human serum albumin using antibody coupled to Sephadex. A sensitivity of 1 nanogram was attained with this assay. A solid phase radioimmunoassay for mouse immunoglobulin M was developed using antibody coupled to Sepharose. The sensitivity attained with this assay was only on the order of 10 micrograms. The mouse immunoglobulin M radioimmunoassay was not sensitive enough to measure the amount of antibody secreted by a single cell.

The number of plaque-forming cells per spleen and the distribution of plaque diameters were studied in the hemolytic plaque assay of mice immunized with sheep erythrocytes. The number of plaques per spleen reached a maximum on the fourth day while the average plaque diameter increased from the second through the fifth days after immunization.

From a theoretical equation, the relationship between antibody affinity, plaque diameter and antibody secretion rate was calculated from the experimental conditions used in this research. By assuming a constant antibody secretion rate, an effective binding constant for the antibody was estimated from the average plaque diameters. This effective binding constant was observed to increase during the immune response.

37
TITLE: Studies of immune lysis of guinea pig line 1 hepatoma cells by xenogeneic antisera and complement (UR/3490/LCP-13)

AUTHOR: J. E. Doran (Supervised by I. L. Spar)

PUBLICATION: *Ph.D. Thesis, University of Rochester School of Medicine and Dentistry* (1978)

ABSTRACT OF THESIS: This research investigates the role that endogenous complement

would play in the serotherapy of a tumor-bearing guinea pig. The *in vitro* and *in vivo* interactions of antibody, complement, and host humoral factors with tumor cells are examined.

The tumor model used in these experiments is the ascites form of the guinea pig Line 1 Hepatoma maintained in Strain 2 guinea pigs by serial intraperitoneal transplantation. Xenogeneic antibody to Line 1 cells was produced in rabbits, adsorbed with sheep erythrocytes and an acetone preparation of normal Strain 2 guinea pig liver. The antisera was shown to be cytotoxic to Line 1 cells *in vitro* in the presence of either guinea pig or adsorbed human sera. The cytotoxic effects of antibody and complement were demonstrated using chromium release assays, as well as trypan blue dye exclusion.

In vivo tumor proliferation was quantified by determining changes in ascites fluid volumes and tumor cell concentrations at times after tumor inoculation. Whole complement titrations (CH50 titers) were performed on aliquots of ascites fluid withdrawn at times during the tumors' growth. The total amount of complement available to the tumor during its growth was thus estimated.

Using *in vitro* chromium release cytotoxicity assays, the sensitivity of Line 1 cells to lysis by xenogeneic cytotoxic antibody and guinea pig or human sera was examined. The relative sensitivities of tumor cells to lysis at different times during the tumor's growth, and with different sources of complement were determined. Sensitized tumor cells were shown to be more readily lysed by human sera than by guinea pig sera as the source of complement. The relative sensitivity of the cells to lysis was also shown to be dependent on the age of the tumor cells. Day 10 tumor cells were shown to require significantly more complement than day 6 cells. However, the amount of antisera required for complete sensitization decreased over the same period. Thus, the resistance of day 10 cells to lysis was not due to lack of antibody sensitization. Due to the relative resistance of Line 1 cells to *in vitro* lysis with guinea pig complement, it was postulated that even though complement was readily available to the tumor *in vivo*, the extent of antibody-mediated complement-dependent lysis of sensitized cells would be limited *in vivo*. Experiments performed to test this hypothesis were inconclusive.

In vitro assays have also shown that there is a factor or factors present in the ascites fluid of Line 1 tumor-bearing guinea pigs which inhibit the antibody-mediated complement-dependent cytotoxicity of Line 1 tumor cells. Some of its physical-chemical characteristics have been determined. The factor was shown to be soluble, TCA precipitable, and nondialyzable. Its activity was not associated with precipitates formed with either 33% or 50% saturated ammonium sulfate. The factor's activity was not a simple function of protein level, it does not act to coat the cells prohibiting antibody binding, nor does it inhibit chromium label release. The factor does not compete with antibody for specific antigenic sites, nor does it alter the ability of bound antibody to fix complement. Factor activity has been shown to be independent of the target system used and has been shown to act strictly as a complement inhibitor. The inhibitory activity of the ascites fluid has been shown to vary during the course of the tumor's growth. Factor activity could not be correlated with tumor cell concentration, or ascites fluid volume measurements.

3^d TITLE: Incorporation of cloned DNA by *Bacillus subtilis* (UR/3490/LCP-14)

AUTHOR: C. H. Duncan (Supervised by F. E. Young)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: Chimeric plasmids, consisting of *Bacillus* DNA coupled to *Escherichia coli* DNA were used to study genetic exchange in the soil bacterium, *Bacillus subtilis*. The *Bacillus* genes *thyP3*, *thyβ22*, and *leuC* were cloned in the vector pMB9 and all three were functionally expressed in the *E. coli* cytoplasm. Four such plasmids were introduced into *B. subtilis* by DNA-mediated transformation. These studies revealed that plasmids containing *thyP3*, a gene which shares nucleotide sequence homology with the *B. subtilis* chromosome, transform *B. subtilis* thymine auxotrophs to prototrophy at a high frequency whether the plasmid DNA is in circular or linear form. Transformation of the same strain with plasmids containing the gene *thyβ22* occurred at a much lower frequency, required circular DNA molecules, and required the presence of DNA sequences homologous to the *B. subtilis* chromosome on the plasmid. Hybridization analysis of chromosomal DNA from clones transformed with *thyβ22* demonstrated that the entire chimeric plasmid was inserted in the chromosome by a Campbell style integration event. This type of additive recombination had not been previously observed during transformation of *B. subtilis*.

To facilitate this work the two site-specific endonucleases from *Bacillus globigii*, *Bgl*I and *Bgl*II, were characterized by genetic and biochemical procedures. These studies led to the development of improved purification techniques for the two enzymes and proved that *Bgl*I and *Bgl*II function as restriction nucleases *in vivo*.

3^a TITLE: Biochemical and genetic properties of site-specific restriction endonucleases in *Bacillus globigii* (UR-3490-1401)

AUTHORS: C. H. Duncan, G. A. Wilson and F. E. Young

PUBLICATION: *J. Bacteriol.*, 134: 338-344 (1978)

SUMMARY: *Bacillus globigii* contains two site-specific endonucleases, *Bgl*I and *Bgl*II. A rapid technique for selection of mutants deficient in each of these enzymes was developed using sensitivity to infection by bacteriophage SP50 as an indication of the levels of enzyme. Mutants defective in *Bgl*I, *Bgl*II, and both *Bgl*I and *Bgl*II retained the wild-type modification phenotype. Genetic and biochemical studies have established that these enzymes are involved in restriction *in vivo*. Simplified purification procedures for *Bgl*I and *Bgl*II using these mutants are described.

4^o TITLE: Mechanism of integrating foreign DNA during transformation of *Bacillus subtilis* (UR-3490-1422)

AUTHORS: C. H. Duncan, G. A. Wilson and F. E. Young

PUBLICATION: *Proc. Natl. Acad. Sci. USA*, 75: 3664-3668 (1978)

SUMMARY: Genes encoding thymidylate synthetase from *Bacillus subtilis* bacteriophages were cloned in *Escherichia coli*. Chimeric plasmids pCD1 and pCD3 were constructed from site-specific endonuclease digests of bacteriophage φ3T DNA cloned in pMB9 in *E. coli*. Similar cloning techniques

with bacteriophage $\beta 22$ DNA yielded chimeric plasmids pCD4, pCD5, and pCD6. Endonuclease digests of DNA from pCD1 and pCD3 propagated in *E. coli* or from DNA isolated from bacteriophage $\phi 3T$ propagated in *B. subtilis* transformed *B. subtilis* from Thy^- to Thy^+ . Intact DNA from bacteriophage $\beta 22$, endonuclease digests of $\beta 22$ DNA, and a chimeric plasmid (pCD5) composed only of the *thy* $\beta 22$ gene and pMB9 did not transform *B. subtilis* from Thy^- to Thy^+ even though pCD5 could transform Thy^- *E. coli* to Thy^+ . However, if the *thy* $\beta 22$ fragment from pCD5 was introduced into another chimeric plasmid, pCD2, that contains a region of homology to the chromosome of *B. subtilis* in addition to pMB9, transformation of Thy^- clones of *B. subtilis* was possible. Furthermore, Southern hybridization analyses of the digests of chromosomal DNA from the Thy^+ transformants established that the entire chimeric plasmid was incorporated into the chromosome of *B. subtilis*. Treatment of these plasmids with site-specific endonucleases abolished transformation. These results indicated that the entire chimeric plasmid can be incorporated into the chromosome of *B. subtilis* by a Campbell-like model. Therefore, an additional mechanism for transformation exists whereby plasmids can be integrated if sufficient chromosomal homology is maintained.

✓ **TITLE:** The interaction of ethanol and mercury body burden in the mouse (UR-3490-1575)

AUTHOR: J. D. Dunn (Supervised by T. W. Clarkson)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The interaction of ethanol with mercury in the body resulting in increased exhalation of the metal was studied in the mouse to gain a further understanding of the phenomenon. Through an apparatus designed to quantitate mercury volatilized by unanesthetized experimental animals, a persistent elimination of the metal in the breath was demonstrated after single, sublethal ($< 1 \text{ mgHg/Kg}$ body weight) exposures to mercury vapor (Hg^0) or mercury II chloride (HgCl_2).

The amount of mercury exhaled per unit time was enhanced by oral or parenteral administration of ethanol solutions. These modifications were investigated in dose-response studies in which the drug was administered in doses ranging from 0.2 g to 5.5 g/Kg to mice pretreated with mercury. The EC_{50} for blood ethanol with respect to mercury exhalation was determined to be approximately 200 mg/dl corresponding to an output rate of approximately 0.1% of the simultaneous body burden in 30 minutes several days after mercury.

A hypothesis that mercury expired by these animals was proportional to the body burden after mercury administration was addressed in experiments whereby mice given one of several doses of mercuric chloride (0.15 to 500 $\mu\text{g/Kg}$) were monitored for pulmonary mercury elimination for a fifteen-day period. The high correlation obtained between the amount of mercury exhaled in a standard time period and the body burden by group indicated that breath sampling could be applied as an indicator of the mercury body burden which may not be limited to the mouse.

In additional studies, the chemical form of the mercury exhaled was detected to be mercury vapor by the use of differential adsorbents and administration of an alkyl-mercury compound.

The question as to the source of the mercury emanated by the mouse was studied *in vitro*. An apparatus suitable for detecting picogram quantities of volatilized mercury was designed and

tissue homogenates assayed for mercury volatilizing activity. Liver and kidney suspensions incubated with a cysteine-mercury complex exhibited heat-labile volatilizing activity in the presence of ethanol in the order of 0.12 and 0.19% of the total mercury in the medium per 30 minutes. Fractionated liver homogenate experiments suggested that the highest activity was associated with the 105,000g supernatant.

These results are consistent with a more dynamic nature of at least a portion of the ionic mercury in the mammalian body than previously shown. That ethanol is a metabolic factor that suppresses reoxidation of, and thus effects a net shift of *in vivo* mercury equilibria promoting mercury vapor exhalation is proposed in an amended model of inorganic mercury metabolism.

↓² **TITLE:** Ethanol-increased exhalation of mercury in mice (UR-3490-1176)

AUTHORS: J. D. Dunn, T. W. Clarkson and L. Magos

PUBLICATION: *Brit. J. Ind. Med.*, 35: 241-244 (1978)

SUMMARY: CBA/J mice injected three days beforehand with $^{203}\text{HgCl}_2$ were given ethanol or water by gavage and placed in a chamber designed to collect exhaled mercury. Ethanol treatment led to an eightfold increase of counts accumulated on a filter over a four-hour period, compared with water-treated mice. The mercury-collection apparatus tested for extracorporeal contribution of volatilised mercury indicated that the counts originated from the air exhaled by the mice.

↓³ **TITLE:** Behavioral toxicology (UR-3490-1029)

AUTHORS: H. L. Evans and B. Weiss

PUBLICATION: Chapt. 9 in *Contemporary Research in Behavioral Pharmacology*, Ed. by D. E. Blackman and D. J. Sanger. Plenum Publishing Corp., New York, N. Y., pp. 449-487 (1978)

SUMMARY: This chapter explores the origins of behavioral toxicology and compares this new discipline with its predecessor, behavioral pharmacology. Distinctive features of behavioral toxicology are its concern for qualitative evaluation, threshold estimates, and chronic exposures. These characteristics require a multidisciplinary approach. Substances of current interest in behavioral toxicology are mercury, lead, carbon monoxide, pesticides, and volatile agents. Behavioral toxicology appears to be playing a more influential role in the Soviet Union, although few detailed research reports are available.

The recent enactment of the Toxic Substances Control Act will increase the demand for behavioral assessment of potential toxicity. A protocol for premarket screening is suggested. We emphasize the continuing importance of basic studies aimed at mechanisms of action. Fundamental variables such as diurnal rhythms, degree of schedule control, discriminative stimuli, and stimulus complexity modulate the behavioral effects of toxins; systematic manipulation of variables such as these will improve the sensitivity and reliability of behavioral tests. Future developments are likely to concern food additives, behavioral teratology, and procedures for behavioral evaluation in the natural environment.

44
TITLE: Amniotic fluid cell culture. II. Evaluation of a red blood cell lysis procedure for culture of cells from blood-contaminated amniotic fluid (UR-3490-1415)

AUTHORS: J. S. Felix and R. A. Doherty

PUBLICATION: *Clin. Genetics*, (in press)

SUMMARY: Second trimester amniotic fluid samples obtained transabdominally for genetic analysis not infrequently are contaminated with blood. There has been disagreement as to whether blood contamination interferes with efficiency of culture of amniotic fluid cells for genetic diagnosis. A procedure using ammonium chloride to lyse contaminating red blood cells has been recommended to increase culture success.

In this report we document that cultures derived from blood-contaminated amniotic fluids form fewer cell colonies than cultures from clear amniotic fluids. We also show that a recommended procedure using ammonium chloride to lyse red blood cells is ineffectual in improving efficiency of cell culture and may be detrimental to successful culturing of cells from bloody amniotic fluids.

An hypothesis concerning the mechanism of interference with culture of amniotic fluid cells by contaminating blood is presented and a means of preventing this complication is suggested.

45
TITLE: Somatic growth: body composition in adolescence (UR-3490-1121)

AUTHOR: G. B. Forbes

PUBLICATION: Chapt. 9 in *Human Growth*, Vol. 2, Ed. by F. Falkner and J. M. Tanner. Plenum Publishing Corp., New York, pp. 239-272 (1978)

SUMMARY: Methods for determining body composition in living human subjects are reviewed together with data in changes in body composition during adolescent growth. Sex differences in body composition are discussed as well as changes due to exercise and certain disease states.

46
TITLE: Nutritional illnesses (UR-3490-1558)

AUTHOR: G. B. Forbes

PUBLICATION: Chapt. 32 in *Principles of Pediatrics. Health Care of the Young*, Ed. by R. A. Hoekelman, S. Blatman, P. A. Brunell, S. B. Friedman and H. M. Seidel. McGraw-Hill, Inc., New York, pp. 873-886 (1978)

SUMMARY: This chapter deals with the evaluation of nutritional status of infants and children, the causes and characteristics of various types of nutritional deficiencies, and their treatment.

47
TITLE: Nutritional requirements. Prevention of obesity (UR-3490-1099)

AUTHOR: G. B. Forbes

PUBLICATION: Sections 12-A and 12-C of Chapt. 12 (Prevention of Disease) in *Principles of Pediatrics. Health Care of the Young*, Ed. by R. A. Hoekelman, S. Blatman, P. A. Brunell, S. B. Friedman and H. M. Seidel. McGraw-Hill, Inc., New York, pp. 129-143; 155-157 (1978)

SUMMARY: Obesity is a major problem in American children and adults. This chapter discusses the factors involved in the pathogenesis of obesity and methods which have been proposed for its prevention.

6
4 TITLE: Bone mineral turnover in a patient with osteogenesis imperfecta estimated by fluoride excretion (UR-3490-1191)

AUTHORS: G. B. Forbes, D. R. Taves, F. A. Smith and R. W. Kilpper

PUBLICATION: *Calc. Tiss. Res.*, 25: 283-287 (1978)

SUMMARY: A child with severe osteogenesis imperfecta was treated with NaF for 8 years, at the end of which time his iliac bone contained 29 mg F/g Ca. Urine F was assayed at intervals for 4.5 years after discontinuing treatment. After the first few days the decline in urinary F excretion can be described by a two-component exponential function, with half-times of 5.4 months (10%) and 8.9 years (90%). The latter half-time value is of the same order of magnitude as those observed for F and other "bone-seeking" elements in normal subjects, which suggests that the turnover rate of bone mineral is normal in this disease.

Three methods for estimating the attained body F burden at the end of NaF treatment — namely, metabolic balance, bone biopsy, and integration of the exponential function — yielded comparable values.

9
4 TITLE: ESR of phosphite radicals trapped in X-irradiated single crystals of O-phosphorylethanolamine (UR-3490-1344)

AUTHORS: G. W. Fouse and W. A. Bernhard

PUBLICATION: *J. Chem. Phys.*, (in press)

SUMMARY: Two different species of phosphite radicals are trapped at 300 K in X-irradiated single crystals of O-phosphorylethanolamine, $\text{H}_3\text{N}^+\text{CH}_2\text{CH}_2\text{OPO}_3\text{H}^-$. One radical, resulting from cleavage of the P-OH bond, is characterized by eigenvalues of 2173 ± 16 MHz, 1733 ± 19 MHz, and 1713 ± 19 MHz, and $2.0065 \pm .0004$, $2.0065 \pm .0004$, and $2.0038 \pm .0004$, for the hyperfine coupling tensor and g-tensor, respectively. The other radical, produced by cleavage of the $\text{P-OCH}_2\text{CH}_2\text{NH}_3^+$ bond, has corresponding eigenvalues of 2131 ± 15 MHz, 1710 ± 15 MHz, and 1689 ± 13 MHz, and $2.0054 \pm .0004$, $2.0052 \pm .0004$, and $2.0044 \pm .0004$.

Both radical species are present in approximately equal concentrations in the crystal, suggesting that both the P-OH and $\text{P-OCH}_2\text{CH}_2\text{NH}_3^+$ bonds are equally susceptible to electron dissociative capture, the assumed mechanism for radical formation.

10
5 TITLE: Mammary tumors and serum hormones in the bitch treated with medroxyprogesterone acetate or progesterone for four years (UR-3490-1550)

AUTHORS: D. W. Frank, K. T. Kirton, T. E. Murchison, W. J. Quinlan, M. E. Coleman, T. J. Gilbertson, E. S. Feenstra and F. A. Kimball

PUBLICATION: *Fertil. Steril.*, (in press)

SUMMARY: After four years of a long-term contraceptive steroid safety study, the incidence and the histologic type of mammary dysplasia produced is similar in beagles treated with medroxyprogesterone acetate (medroxyprogesterone) or progesterone.

Serum insulin, thyroid stimulating hormone (TSH), triiodothyronine, growth hormone, prolactin, 17β -estradiol, progesterone, and cortisol were determined by radioimmunoassay on samples

collected after 45 months of treatment. Serum growth hormone and insulin concentrations were elevated in a dose-related manner in both treatment groups. Triiodothyronine, cortisol, and 17β -estradiol (medroxyprogesterone only) were lowered. TSH and prolactin concentrations were not changed. Pituitary-gonadal hormone interaction in the pathogenesis of mammary neoplasia of the dog is discussed. Prolonged treatment of the beagle with massive doses of progesterone or medroxyprogesterone results in a dose-related incidence of mammary nodules.

15) **TITLE:** Effects of ultrasound, cysteamine, and X-rays on V79 Chinese hamster cells (UR-3490-1408)

AUTHOR: Y-K. Fu (Supervised by M. W. Miller)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The use of ultrasound in medical diagnosis and therapy is rapidly increasing and may some day equal or surpass that of X-rays. Ultrasound, as a diagnostic tool, can differentiate different soft tissues more easily than can X-rays, and appears to have no detrimental biological effect. While at present there is no convincing evidence that ultrasound used in diagnostic procedures damages biological tissues, there is much that is not understood about the interaction of ultrasound with biological material. Additional research on the biological effects of ultrasound is required to establish its safety.

The effects of biomedical ultrasound on a subline of Chinese hamster V79 cells were examined for the following endpoints:

1. Cell lysis, loss of viability and growth alteration induced by ultrasound.
2. Cell sensitivity to ultrasound as a function of cell cycle position after synchronization by mitotic collection.
3. Cell lysis and survival after addition of cysteamine before and during ultrasound or X-ray treatment.

Chinese hamster V79 cells were exposed to different intensities and durations of 1 MHz ultrasound and were studied for cell lysis and colony-forming ability. The threshold for cell lysis and loss of viability (reduction in colony-forming ability) were found to be ultrasonic intensity, sonication duration, and energy dependent. About the threshold there was an initial correlation between ultrasound intensity and biological effect: the higher the intensity, the greater the amount of cell lysis and reduction in colony-forming ability. These effects were maximal at an intensity of 10 to 20 W/cm² and were less at 30 W/cm².

The sensitivity of the different stages of the cell cycle (M, G₁, S, and G₂) to ultrasonically-induced lysis and loss of reproductive integrity was studied. The results were examined statistically by a two-way analysis of variance. Intensity and time after mitotic collection were significant factors which affect both cell lysis and the viability of the remaining intact cells. The M and S phases of the cell cycle are more resistant to lysis and reduction in colony-forming ability than are the G₁ and G₂ phases.

Cells were exposed to ultrasound in the presence of 8 mM cysteamine. The results show that at 10, 20, and 30 W/cm² there is no detectable cysteamine-induced modification effect on percent intact cells following sonication. Cysteamine acts as a survival modifier when colony-forming ability

is assayed, yielding a survival modification factor of $2.0 \pm .36$ at an intensity of 20 W/cm^2 and $1.55 \pm .05$ at 30 W/cm^2 , but there is no detectable survival modification at 10 W/cm^2 . These results indicate that at high, but not low, intensities ultrasonically-induced free radicals perturb the reproductive integrity of cells which survive lysis although they do not play a role in cell lysis. Thus, at least at high intensities, free radical formation is one but not the only mechanism responsible for ultrasound's effects on cells.

✓
5 TITLE: The absence of an effect of photoreactivation on sub-lethal damage accumulation in a photoreactive wallaby cell-line (UR-3490-222)

AUTHORS: Y-K Fu, C. S. Lange and M. W. Miller

PUBLICATION: *Intern. J. Radiation Biol.*, 34: 73-79 (1978)

SUMMARY: Monolayer cultures of JU56 wallaby cells were exposed to germicidal U.V. and/or photoreactivating (PR) light. The U.V. exposures induced dose-dependent cell death. The survival data are consistent with a common extrapolation number (n) of 6.17 ± 0.98 with a D_0 of $123.0 \pm 6.8 \text{ erg/mm}^2$ for photoreactivated cells and a D_0 of $87.0 \pm 4.9 \text{ erg/mm}^2$ for non-photoreactivated cells; The photoreactivation protected the cells with a dose-modification factor of 1.41 ± 0.02 . Therefore PR is not a shoulder phenomenon and so has no relationship to the repair of sub-lethal damage.

✓
5 TITLE: Effects of various drugs on canine tracheal mucociliary transport (UR-3490-1517)

AUTHORS: A. Giordano, D. Holsclaw and M. Litt

PUBLICATION: *Ann. Otol., Rhinol. Laryngol.*, 87: 484-490 (1978)

SUMMARY: A study of the effects of dehydration, atropine, terbutaline and N-acetylcysteine on canine tracheobronchial mucus is presented. Mucociliary clearance rates, mucus secretion volumes and mucus rheologic properties were studied. Clearance rates were studied by a radioisotope technique, mucus collected by a canine "tracheal pouch" method and rheologic studies performed by N-acetylcysteine and decreased by atropine. Secretion volume was increased by terbutaline while dehydration and atropine were without effect. Rheologic factors were increased by dehydration and atropine while terbutaline was without an effect. The effects of N-acetylcysteine on secretion volume and rheologic properties could not be studied because of the nature of the techniques employed.

✓
5 TITLE: Mucus rheology and mucociliary clearance: normal physiologic state (UR-3490-1516)

AUTHORS: A. M. Giordano, D. Holsclaw and M. Litt

PUBLICATION: *Am. Rev. Resp. Disease*, 118: 245-250 (1978)

SUMMARY: Tracheal mucociliary clearance studies, mucus collections, and rheologic studies were performed on a weekly basis in seven adult purebred beagles in an attempt to correlate clearance rate with rheology of mucus. Clearance rates were determined by a percutaneous transtracheal, radioisotope injection technique. Mucus was collected from dogs equipped with a tracheal pouch, and

rheologic determinations were performed on a dynamic microrheometer. Individual analysis of data for each dog failed to reveal any significant relationship between clearance rate and any parameter of elasticity or viscosity. However, when data from all seven dogs were pooled, covering a much wider range of the measured variables, it was seen that as the elastic modulus increased, the rate of clearance decreased. The mucociliary clearance rate was halved by an approximate tenfold increase in elastic modulus of mucus.

TITLE: An investigation of the interactions of two potential sensing cyanine dyes, 3,3'-dipropylthiadicarbocyanine iodide and 3,3'-dipropylloxadicarbocyanine iodide with erythrocytes, ghosts and phospholipid vesicles (UR-3490-1436)

AUTHOR: E. G. Guillet (Supervised by G. A. Kimmich)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The main goals of the experiments described in this thesis were: (1) to identify the similarities and differences in the manner in which two potential sensing cyanine dyes, 3,3'-dipropylloxadicarbocyanine iodide [di-O-C₃(5)] and 3,3'-dipropylthiadicarbocyanine iodide [di-S-C₃(5)], interact with erythrocytes, ghosts and phospholipid vesicles and (2) to construct a theoretical model, based on potential energy considerations, which accurately describes the binding of di-O-C₃(5) to intact rat erythrocytes.

The experimental methods employed relied on two types of spectroscopic information. Dye absorption spectra were evaluated in the presence of normally polarized and hyperpolarized membrane preparations (whole cells, ghosts and vesicles) while dye binding to the various preparations was evaluated using fluorometric assay techniques. The experimentally determined binding of di-O-C₃(5) to rat erythrocytes was compared to theoretical calculations of membrane dye binding which were based on considerations of the potential energy profile of lipophilic ions across membranes.

The absorption results indicate that the two dyes interact with the membrane preparations in qualitatively dissimilar fashions. The thiadicarbocyanine dye dimerizes on human hemoglobin and aggregates in the presence of hyperpolarized ghosts and vesicles. The oxadicarbocyanine dye may dimerize to human hemoglobin but only in suspensions of hyperpolarized, intact, human erythrocytes. Oxadicarbocyanine dye dimerization is not detected in concentrated human erythrocyte lysates, nor is aggregation detected in any of the normally polarized or hyperpolarized membrane suspensions. The binding studies surprisingly indicate that similar amounts of di-S-C₃(5) can be bound to hyperpolarized whole cells as well as hyperpolarized ghosts and vesicles. If binding to hemoglobin accounts for a majority of whole cell binding (as indicated in previous reports) then there must exist other binding mechanisms which account for the considerable dye binding to ghosts and vesicles. Equivalent amounts of di-O-C₃(5) are bound to all three membrane preparations but generally in lower molar quantities than di-S-C₃(5). Based on empirical binding slopes (amount bound/extracellular dye concentration) di-S-C₃(5) appears to be a more sensitive indicator of potential than di-O-C₃(5), but it also binds to cells, ghosts and vesicles in a more complex manner with dimer and aggregate formation.

The theoretical model proposed implicates concentrated dye binding at the membrane interfaces. Computer searches for the appropriate binding parameters (potential depth and fractional transmembrane potential sensed by interfacial dye) result in theoretical calculations which agree closely with experimental findings. The predicted well depth at the membrane interfaces approximates estimates of the potential energy barrier to the transport of lipophilic ions across bilayers. The predicted transmembrane potential fraction overestimates measurements of the membrane potential. The model needs modification to satisfactorily explain all facets of membrane binding. It is felt that the modifications needed are relatively minor and that the basic assumption of concentrated dye binding at the membrane interfaces is still valid.

5 TITLE: Differential effects of erythrocyte lysates on spectra of potential-sensing carbocyanine dyes (UR-3490-1263)

AUTHORS: E. Guillet and G. Kimmich

PUBLICATION: *Biochim. Biophys. Acta*, 509: 385-389 (1978)

SUMMARY: A recent report by Hladky, S. B. and Rink, T. J. ((1976) *J. Physiol.* 263, 287-319) demonstrates the binding of a thiocarbocyanine dye (di-S-Cg(5)) to an intracellular constituent from human erythrocytes. Evidence presented shows that the binding of carbocyanine dyes depends on the particular type of dye used and on the species of erythrocyte from which cellular constituents are prepared. It is recommended that dyes which show minimal binding to intracellular components be used for investigations where carbocyanine dyes are employed as probes of membrane potential.

5 TITLE: A highly active glutathione peroxidase in red blood cells of normal and acatalasemic mice (UR-3490-1138)

AUTHOR: S. Halbach

PUBLICATION: *Experientia*, 33: 1571-1572 (1977)

SUMMARY: The activities of catalase (E.C.1.11.1.6) and glutathione peroxidase (E.C.1.11.1.9) were compared in red blood cells from humans, ducks and normal and acatalasemic mice. In the cells from both strains of mice, an equally high activity of GSH-Px was found which could be inhibited completely by iodoacetate but was not sensitive to N-ethylmaleimide.

5 TITLE: Enzymatic oxidation of mercury vapor by erythrocytes (UR-3490-1205)

AUTHORS: S. Halbach and T. W. Clarkson

PUBLICATION: *Biochim. Biophys. Acta*, 523: 522-531 (1978)

SUMMARY: The formation of glutathione radicals, the evolution of nascent oxygen or the peroxidatic reaction with catalase complex I are considered as possible mechanisms for the oxidation of mercury vapor by red blood cells. To select among these, the uptake of atomic mercury by erythrocytes from different species was studied and related to their various activities of catalase (hydrogen-peroxide:hydrogen-peroxide oxidoreductase, EC 1.11.1.6) and glutathione peroxidase (glutathione:hydrogen-peroxide oxidoreductase, EC 1.11.1.9). A slow and continuous infusion of diluted H₂O₂

was used to maintain steady concentrations of complex I. 1% red cell suspensions were found most suitable showing high rates of Hg uptake and yielding still enough cells for subsequent determinations. The results indicate that the oxidation of mercury depends upon the H_2O_2 -generation rate and upon the specific activity of red cell catalase. The oxidation occurred in a range of the catalase- H_2O_2 reaction where the evolution of oxygen could be excluded. Compounds reacting with complex I were shown to be effective inhibitors of the mercury uptake. GSH-peroxidase did not participate in the oxidation but rather was found to inhibit it by competing with catalase for hydrogen peroxide. These findings support the view that elemental mercury is oxidized in erythrocytes by a peroxidatic reaction with complex I only.

7 TITLE: Quantitation of mRNAs for α_1 -acid glycoprotein and for serum albumin in livers of normal, stressed, fasted and refed rats (UR-3490-1495)

AUTHOR: L. J. Harris (Supervised by L. L. Miller)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: A new procedure for determining the relative levels of a specific mRNA species has been developed and applied to mRNA for rat serum albumin (RSA) and α_1 -acid glycoprotein (α_1 -AGP) in rat liver. The method is a radioimmunoassay for the completed protein, but which also detects antigenic determinants in nascent polypeptide chains on polysomes synthesizing the specific protein.

Results show that 24 hours after stressing the rat by turpentine injection, the total number of polysomes per mg DNA has increased by 20% to 25%; however, the number of RSA synthesizing polysomes per mg DNA has decreased slightly. These results are in contrast to those from isolated *in vitro* rat liver perfusion studies which show that following turpentine treatment both the absolute rate of RSA synthesis and its rate relative to total serum protein synthesis fall to approximately 30% of normal values. This discrepancy indicates that the translation of RSA mRNA may be slower following turpentine treatment. One might speculate that this is due to either a decrease in initiation rate or elongation rate (which may then slow initiation) caused by competition from other mRNAs for initiation and/or elongation factors.

In rats fasted for 6 days, the number of RSA synthesizing polysomes per mg polysomal RNA is only slightly below normal but the total number of RSA synthesizing polysomes per mg DNA has decreased by 40%. Results from liver perfusion studies show that the rate of synthesis of almost all (not α_1 -AGP) serum proteins is reduced to 20% to 25% of normal rates. Again, it is seen that RSA mRNA levels do not decrease as sharply as the rate of RSA synthesis. Twelve hours after refeeding rats which had been fasted for 6 days, the number of RSA synthesizing polysomes (on both a per mg DNA and per mg RNA basis) begins to increase reaching a peak two to three times normal levels 24 to 48 hours after commencement of refeeding.

During the first 24 hours after turpentine injection, there is a linear increase in the number of α_1 -AGP synthesizing polysomes (on both a per mg DNA and per mg RNA basis). The increase is smaller during the next 24 hours and there is a small decrease between 48 and 72 hours. The serum concentrations of α_1 -AGP following turpentine treatment reflect these changes in polysome levels.

It was not possible to compare the number of α_1 -AGP synthesizing polysomes in livers of normal, fasted and refed rats because the levels detected were only slightly higher than those seen in rabbit liver and rat kidney polysome controls. It may be possible to eliminate this background activity by using only the F_{ab} fragment of the antibody. This background activity must be eliminated before the technique can be applied to quantitating mRNA for proteins synthesized in very small quantities.

This technique offers several advantages over other procedures commonly used to quantitate mRNA — it requires very little purified antigen and antibody, is not dependent upon efficiency of translation of a particular mRNA, and it uses gamma counting instead of liquid scintillation counting.

The polysome isolation procedure used gives 70% recovery of polysomal RNA from all livers except those from animals fasted and then refed for 12 to 48 hours. Using assays sensitive to less than 1 ng protein, no free serum RSA has been detected isolating with these polysomes.

2
✓ TITLE: X-ray fluorescence analysis applied to small samples (UR-3490-1236)

AUTHORS: M. J. Jaklevic, W. F. French, T. W. Clarkson and M. R. Greenwood

PUBLICATION: In *Advances in X-ray Analysis*, Vol. 21, Ed. by C. S. Barrett, D. E. Leyden, J. B. Newkirk and C. O. Ruud. Plenum Publishing Corp., New York, pp. 171-185 (1978)

SUMMARY: We describe an adaptation of photon-excited X-ray fluorescence analysis which is optimized for the analysis of small samples. A fine focus X-ray tube is used in conjunction with small diameter detector collimators in order to focus on a small sample volume with as high sensitivity as possible. Sample areas of less than 1 mm diameter can be analyzed with ppm detectability. In applications involving the analysis of human hair samples, a minimum detectable limit of 10 ppm Hg can be realized in a 1 mm long segment of a single hair in a counting time of 200 seconds. Simultaneous measurements of the sample mass can be obtained from the intensity of the incoherent scattering. An automated X-ray fluorescence analysis system using the technique for the scanning of elemental profiles in such hair samples is described.

✓ TITLE: Isolation of a low molecular weight Ca^{2+} carrier from calf heart inner mitochondrial membrane (IIR-3490-1256)

AUTHORS: A. Y. Jeng, T. E. Ryan and A. E. Shamoo

PUBLICATION: *Proc. Natl. Acad. Sci. USA*, 75: 2125-2129 (1978)

SUMMARY: A protein was isolated from calf heart inner mitochondrial membrane with the aid of an electron paramagnetic resonance assay based on the relative binding properties of Ca^{2+} , Mn^{2+} , and Mg^{2+} to the protein. The molecular weight of this protein has been estimated to be about 3000 by urea/sodium dodecyl sulfate gel electrophoresis and amino acid analysis. The protein is shown to have two classes of binding sites for Ca^{2+} by flow dialysis studies and can extract Ca^{2+} into an organic phase. The selectivity sequence of this protein determined from the organic solvent extraction experiments shows that it favors divalent cations over monovalent cations. Also, the relative selectivity sequence for divalent cations is $Ca^{2+} > Sr^{2+} > Mn^{2+} > Mg^{2+}$. Ruthenium red and La^{3+} are shown to inhibit the protein-mediated extraction of Ca^{2+} into the organic solvent. The calcium translocation

in a Pressman cell by this protein is selectively driven by a hydrogen ion gradient. Control experiments indicate that the Ca^{2+} transport properties of the protein are not due to the contaminating phospholipids. It appears that we have isolated from the inner mitochondrial membrane a calcium carrier which we have named "calciphorin".

✓ **TITLE:** Growth retardation in Chinese hamster V-79 cells exposed to 1 MHz ultrasound (UR-3490-1279)

AUTHORS: G. E. Kaufman and M. W. Miller

PUBLICATION: *Ultrasound Med. Biol.*, 4: 139-144 (1978)

SUMMARY: Asynchronous Chinese hamster V-79 cells were exposed in suspension to continuous wave 1 MHz ultrasound for 1 minute at an axial intensity of 2.5 W/cm^2 , then allowed to grow in monolayer culture. There was little if any growth, as determined by changes in the number of attached cells, for 24 hours after sonication, then a return to normal growth approximately 36 hours after sonication. The lack of growth during the first 24 hours appears to be due to an approximate balance between proliferation of viable cells and loss of nonviable cells into the medium.

3
✓ **TITLE:** Membrane potentials and the energetics of intestinal Na^+ -dependent transport systems (UR-3490-1357)

AUTHORS: G. A. Kimmich and C. Carter-Su

PUBLICATION: *Am. J. Physiol.*, 235: C73-C81 (1978)

SUMMARY: The transmembrane chemical gradient for Na^+ that most living cells maintain represents an energy source which is not sufficient to account for observed cellular sugar or amino acid gradients. This short review summarizes the literature pointing to the above conclusion and describes experimental evidence from a variety of model systems which indicates that the membrane potential can provide an additional driving force. Ordinarily, solute leak pathways compromise the full gradient forming capability of the Na^+ -dependent concentration systems and obscure the extent to which membrane potentials are important. When these "leaks" are experimentally controlled, solute gradients are established that identify the membrane potential as a quantitatively very important energy input. Furthermore, if the electrochemical gradient for Na^+ is the sole source of energy, an extremely high efficiency of energy transduction must occur during gradient-coupled transport. An experimental approach is described here which can provide clues to the mechanistic role for membrane potentials in intestinal Na^+ -dependent sugar transport.

62
✓ **TITLE:** A study of irradiated bone. I. Histopathologic and physiologic changes (UR-3490-1406)

AUTHORS: M. A. King, G. W. Casarett and D. A. Weber

PUBLICATION: *J. Nucl. Med.*, (in press)

SUMMARY: Histologic and isotopic techniques were used to investigate and document alterations in bone pathophysiology subsequent to irradiation of experimental animals. These studies were carried out for comparison with the *in vivo* and *in vitro* distribution and clearance of $^{99\text{m}}\text{Tc}$ pyrophosphate in the same animals as reported in the second of this series of papers and thus provide

a means for correlating bone and associated soft-tissue pathophysiology with radiopharmaceutical deposition. Assays of blood perfusion with $^{86}\text{RbCl}$ and erythrocyte volume with ^{51}Cr RBCs were obtained in irradiated and normal skin, muscle, marrow, and bone of rabbits which had received a single X-ray dose of 1756 rad or a fractionated dose of 4650 rad to the left hind limb. Tissue specimen assays were obtained from three animals at 1 day (single dose rabbits only), 1, 3, 6 and 12 months postirradiation. Three additional animals from each of the two irradiation regimens were sacrificed at 1, 3, 6, and 12 months postirradiation to investigate alterations in bone remodeling and vascular patency.

5
6 TITLE: A study of irradiated bone. II. $^{99\text{mTc}}$ pyrophosphate bone imaging and radiographic changes (UR-3490-1486)

AUTHORS: M. A. King, D. A. Weber, G. W. Casarett and F. A. Burgener

PUBLICATION: J. Nucl. Med., (in press)

SUMMARY: The deposition and distribution characteristics of $^{99\text{mTc}}$ pyrophosphate *in vivo* were evaluated in locally irradiated and control bone of experimental animals to evaluate the potential use of $^{99\text{mTc}}$ pyrophosphate imaging as an indicator or test of radiation effects in bone and surrounding tissues. Quantitative bone images, *in vitro* specimen assays of tissue deposition, and autoradiography were used to document the radiopharmaceutical distribution characteristics of $^{99\text{mTc}}$ pyrophosphate before and following irradiation. Serial radiographs of the irradiated and contralateral limbs were obtained at regular intervals over the first 12 months following irradiation. The deposition and distribution characteristics of $^{99\text{mTc}}$ pyrophosphate were correlated with the radiographic studies as well as with the serial assays of histopathology and physiology in the irradiated and contralateral limbs reported in Part I of this series. The results show that $^{99\text{mTc}}$ pyrophosphate bone imaging is a sensitive *in vivo* indicator of early radiation effects in the skeleton. The findings suggest that the quantitative bone imaging technique may offer considerable assistance in the evaluation of the effects of treatment modalities on the skeleton in experimental animals. If a similar correlation can be demonstrated at sites of osseous abnormalities in man, this procedure would offer great potential as a noninvasive indicator for the evaluation of treatment modalities in both benign and malignant conditions.

6
7 TITLE: The myosin-like ATPase of spectrin (UR-3490-1528)

AUTHOR: F. H. Kirkpatrick

PUBLICATION: In The Red Blood Cell Membrane and its Functions, Ed. by M. Boulard and P. Boivin. INSERM, Paris, (in press)

SUMMARY: Previous studies on water-soluble erythrocytic ATPase are briefly summarized and current data on the ATPase activities of spectrin are described. Native spectrin-actin complexes have a myosin-like catalytic center while "pure" spectrin tetramers and dimers have no ATPase activity; hence, pure spectrin represents a somewhat denatured form. A preliminary model of ATP-consuming spectrin-actin interactions is presented which can explain erythrocytic membrane elasticity under stress of short duration and plasticity under prolonged stress.

67 **TITLE:** New models of cellular control: membrane cytoskeletons, membrane curvature potential and possible interactions (UR-3490-1453)

AUTHOR: F. H. Kirkpatrick

PUBLICATION: *BioSystems*, (in press)

SUMMARY: The concepts of "membrane cytoskeletons" (proteins attached to the cytoplasmic face of the membrane to give rigidity and control of lateral protein diffusion) and of membrane curvature potential are briefly reviewed. Possible model of attachment of the membrane cytoskeleton to the bilayer are discussed and a detailed calculation of possible sources of membrane curvature potential in the red cell is made. The two control systems are then used to illustrate possible mechanisms for some cellular processes such as vesicle formation and release, pseudopod formation, and red cell aging. It is concluded that combination of these concepts allows control mechanisms which appear to act at a distance or have other unusual systems properties.

68 **TITLE:** Crossed immunoelectrophoresis from sodium dodecyl sulfate — polyacrylamide gels into antibody-containing agarose: an improved method for evaluation of the number of immunochemical determinants in polypeptides, with reference to spectrin (UR-3490-1131)

AUTHORS: F. H. Kirkpatrick and D. J. Rose

PUBLICATION: *Anal. Biochem.*, 89: 130-135 (1978)

SUMMARY: A simple method is described for performing cross immunoelectrophoresis into antibody-containing agarose when the first-dimension gel contains peptides separated by electrophoresis in sodium dodecyl sulfate. Artifacts produced by sodium dodecyl sulfate are avoided by incorporation of Triton X-100 in the agarose layer. Peptides are located by prestaining (before SDS-acrylamide electrophoresis) with the cycloheptylamylose complex of fluorescamine. Injection of ink into prestained peptide bands produces a line extending from the peptide band location to its precipitin arc, thereby allowing unambiguous assignment of arcs to peptides in situations where peptide bands are not widely separated. The utility of this procedure is illustrated for the erythrocyte membrane protein spectrin.

69 **TITLE:** Lymphocytosis (UR-3490-1227)

AUTHORS: M. R. Klemperer, J. M. Rubins and M. A. Lichtman

PUBLICATION: Chapt. 9 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 177-193 (1978)

SUMMARY: This chapter deals with those clinical disorders that are manifested by an elevation in blood lymphocyte counts.

70 **TITLE:** Fluorescence and ultracentrifugation studies of yeast hexokinase isoenzymes (UR-3490-1327)

AUTHOR: D. C. Kramp (Supervised by I. Feldman)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: Yeast hexokinase (Hk) exists as isoenzymes, each of which is a dimer

of molecular weight 104,000. These isoenzymes, A (P-I), B (P-II), and C have been isolated and purified previously by others. Kinetic studies of the enzymes have shown them to be complex allosteric enzymes. Enzymatic activity can be increased several fold by several anions at slightly acidic pH. Furthermore, HkB demonstrates 'hysteretic' properties in that substrates or activators can induce a slow change in its kinetic properties. Some of the kinetic and binding properties have been ascribed to changes in the monomer-dimer association of the enzyme.

In order to elucidate some of the kinetic data, a study of the binding of the substrate glucose to isoenzyme A and B was performed. Fluorescence-quenching measurements were used to determine the strength of glucose binding. Ultracentrifugation was employed to determine the extent of enzyme dissociation into monomers.

These studies demonstrate that there is negative cooperativity for glucose binding to aqueous dimeric hKb at pH 5.5. Anderson and Steitz had previously observed this for crystalline dimeric HkB and attributed it to preferential glucose binding to one monomer of the asymmetrical HkB dimer molecule. In contrast, HkA demonstrates positive cooperativity of glucose binding at pH 5.5 as a result of site-site interactions between subunits.

Also demonstrated is the apparently-equal strength of glucose binding by both monomeric and dimeric enzyme. This occurs over a range of ionic strengths, enzyme concentrations, pH, and temperature. In view of the fact that glucose-induced dissociation of enzyme is also demonstrated (in 0.05 M glycylglycine at pH 8.3 and in 0.025 M Na acetate at pH 5.5), exact equality between monomer and dimer glucose binding constants cannot be correct. It is believed that the ratio of binding constants is not greater than a factor of two, that is, within the experimental error of this work.

Fluorescence quenching of HkB fluorescence by cesium and iodide ions in conjunction with glucose showed that all four of the tryptophan residues per monomer subunit are fluorescent. One tryptophan is located on the surface of the enzyme and is very accessible to solvent. A second tryptophan is accessible to solvent but is probably located in a sterically-restricted surface environment such as a crevice. The third is also located in a sterically-restricted solvent accessible environment and its fluorescence is quenchable by a glucose-induced conformation change. The fourth tryptophan is in a subsurface location (i.e., buried). The emission from the buried tryptophan residue seems to account for more than half of the total fluorescence.

Tyrosine fluorescence of hexokinase is not fully quenched by Forster resonance energy transfer to the tryptophan residues. Also, glucose-binding enhances tyrosine fluorescence while it quenches the tryptophan fluorescence. This accounts for the difference in maximum glucose-quenchable fluorescence that has been observed by different workers who employ different excitation and emission wavelengths.

^ TITLE: Tryptophan distribution in yeast hexokinase isoenzyme B (UR-3490-1272)

AUTHORS: D. C. Kramp and I. Feldman

PUBLICATION: *Biochim. Biophys. Acta*, 537: 406-416 (1978)

SUMMARY: Titrations of the quenching of the tryptophan fluorescence of yeast hexokinase

isoenzyme B by Cs^+ , I^- and glucose as quenchers, singly and in various combinations, have been performed at pH 5.5, 8.3, and 10.1 at 20° C. The iodide and glucose titrations at pH 8.3 indicated that the four tryptophan residues of the monomer subunit can be classified as: (1) a highly accessible surface tryptophan (Trp-S₁); (2) a surface tryptophan (Trp-S₂) with restricted accessibility (possibly in a crevice); (3) a glucose-quenchable cleft tryptophan (Trp-G); and (4) a 'buried' tryptophan (Trp-B) in the hydrophobic interior. The Stern-Volmer constants, k_I , calculated for iodide quenching of the two surface residues at pH 8.3 are 22 and 3.3 M⁻¹. The k_I value of Trp-G at this pH is iodide dependent, increasing from 1.2 to 1.4 M⁻¹ as the iodide concentration increases from 0.1 to 0.65 M, probably because of iodide-induced alteration of the cleft structure. An iodide concentration above 0.65 M quenches Trp-B detectably, demonstrating that a high iodide concentration produces a large structural change in the isoenzyme. The percentages of the total 350 nm emission attributable to the individual tryptophan residues at pH 8.3 are 9, 22, 28, and 41%, for Trp-S₁, Trp-S₂, Trp-G, and Trp-B, respectively. These results agree qualitatively with previous results deduced from the wavelength dependence of glucose quenching. I^- and glucose bind non-competitively to produce a synergistic enhancement of the quenching of the cleft tryptophan fluorescence. At pH 5.5 even a low iodide concentration causes some quenching of Trp-B, especially in presence of saturating glucose. Glucose increases the iodide quenchability at this pH. At pH 10.1 glucose does not quench the tryptophan emission, and it does not influence the iodide-quenching action. However, at this high pH the k_I of Trp-S₁ is reduced to the point where it is not resolvable from the k_I values of Trp-S₂ and Trp-G, even though the sum of the fractional fluorescence contributions of these three residues is the same as at pH 8.3.

72 TITLE: Anemia with reticulocytosis: hemolytic disorders (UR-3490-1233)

AUTHORS: P. L. La Celle and M. A. Lichtman

PUBLICATION: Chapt. 3 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 51-86 (1978)

SUMMARY: This chapter discusses the major hemolytic anemias that afflict man.

73 TITLE: Effects of three diets on mercury excretion after methylmercury administration (UR-3490-1232)

AUTHORS: T. D. Landry, R. A. Doherty and A. H. Gates

PUBLICATION: *Bull. Environ. Contam. Toxicol.*, (in press)

SUMMARY: Since methylmercury (MeHg) is nearly 100% absorbed, elimination rate is a critical determinant of body burden resulting from ingestion of MeHg containing foods. Mouse studies were undertaken to assess the potential significance of diet on Hg kinetics. Female mice (BALB/c, 8 months old) were fed three diets. Each group of mice received Charles River RMH 3000 pelleted diet, Pet evaporated whole milk, or GIBCO 116EC liquid diet ad lib for one week prior and two weeks subsequent to a single p.o. dose of MeHg (0.5 mg/kg, labelled with ²⁰³Hg). The estimated whole body Hg elimination half-time (days 1 through 7 after MeHg administration) were 10.4 days (pelleted diet), 19.7 days (mild diet), and 5.8 days (GIBCO diet). The 95% confidence intervals for elimination half-times of each group do not overlap. Relative whole body elimination rates (as

measured by whole body gamma counting) were confirmed by fecal ^{203}Hg excretion. Urinary excretion accounted for 7% (GIBCO diet group) to 19% (milk diet group) of the whole-body elimination by day 7. Brain, blood, liver, and kidney Hg concentrations (14 days after MeHg administration) were consistent with the relative mercury body burdens. There are many differences between the three diets; this experiment alone does not define the relative importance of specific dietary factors. Non-Hg containing dietary components can affect MeHg body burden and brain levels. Because the brain is a critical organ for MeHg toxicity, dietary factors could play a role in MeHg poisoning.

74 **TITLE:** The mechanism of anterior-posterior polarity control in planarians (UR-3490-768)

AUTHORS: C. S. Lange and V. E. Steele

PUBLICATION: *Differentiation*, 11: 1-12 (1978)

SUMMARY: The substance which inhibits brain formation in the regenerating planarian *Dugesia etrusca* was found to be a large molecule, at least in part protein, which electrophoreses as an electro-negative moiety in pH 6.8 buffer. A model is presented, based on this finding and previous studies, which proposes an electrochemical mechanism for the control of polarity and possibly for the maintenance of tissue organization in planarians. It is proposed that a bioelectric field exists and moves the electronegative brain-inhibiting substance in a posterior direction, establishing polarity. This model explains the polarity reversal experiments using external fields and many of the previously unexplained classical planarian experiments. Data are presented demonstrating the existence, magnitude, and polarity of this bioelectric field, which is not greatly altered upon decapitation, all in accord with predictions of the model.

75 **TITLE:** Behavioral effects of carbon monoxide on animals and man (UR-3490-1435)

AUTHORS: V. G. Laties and W. H. Merigan

PUBLICATION: *Ann. Rev. Pharmacol. Toxicol.*, (in press)

SUMMARY: Despite the fact that experimental observations of the behavioral effects of carbon monoxide (CO) date back to J. S. Haldane in 1895, there has not been enough literature on this subject until recently to warrant an entire Annual Review chapter. Haldane, in order to ascertain the relationship between carboxyhemoglobin (COHb) level and symptomatology, exposed himself to the gas and recorded his own behavior. He described deficiencies in vision, audition, balance, reading, and writing at COHb levels ranging from 25% to 50%.

Surprisingly little more was done during the next half century. It was only during World War II that work on CO's behavioral effects started in earnest. For instance, the work of McFarland and his colleagues dates from that time. Then followed almost 20 years of relative inactivity disturbed only when governments became concerned with the possible effects of CO levels in aircraft, space-ships, and nuclear submarines. Finally, a surge of interest in the environment led to the very influential "Restoring the Quality of Our Environment" report by the Environmental Pollution Panel of President Lyndon B. Johnson's Science Advisory Committee in 1965; to a comprehensive CO bibliography published in 1966; to a report on the health effects of CO by the National Research Council

in 1969; to a New York Academy of Sciences symposium in 1970; and especially to the passage by the U. S. Congress of legislation that mandated air quality standards. This set the stage for the proliferation of research in this area in the seventies.

Studies of the behavioral effects of CO have been briefly reviewed several times in the past ten years, usually in the context of a general review of the CO literature. A recent monograph contained a broad examination of CO's behavioral effects on humans by one of the present authors. The subsequent appearance of much new behavioral material prompted the present effort which attempts a comprehensive treatment of both animal and human behavioral studies of CO.

With few exceptions, this review is confined to experimental laboratory studies.

✓
✓ TITLE: Effects of localized ultrasonic irradiation on *Pisum sativum* roots (UR-3490-1264)

AUTHORS: W. K. Law, E. L. Carstensen and M. W. Miller

PUBLICATION: *Environ. Exptl. Botany*, 18: 207-218 (1978)

SUMMARY: Histological studies on pea roots sonicated by a broad beam of ultrasound indicated that most of the damage occurs in the elongation region. There is little microscopic evidence of cell destruction in the meristem and yet this region of dividing cells shows a marked cytokinetic response to sonication. Indirect effects of ultrasound were therefore suspected to exist.

By using focused ultrasound to irradiate root segments as small as 1 mm², and then observing changes in growth and mitotic index outside the region of sonication, the existence of indirect effects of ultrasound was established. Histological observations on sections of treated roots indicated necrotic nuclei within and without the region of sonication.

✓
✓ TITLE: Ultraviolet-induced reversion of *cyc1* alleles in radiation sensitive strains of yeast. III. *rev3* mutant strains (UR-3490-1425)

AUTHORS: C. W. Lawrence and R. B. Christensen

PUBLICATION: *Genetics*, (in press)

SUMMARY: The role of the *REV3* gene function in UV-induced mutagenesis in the yeast *Saccharomyces cerevisiae* has been examined by determining the reversion of twelve well-defined *cyc1* mutations in diploid strains homozygous for the *rev3-1* or *rev3-3* allele. The twelve *cyc1* alleles include one ochre, one amber, four initiation, two proline missense, and four frameshift mutations. We find that the *rev3* mutations reduce the frequency of UV-induced reversion of all of the *cyc1* alleles, though different classes of alleles respond to a different extent. These results imply that the *REV3* gene function is required for the production of a wide variety of mutational events, though probably not all, and show that each of the three *REV* loci have different mutational phenotypes. Such diverse phenotypes are not predicted by the unitary model for bacterial mutagenesis suggesting that this is at best an incomplete description of eukaryotic mutagenesis.

2
TITLE: Ultraviolet light induced mutagenesis in *Saccharomyces cerevisiae* (UR-3490-1342)

AUTHORS: C. Lawrence and R. B. Christensen

PUBLICATION: In DNA Repair Mechanisms, Ed. by P. C. Hanawalt, E. C. Friedberg and C. F. Fox. Academic Press, New York, pp. 437-440 (1978)

SUMMARY: UV-induced mutations in *Saccharomyces* appear to arise from the action of a multi-step, branching process, different branches giving rise to mutations of different kinds or at different genetic sites. Mutations may occur at some distance from the causal photoproduct, and almost always involve single base pair changes. These observations are difficult to explain according to a single-step unitary model of the kind proposed by Radman and may indicate that prokaryotes and eukaryotes differ in this respect.

4
TITLE: An approach to the diagnosis of reduced blood cell counts (UR-3490-1015)

AUTHOR: M. A. Lichtman

PUBLICATION: Chapt. 1 in Hematology for Practitioners, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 1-19 (1978)

SUMMARY: One of the practical results from the increase in our understanding of organ pathology is the ability to arrive at a conclusion regarding the pathogenesis of disease. This often allows a physician to narrow his diagnostic considerations and select laboratory tests in a more precise manner. If one could decide whether a patient was suffering from an infectious, inflammatory, neoplastic, toxic, or degenerative disease of an organ promptly, using simple techniques, further diagnostic efforts could be focused and thus made more informative and cost efficient.

The history and physical examination are important in the approach to cytopenias. A history of excessive menses, folate-poor diets, alcohol abuse, drug ingestion, a family history of anemia, geographical origins where red cell abnormalities are prevalent, represent only a few key findings which may provide clues to the etiology of the disturbance.

Usually clinical laboratory tests are required to achieve a firm diagnosis. Simple tests are useful in arriving at a diagnosis. In hematopoietic disorders, especially cytopenias, the pathogenesis of the disturbance frequently can be discovered rapidly with studies that can be performed in a physician's office. The ability to decide that a cytopenia is due either to decreased production of cells, to increased destruction of cells, or loss of cells, allows the physician to select tests most likely to identify the causative factor in the cytopenia.

90
TITLE: Hematology for Practitioners

EDITOR: M. A. Lichtman

PUBLICATION: Little, Brown and Co., Boston (1978)

SUMMARY: The physician has access to several excellent textbooks of hematology. These texts describe in a comprehensive fashion the anatomy, physiology, biochemistry, and pathology of blood-forming organs, blood cells, and blood proteins. They are excellent resources for students, basic scientists, and physicians, particularly specialists. Although valuable for the student and

specialist; the comprehensive subspecialty textbook is difficult for the practitioner to use prospectively as he care for patients. Introductory texts, on the other hand, often emphasize physiologic and biochemical aspects of the blood and are oriented, therefore, toward the student.

The general physician does not share the luxuries of the medical student who has neither the responsibility for decisions nor the pressures of time limitations in which to make them; of the basic scientist who does not have to make decisions that affect the life of a patient; or of the specialist who is versed in the measurements he uses often, in the uncommon diseases he sees frequently, and in the difficult therapeutic decisions that he faces repeatedly.

General physicians may find hematologic problems difficult because their diagnosis is dependent on laboratory signs rather than physical signs. Moreover, the laboratory tests, such as the blood or marrow smear used to validate the presence of many hematologic diseases, may not be examined frequently by the physician, who thus may not have developed high competency with their interpretation.

In this text we have tried to maximize the information that is relevant for the diagnosis of major hematologic diseases. We have done this from the vantage point of the key or most consistent sign that a blood disease produces. In this way we hope to facilitate the use of the book by the general physician, who can enter the book at the chapter or chapters that discuss the major hematologic sign or signs manifested by the patient. This also imposes on the physician the requirement to crystallize the chief sign. For example, he should decide whether an isolated cytopenia or multicytopenia is present. If anemia alone is present, the pathophysiology of the anemia — reticulocytopenic, implying marrow failure, or reticulocytotic, implying hemolysis or hemorrhage — needs to be determined.

Treatment of patients with hematologic diseases can also be troublesome for the general physician. The management of hematology patients who require drugs with a high toxic-to-therapeutic ratio, component transfusion therapy, repeated evaluation of marrow examinations, and intensive care is difficult since the infrequency of these diseases prevents experience and thus limits wisdom in making decisions. Treatment is often orchestrated by the specialist. However, the general physician can play a valuable role in the care of the patient. Too often this role is abdicated because of an unfamiliarity with the essentials of the natural history of the disease, the principles of treatment, and the effects of drugs that are used infrequently.

For these reasons we have included chapters on surgical, medical, and radiotherapeutic treatments of hematologic disorders. Knowledge of the principles, utility, and consequences of therapy will help the general physician participate in the care of a patient who may have to travel long distances to be evaluated by a specialist.

The Hematology Unit at The University of Rochester School of Medicine and Dentistry and some of its alumni delivered a course in hematology sponsored by the American College of Physicians in June 1976. Following this course, we proposed to prepare a book in which the chapters were entitled by common signs of hematologic diseases. In general, each sign of a hematologic disease may be pursued by a parsimonious diagnostic strategy. Our treatment of these disorders is meant neither to underestimate the complexities of human biology and the difficulties of diagnosis and management nor to foster medicine by algorithm. Rather we have tried to use the physiologic, biochemical, and biophysical knowledge that has accrued in the study of hematologic diseases to instruct in the pro-

cesses of diagnosis. There are many texts and articles in which additional facts about hematologic diseases can be found. We have tried to provide a practical framework for the diagnosis and management of hematologic disorders for the unspecialized physician and the nonhematologist.

6¹ **TITLE:** Immature granulocytes or nucleated red cells in the blood (UR-3490-1226)

AUTHORS: M. A. Lichtman and J. K. Brennan

PUBLICATION: Chapt. 7 in Hematology for Practitioners, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 143-157 (1978)

SUMMARY: This chapter reviews the clinical disorders that are associated with the appearance of immature granulocytes and nucleated red cells in the blood.

4² **TITLE:** The leukemias (UR-3490-1337)

AUTHORS: M. A. Lichtman and M. R. Klemperer

PUBLICATION: Chapt. 22 in Clinical Oncology for Medical Students and Physicians, 5th Edition, Ed. by P. Rubin. American Cancer Society, pp. 245-258 (1978)

SUMMARY: This chapter discusses the clinical features of the leukemias.

4³ **TITLE:** Pancytopenia (UR-3490-1185)

AUTHORS: M. A. Lichtman and G. B. Segel

PUBLICATION: Chapt. 6 in Hematology for Practitioners, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 121-141 (1978)

SUMMARY: This chapter discusses the diagnosis and management of human diseases that result in a depletion in blood red cells, neutrophils, and platelets.

4⁴ **TITLE:** Parasinusoidal location of megakaryocytes in marrow: a determinant of platelet release (UR-3490-1152)

AUTHORS: M. A. Lichtman, J. K. Chamberlain, W. Simon and P. A. Santillo

PUBLICATION: *Am. J. Hematol.*, 4: 303-312 (1978)

SUMMARY: Megakaryocytopoiesis occurs in the hematopoietic (extravascular) compartment of marrow. Thus, platelets must traverse the wall of the vascular sinuses of marrow to enter the circulation. We have examined mouse and rat marrow, fixed by rapid immersion so as to maintain anatomical relationships as close to the natural state as possible. Quantitative transmission electron microscopy (TEM) of random transections of femurs established that megakaryocytes reside less than 1 μ from a marrow sinus wall with a probability unlikely to be the result of chance ($P < 0.001$). An intimate relationship exists between the megakaryocyte periphery and the abluminal surface of the endothelial lining cell. At the time of platelet release megakaryocyte cytoplasm invaginates and penetrates the endothelial lining cell. The penetrating cytoplasm is detached and enters the marrow circulation. From their dimensions in comparison to circulating platelets, the released cytoplasm represents a packet of platelets that undergoes further fragmentation in the circulation.

The parasinusoidal location of megakaryocytes and the process of sinus-wall penetration and platelet delivery was observed by TEM and scanning electron microscopy. These studies provided quantitative support for a specific anatomical arrangement of megakaryocytes in marrow. Moreover, the process of platelet release appears to be a physiological form of metastasis with invasion of vascular walls and vascular spread of cells, that are in this case amitotic.

5 **TITLE:** ESR-ENDOR study of X-irradiated single crystals of α -methyl-D-glucopyranoside (UR-3490-1460)

AUTHORS: K. P. Madden and W. A. Bernhard

PUBLICATION: *J. Chem. Phys.*, (in press)

SUMMARY: Single crystals of α -methyl-D-glucopyranoside X-irradiated at 77K contain five free radical species observed by ESR and ENDOR spectroscopy. Four of these have been assigned molecular loci: a primary alkoxy radical at O₆, a secondary alkoxy radical at O₂, a deprotonated hydroxyalkyl radical at C₆, and a radical due to hydrogen abstraction at C₅. Structural considerations and mechanisms of formation are discussed.

86 **TITLE:** Role of catalase in the oxidation of mercury vapor (UR-3490-1075)

AUTHORS: L. Magos, S. Halbach and T. W. Clarkson

PUBLICATION: *Biochem. Pharmacol.*, 27: 1373-1377 (1978)

SUMMARY: In human red blood cells the slow rate of production of hydrogen peroxide limits the rate of oxidation of mercury vapor. When H₂O₂ was added to blood samples, the rate of mercury uptake increased six time but the inhibitory effect of KCN was less pronounced than in samples without H₂O₂. Only in the absence of exogenous H₂O₂ did the inhibition of oxidation of mercury vapor by different concentrations of KCN parallel the inhibition of catalase.

Addition of peroxide to liver homogenates was without effect. When 20% (w/v) liver homogenates were exposed to mercury vapor at 37° C neither acatalasemia in mice nor pretreatment of rats with 2 g/kg aminotriazole produced an appreciable decrease in the uptake of mercury during the 90-minute incubation period. However, that catalase was responsible for the oxidation of mercury was clear from the correlation ($r^2 = 0.85$) between catalase activity and mercury uptake when 0.4 mg liver in 2 ml incubation medium was exposed to mercury vapor. With higher concentrations of homogenates the availability of mercury limited the oxidation process.

Experiments with horseradish peroxidase, beef liver catalase and inorganic catalysts of H₂O₂ decomposition indicate that the elemental mercury atom serves as the electron donor for complex I of catalase. Other possible pathways of oxidation such as oxidation by nascent oxygen released from H₂O₂ do not appear to be important.

87 **TITLE:** Single-stranded DNA mycoplasmaviruses (UR-3490-1428)

AUTHORS: J. Maniloff, J. Das and J. A. Nowak

PUBLICATION: *Proc. Meeting of Single-Stranded DNA Phages, August 1978, Cold Spring Harbor Laboratory, Cold Spring Harbor, N. Y., (in press)*

SUMMARY: Two general types of single stranded DNA bacteriophages have been described, icosahedral virions (e.g., Φ X174) and filamentous virions (e.g., M13). Mycoplasmavirus MVL51 appears to represent another type of single-stranded DNA phage with a genome size close to that of Φ X174 and a nonlytic mode of infection like that of filamentous phages. The bullet-shaped MVL51 morphology is unlike that of other known phages.

88 **TITLE:** Fetal methylmercury poisoning: new data on clinical and toxicological aspects (UR-3490-1343)

AUTHORS: D. O. Marsh, G. J. Myers, T. W. Clarkson, L. Amin-Zaki and S. Tikriti

PUBLICATION: *Trans. Am. Neurol. Assoc.*, 102: 69-71 (1977)

SUMMARY: Fetal methylmercury (MeHg) poisoning causing severe brain damage has been reported previously but dose-response data for critical levels of MeHg have been inadequate. Following the consumption of MeHg-contaminated bread in Iraq, hair samples were obtained from women who had been pregnant during MeHg exposure and consecutive segments of hair were analysed to provide peak hair mercury concentrations. When last examined the children were aged 4½ to 5 years. Only four of the 29 children had severe neurological signs but mild spastic diplegia was also observed. Ten mothers had peak hair mercury concentrations between 112 and 384 parts per million (ppm). Their children had the following abnormalities (percentages in parentheses refer to findings in the children of 15 mothers with peak hair mercury levels less than 25 ppm); early motor retardation 50% (0%); delayed speech 70% (7%); mental retardation 40% (7%); convulsive disorder 30% (0%); extensor plantar 55% (17%); neurological signs other than plantars 40% (7%); small head 40% (13%); short stature 70% (14%). MeHg induced fetal brain damage with peak maternal hair mercury concentrations as low as 112 to 384 ppm has not been reported in the past and indicates the particular susceptibility of the fetal brain.

89 **TITLE:** QUARTR: A FORTRAN IV subroutine to calculate quarter life (UR-3940-1367)

AUTHOR: J. P. J. Maurissen

PUBLICATION: *Behav. Res. Methods Instru.*, 10: 727-728 (1978)

SUMMARY: This paper describes a subroutine written in FORTRAN IV that calculates quarter life, a measure of fixed-interval performance, from interresponse times.

90 **TITLE:** CURVAT: A FORTRAN IV subroutine to calculate the index of curvature (UR-3490-1360)

AUTHORS: J. P. J. Maurissen and G. B. Inglis

PUBLICATION: *Behav. Res. Methods Instru.*, 10: 729-730 (1978)

SUMMARY: This paper describes a FORTRAN IV subroutine for the calculation of the index

of curvature from the distribution of interresponse times in a fixed-interval schedule of reinforcement.

u\ TITLE: Pulmonary surfactant synthesis. A highly active microsomal phosphatidate phosphohydrolase in the lung (UR-3490-1166)

AUTHORS: R. D. Mavis, J. N. Finkelstein and B. P. Hall

PUBLICATION: *J. Lipid Res.*, 19: 467-477 (1978)

SUMMARY: Lung cell-free homogenate, which contains about twice the units of phosphatidate phosphohydrolase per mg of protein compared to liver, was fractionated by differential centrifugation and the fractions were assayed for phosphatidate phosphohydrolase and marker enzymes of endoplasmic reticulum, mitochondria, and lysosomes. Over 60% of the lung phosphatidate phosphohydrolase was associated with the endoplasmic reticulum, compared to 50% of the total liver enzyme. Thus a major portion of the more active lung enzyme is potentially involved in lipid biosynthesis by the endoplasmic reticulum. Less than 0.2% of the total lung enzyme was found in a lamellar body fraction, consistent with previous findings. The lung microsomal phosphohydrolase was specific for lipid substrates, showing equal activity towards phosphatidic acid or lysophosphatidic acid and relatively low activities towards glycerophosphates. It had a neutral pH optimum, similar to the liver enzyme, but differed somewhat in its relative activity at extremes of pH. Stability at 65° C was greater for the lung enzyme. Fluoride inhibited lung (or liver) microsomal phosphatidate phosphohydrolase, while tartrate, MgCl₂, or EDTA had no effect. The presence of a high activity of phosphatidate phosphohydrolase in lung endoplasmic reticulum is consistent with the rapid synthesis of pulmonary surfactant phosphatidylcholine.

g2 TITLE: Genetic analysis of gamma ray mutagenesis in yeast. I. Reversion in radiation-sensitive strains (UR-3490-1490)

AUTHORS: R. H. McKee and C. W. Lawrence

PUBLICATION: *Genetics*, (in press)

SUMMARY: The frequency of revertants, induced by ⁶⁰Co gamma rays, of the ochre allele *cyc1-9* has been measured in radiation-sensitive strains carrying one of nineteen non-allelic mutations, and in wild-type strains. The results indicate that nonionizing radiation mutagenesis depends on the activity of the *RAD6* pathway, and that the gene functions employed are very similar, but not identical, to those which mediate UV mutagenesis. The major pathway for the repair of damage caused by ionizing radiation, that is dependent on the functions of the *RAD50* through *RAD57* loci, does not appear to play any part in mutagenesis. A comparison between the gamma ray data and those obtained previously with UV and chemical mutagens suggests that the *RAD6* "pathway" is in fact composed of a hierarchy of interrelated processes, some of which are concerned with error-prone, and some with error-free, recovery activities. Some gene functions, for example that of the *RAD9* locus, are involved in error-free repair of some kinds of lesions, but error-prone recovery from other types of mutagenic damage

Q3 **TITLE:** Genetic analysis of gamma ray mutagenesis in yeast. II. Survival and reversion in double mutant strains (UR-3490-1491)

AUTHORS: R. H. McKee and C. W. Lawrence

PUBLICATION: *Genetics*, (in press)

SUMMARY: Comparisons between the gamma ray survival curves of diploid strains homozygous for two radiation-sensitive mutations and the corresponding single mutant diploids suggest that there are two types of repair of ionizing radiation damage in the yeast *Saccharomyces cerevisiae*. The major pathway for gamma ray repair, which is dependent on the function of the *RAD52* gene, appears to be essentially error-free while the other type of repair, dependent on *RAD6*, is responsible for the production of all mutations induced by ionizing radiation. The sensitivity of all strains, including those deficient in both kinds of repair, was enhanced by irradiation in oxygen and although the oxygen enhancement ratio varied from strain to strain, there was no evidence to support the idea that oxygen-dependent damage is repaired by only one pathway or that it is not repaired at all.

Q4 **TITLE:** Genetic analysis of gamma ray mutagenesis in yeast. III. Allele specific control of mutagenesis (UR-3490-1492)

AUTHORS: R. H. McKee and C. W. Lawrence

PUBLICATION: *Genetics*, (in press)

SUMMARY: We find that partially different sets of gene functions are required for the production of different kinds of mutations induced by ^{60}Co gamma rays in the yeast *Saccharomyces cerevisiae*. This observation is very similar to others made previously with respect to UV mutagenesis and confirms the conclusion that such distinctive patterns of genetic control reflect properties of the test alleles, and their genetic locations, rather than the kinds of lesions required to revert them. The data also support the hierarchical model of mutagenic repair outlined in the first paper of this series, in which partially different sets of gene functions are required for the production of different kinds of mutations, the formation of mutations at different genetic sites, and the induction of mutations by different mutagens.

Q5 **TITLE:** Regulation of metabolism in rat thymic lymphocytes: involvement of mRNA in glucocorticoid action, energy metabolism in protein synthesis, and composition and function of the ribosomal dimer (UR-3490-1379)

AUTHOR: S. L. Mendelsohn (Supervised by D. A. Young)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The isolation of RNA from rat thymic lymphocytes requires extensive inhibition of RNase. The effectiveness of several commonly used inhibitors has been studied in Chapter I using the removal of leucine from leucyl-tRNA as a sensitive assay for RNase activity. The inhibitors were tested under a variety of conditions, varying temperature, pH, and source of RNase. Although when each inhibitor is used separately sodium dodecyl sulfate (SDS) is the most effective, during exposures above 0° considerable RNA is still degraded. Proteinase K in combination with SDS is effective; however, alone it has significant RNase activity. Diethyl pyrocarbonate at high

concentrations reacts with RNA; however, when it is used in smaller amounts the effects on RNA are minimal and in combination with SDS it most effectively inhibits RNase.

The involvement of RNA in glucocorticoid hormone action in thymic lymphocytes has been examined in Chapter II. Cordycepin (3'-deoxyadenosine), when used *in vitro* at doses that block the emerging dexamethasone (or cortisol) inhibition on glucose uptake (between 15 to 35 minutes), equally blocks poly(A) synthesis and the migration of mRNA(+)poly(A) from the nucleus. An $\approx 80\%$ block in hormone action is associated with a blockage in the arrival of newly-made poly(A) by $\approx 70\%$ and mRNA by $\approx 65\%$. Only those events limited to the first 10 minutes after hormone addition are sensitive to cordycepin. The effective dose of cordycepin just slightly decreases protein synthesis but has no effect on total RNA or DNA synthesis. Possible nonspecific effects of cordycepin on ATP and hormone-receptor complex function were ruled out as a cause of the blockage on glucose. These results, when interpreted within the context of previous evidence for sequential RNA- and protein-synthetic steps in hormone action, provide highly suggestive evidence that the synthesis of mRNA is a primary event in initiating the most rapid of the metabolic effects of steroid hormones.

The previous proposal that rates of protein synthesis are regulated via the balance of adenine nucleotides has been tested in Chapter III. Depriving thymocytes of energy-providing substrates for two hours results in a 75% to 80% drop in rates of protein synthesis, a shift of ribosomes from active polysomes to inactive regions and a 7% decline in adenylate energy charge. Glucose prevents these changes or, when added to starved cells, rapidly reverses them. The data is consistent with the hypothesis that initiation of protein synthesis is regulated in part via the balance of adenine nucleotides. Data with other substrates and with metabolic inhibitors support this concept.

The composition and protein synthetic activity of ribosomes from thymic lymphocytes found in the relatively large monomer (80S) and dimer peaks, and polysomal region of sucrose gradient profiles have been studied in Chapter IV. Several methods were employed to demonstrate that ribosomal material in the monomer-dimer region is neither a degradation product of larger polysomes, nor an artifactual aggregate of ribosomal subunits.

The composition of these regions was determined using high salt sucrose gradients (500 mM KCl), which dissociate synthetically inactive ribosomes into subunits. The results show that the polysomal region is composed of synthetically active polyribosomes, whereas the monomer region consists of about 80% inactive ribosomes (monomers) and about 20% active ribosomes (native monosomes). In contrast, the dimer peak is primarily composed of equal amounts of active ribosomes (derived monosomes) and inactive ribosomes; there are only a few disomes. The results also show that only about half of the ribosomes are active, suggesting that initiation of protein synthesis is limited. The protein synthetic activity of the ribosomes in these regions is estimated from the time course and amount of incorporation of radiolabelled amino acids into nascent peptide chains. These results show that derived monosomes are the least synthetically active and that they appear to have decreased rates of elongation. This suggests a new working hypothesis that derived monosomes are associated with an inactive ribosome and that this dimer formation is either due to, or the cause of, their decreased activity.

96
TITLE: Inhibition of ribonuclease. Efficacy of sodium dodecyl sulfate, diethyl pyrocarbonate, proteinase K and heparin using a sensitive ribonuclease assay (UR-3490-1127)

AUTHORS: S. L. Mendelsohn and D. A. Young

PUBLICATION: *Biochim. Biophys. Acta*, 519: 461-473 (1978)

SUMMARY: The effectiveness of several commonly used inhibitors of ribonuclease (RNAase) has been studied using the removal of radiolabelled leucine from leucyl-tRNA as a sensitive assay for RNAase activity. The inhibitors were tested under a variety of conditions, varying the temperature, the pH, and the source of RNAase. When each inhibitor is used separately in the presence of pancreatic RNAase, sodium dodecyl sulfate (SDS) is the most effective; but during long exposures to temperatures above 0° C considerable amounts of RNA are still degraded. Combinations of inhibitors are more effective in preserving RNA; with this assay, a combination of SDS with diethyl pyrocarbonate is the most effective. Proteinase K acts as an inhibitor when used in combination with SDS; however, it has RNAase activity when used by itself. Diethyl pyrocarbonate, when used at the high range of concentrations employed by others for RNAase inhibition, reacts with RNA changing its charge. However, when diethyl pyrocarbonate is used in smaller amounts the effects on RNA are minimal and when used in combination with SDS it effectively inhibits RNAase.

97
TITLE: Adsorption of mercury vapor by gold and silver (UR-3490-1505)

AUTHOR: T. T. Mercer

PUBLICATION: *Anal. Chem.*, (in press)

SUMMARY: The sticking probability is unity for mercury vapor hitting a gold or freshly-formed silver surface. Adsorption isotherms for gold films indicate that it is not significantly affected by film aging, at least over periods as long as 235 hours. Adsorption isotherms for silver films deteriorate rapidly with aging indicating a marked decline in sticking probability. The adsorptive capacity of gold films is approximately 0.7 $\mu\text{g Hg per cm}^2$ of superficial film area. The adsorptive capacity of silver films varies significantly with aging time. Silver wool, silvered chromosorb P and silver membrane filters adsorb amounts of mercury equivalent to 2/3 to 1½ monolayers ($\approx 0.36 \mu\text{g/cm}^2$).

98
TITLE: SZOLD: its properties and relationships to other distributions (UR-3490-943)

AUTHOR: T. T. Mercer

PUBLICATION: *J. Macromol. Sci-Chem.*, A12: 1083-1090 (1978)

SUMMARY: SZOLD is a form of the three-parameter lognormal distribution. As originally defined, its normalization factor permits negative values of the distributed variable for some positively skewed distributions and for all negatively skewed distributions. Correct normalization factors are given here and the degree of truncation is shown as a function of the distribution parameters.

99
TITLE: Particle Size Analysis in Estimating the Significance of Airborne Contamination

AUTHORS: T. T. Mercer, Chairman and IAEA Panel

PUBLICATION: *International Atomic Energy Agency Tech. Reports Series No. 179, Vienna, (1978)*

SUMMARY: A better understanding of the exposure pathways leading to internal irradiation is needed. Assessing the hazards is a complicated task which involves both biological and physical considerations. Aerosols play the most important role in the transport of radioactivity to man. They can enter the human body by a direct pathway through inhalation or by indirect pathways through deposition in the food chain. Their toxicity depends not only on their physical and chemical properties but also on their aerodynamic characteristics. One of the most important aerosol properties governing aerodynamic characteristics is the particle size distribution.

In this report, information on pertinent methods and techniques for analysing particle size distributions is compiled. It is hoped that the publication will make for the more reliable evaluation, assessment and control of the potential hazards of suspended particulate matter.

101
TITLE: Visual thresholds and visual evoked responses in methylmercury-poisoned monkeys
(UR-3490-1555)

AUTHOR: W. H. Merigan

PUBLICATION: In *Visual System Neurotoxicity*, Ed. by W. H. Merigan and B. Weiss. (Proc. 11th Rochester Intern. Conf. on Environmental Toxicity, June 1978, Rochester, N. Y.)
Raven Press, New York, (in press)

SUMMARY: The extent of the visual field and thresholds of flicker detection were measured in two methylmercury-exposed and one control macaque monkeys. Bilateral concentric visual field constrictions were found in one of the two methylmercury-treated monkeys. This monkey had had a higher blood level of mercury during exposure than the other treated monkey. The flicker sensitivity of this monkey (expressed as modulation threshold) was reduced at high flicker frequencies and extremely low (scotopic or rod) luminance levels. These results indicate that the macaque provides an ideal model for investigating human visual loss in methylmercury poisoning. Insight provided by this study into mechanisms of visual loss in methylmercury poisoning suggest new and sensitive tests for the early detection of this toxic syndrome.

101
TITLE: Visual System Neurotoxicity. (Proc. 11th Rochester Intern. Conf. on Environmental Toxicity, June 1978, Rochester, N. Y.)

EDITORS: W. H. Merigan and B. Weiss

PUBLICATION: *Raven Press, New York, (in press)*

SUMMARY: The Eleventh Rochester International Conference focused on the visual system as the target, both primary and secondary, of a wide range of environmental contaminants. Numerous toxic agents such as methylmercury, methanol, and carbon disulfide act directly on the visual system. Although these substances have been recognized as hazardous for many years, our understanding of their mechanisms of neurotoxicity and grasp of dose-effect relationships remain rudimentary. Other

substances, such as lead, sulfur dioxide, sulfuric acid mist, carbon monoxide and organophosphate pesticides do not act primarily on the visual system. Visual tests have proven exceptionally sensitive, however, in detecting low levels of exposure to these agents.

The primary goal of the conference was to improve communication within the fledgling discipline of visual toxicology, since the further development of this field has been hampered by the geographical and professional dispersion of its practitioners. For example, the visual effects of methylmercury and carbon disulfide in humans have been studied extensively in Japan and Scandinavia while most studies of the visual effects of atmospheric agents have been carried out in the Soviet Union. An even more serious lack of communication has arisen from the wide range of professional affiliations of investigators in this field. Not only toxicologists, but epidemiologists, ophthalmologists, psychologists, neurophysiologists, anatomists, and other specialists investigate visual toxicity. No common outlets are available in which to discuss and compare their findings. The result is that the literature on visual toxicity is scattered through numerous journals, in many languages, and is not easily accessible to the new investigator.

The Rochester conference addressed these vexing communication problems in several ways. Substantive findings with a wide spectrum of agents were presented and discussed. Other speakers stressed the application of new visual and toxicologic techniques. The organization of the conference also emphasized the indispensable connection between clinical and laboratory investigations of toxic visual disorders. The proceedings of the conference will provide an important resource for investigators in this field.

TITLE: Biologic and pathophysiologic effects of exposure to microwaves (UR-3490-1381)

AUTHOR: S. M. Michaelson

PUBLICATION: In Microwave Bioeffects and Radiation Safety, Vol. 8, Ed. by M. A. Stuchly. Intern. Microwave Power Inst., Edmonton, Alberta, Canada, pp. 55-94 (1978)

SUMMARY: During the last 35 years there has been a remarkable development and increase in the number of processes and devices that utilize or emit nonionizing radiant energy in the microwave frequency domain of the electromagnetic energy spectrum. These energies are used in all sectors of our society; for military, industrial, telecommunications, medical, and consumer applications. Although there is information on biologic effects and potential hazards in man from exposure to microwaves, considerable confusion and misinformation have permeated not only the public press but also some scientific and technical publications. It is important, therefore, to maintain a proper perspective and assess realistically the biomedical effects of microwave energy so that the worker or general public will not be unduly exposed nor will research development and beneficial utilization of this energy be hampered or restricted by an undue concern for effects which may be nonexistent or minimal in comparison to other environmental factors. The goal of this lecture is to review and place the available information and concepts in proper perspective to understand and encourage the full potential for the beneficial use of this energy at the same time preventing adverse effects to individuals exposed to microwaves.

For the purpose of this lecture, microwaves are defined as that portion of the electromagnetic radiant energy spectrum which encompasses the frequency range of 300 MHz to 300 GHz with wave-

lengths in free space of 1 m to 1 mm. The following topics are covered: biophysics energy absorption and distribution; thermal effects; nonthermal interactions; threshold for perception; lenticular opacities; the gonads; chromosome changes; hematopoiesis; cardiovascular effects; endocrine and central nervous system effects; acoustic effects; electromagnetic interference of cardiac pacemakers.

103
TITLE: Human responses to power frequency exposures (UR-3490-1385)

AUTHOR: S. M. Michaelson

PUBLICATION: *Proc. 18th Ann. Hanford Life Sciences Symp., October 1978, Richland, Washington, (in press)*

SUMMARY: A review of the literature indicates that most research on possible health effects of electric and magnetic fields on man has comprised clinical studies of longitudinal or cross-sectional design or isolated studies on human volunteers. In the former, relatively small groups of workers have been clinically examined and investigated for a variety of physiological parameters and for signs and symptoms of disease, either on a one time prevalence basis or longitudinally over a period of time. The selection of questions, clinical examinations, laboratory investigations, etc., has been influenced by pragmatic or theoretical considerations, often reinforced or complemented by published observations which have been made on small numbers of volunteers or animals under experimental conditions of exposure.

A systematic study to determine the effects of electric fields on linemen has been conducted in the United States and in Canada. Isolated occupational studies have been reported from Canada, Spain, and the United Kingdom. The reports from Soviet and other East European countries are based on surveys performed on substation personnel. Studies on small numbers of human volunteers have originated in the United States, Germany, and Sweden.

In general, the studies have been limited, lack statistical power, and are oriented toward particular end results, i.e., comprehensive medical examinations in some cases in contrast to the special sensitivity of a particular body system, i.e., the central nervous system. Many of the reported studies present serious difficulties because pertinent material is not presented and in many cases the data are variable and internally inconsistent.

Careful review of the information that is available, however, indicates that if a hazard does exist, it is not from the electric field *per se* but the secondary shock.

104
TITLE: Comparison of micronuclei induction for X-ray and ultrasound exposure of *Vicia faba* root meristem cells (UR-3490-1461)

AUTHOR: M. W. Miller

PUBLICATION: *Ultrasound Med. Biol., (in press)*

SUMMARY: X-irradiation (200 R) but not ultrasound (1.1 MHz, 8 W/cm², 1 minute exposure) induced micronuclei in root meristem cells of *Vicia faba*.

105
TITLE: Letters (High Tension) (UR-3490-1361)

AUTHORS: M. W. Miller, G. E. Kaufman and E. L. Carstensen

PUBLICATION: *The Sciences*, 18/8: 2-3 and 27-28 (1978)

SUMMARY: A number of reports dealing with electromagnetic fields and biological effects is discussed. These reports were previously cited in *The Sciences* to indicate that the electromagnetic fields associated with high voltage transmission lines can produce biological effects. The reports, when critically reviewed, provide no evidence that electromagnetic fields associated with transmission lines cause biological effects. A National Academy of Sciences report is cited to support our evaluation that somewhat similar electromagnetic fields are unlikely to cause serious adverse biological effects. However, electric power lines do affect people and the environment in a variety of ways. Claims that the electric and magnetic fields from such lines cause biological effects appear to be without basis.

106
TITLE: 60 Hz electric field parameters associated with the perturbation of a eukaryotic cell system (UR-3490-1409)

AUTHORS: M. W. Miller, E. L. Carstensen and G. E. Kaufman

PUBLICATION: *Proc. 18th Ann. Hanford Life Sciences Symp.*, October 1978, Richland, Washington, (in press)

SUMMARY: Roots of *Pisum sativum* were exposed for seven days to 60 Hz electric fields ranging from 70 to 430 V/m in an aqueous medium whose conductivity was approximately 0.07 mho/m. (Corresponding current densities in the exposure medium associated with these field strengths ranged from 0.5 to 3.0 mA/cm².) Control and exposed roots were grown concomitantly in the same tank whose growth medium was continuously circulated. Temperature in the exposure medium was held at a constant 19° C. All experiments were conducted "double blind." Root growth rates were determined daily. No perturbations in root growth were observed with electric fields of 150 V/m; there was a slight effect at 360 V/m, and a pronounced decrease in growth rate occurred at 430 V/m. Comparable fields could not be obtained by exposure of the medium through air because the required fields would exceed the dielectric strength of air. Under conditions in which growth inhibition occurs, it is estimated that induced 60 Hz cell membrane potentials would be of the order of 3 mV.

107
TITLE: Studies on methylene chloride-induced fatty liver (UR-3490-1434)

AUTHORS: J. B. Morris, F. A. Smith and R. H. Garman

PUBLICATION: *Exptl. Mol. Pathol.*, (in press)

SUMMARY: The fatty liver induced by methylene chloride inhalation in the guinea pig was investigated by studying the effects of this solvent on several pathways of hepatic lipid metabolism. Inhalation of 5200 ppm (18,000 mg/m³) methylene chloride for six hours resulted in a 2.5-fold increase in hepatic triglyceride. Electron microscopy revealed the hepatocytes following exposure to be of normal appearance except for the presence of numerous lipid droplets in the cell periphery. No changes were evident by light microscopy.

Serum-free fatty acid levels were unaffected by exposure. The incorporation of palmitic acid into triglyceride by liver slices was also unchanged by methylene chloride. These results suggest that increased triglyceride synthesis rates were not responsible for the fatty liver. Exposure resulted in a 63% decrease in serum triglyceride suggesting a defect in triglyceride secretion as a cause of the fatty liver. This defect cannot be explained by decreased hepatic protein synthesis inasmuch as incorporation of 1-¹⁴C leucine into hepatic proteins was unaltered, or by decreased availability of phospholipids, because hepatic phospholipids actually increased with triglyceride. Liver slices from exposed animals incubated with control guinea pig serum containing 1-¹⁴C palmitic acid were able to synthesize and then secrete triglyceride into the medium at control rates. In toto, the results suggest that methylene chloride inhalation leads to the depletion or alteration of some serum component necessary for the maintenance of normal hepatic triglyceride secretion.

108
TITLE: Book review of "Recommendations of the International Commission on Radiological Protection". ICRP Publication 26, Ed. by F. D. Sowby. Annals of ICRP, 1: no. 3, 1977. Pergamon Press, New York, Oxford, Frankfurt (UR-3490-1380)

AUTHOR: P. E. Morrow

PUBLICATION: *Health Phys.*, (in press)

SUMMARY: This review discusses the newest set of radiation protection guidelines from the International Commission on Radiological Protection. The ICRP recommendations contain basic limits for ionizing radiations for the public and occupational workers, as well as certain secondary and derived limits of value in the implementation of the basic units. The new recommendations herald a new radiation protection philosophy wherein various radiation dose estimations are equated to risk and thereby lend themselves to simple addition. Thus the new basic limits pertain to the total annual radiation exposure from all sources rather than dose to the "critical organ".

109
TITLE: The blood:bone disequilibrium. III. The linkage between cell energetics and Ca fluxes (UR-3490-1407)

AUTHORS: W. F. Neuman, M. W. Neuman and C. R. Myers

PUBLICATION: *Am. J. Physiol.*, (in press)

SUMMARY: Specially designed Ussing chambers were used for the quantitation of fluxes of Ca²⁺ and lactate ions to and from calvaria taken from two- to three-day-old rat pups and young, adult mice. The effects of various metabolic inhibitors and parathyroid hormone were studied. The results support previous findings that Ca influx into bone is a passive, concentration-dependent process not significantly affected by alterations in the energy status of the bone cells. In large measure, the efflux from bone also appears to be passive. However, significant alterations in the calcium levels supported by efflux from bone were observed as acute effects of metabolic inhibitors. Part of the metabolically-derived efflux can be attributed to acid production (aerobic glycolysis). However, part must be ascribed to cellular activities not yet defined.

0
TITLE: Effects of PTH and Ca^{2+} on renal adenyl cyclase (UR-3490-1362)

AUTHORS: S. T. Nielsen and W. F. Neuman

PUBLICATION: *J. Supramol. Struc.*, 9: 391-398 (1978)

SUMMARY: The effects of calcium ion on the adenylate cyclase system was studied in isolated, renal basal-lateral plasma membranes of the rat. Bovine parathyroid hormone (bPTH) and a guanyl triphosphate analogue, Gpp(NH)p were used to stimulate cyclase activity.

Under conditions of maximal stimulation, calcium ions inhibited cyclic adenosine monophosphate (cAMP) formation, the formation rate falling exponentially with the calcium concentration. Fifty percent inhibition of either bPTH- or Gpp(NH)p-stimulated activity was given by approximately $50 \mu\text{M}$ Ca^{++} . Also the Hill coefficient for the inhibition was close to unity in both cases. The concentration of bPTH giving half-maximal stimulation of cAMP formation ($1.8 \times 10^{-8} \text{ M}$) was unchanged by the presence of calcium.

These data suggest that calcium acts at some point other than the initial hormone-receptor interaction, presumably decreasing the catalytic efficiency of the enzymic moiety of the membrane complex.

11 TITLE: The electrolytic preparation of bioactive radioiodinated parathyroid hormone of high specific activity (UR-3490-1217)

AUTHORS: S. T. Nielsen, P. Q. Barrett, M. W. Neuman and W. F. Neuman

PUBLICATION: *Anal. Biochem.*, (in press)

SUMMARY: A technique for the preparation of microgram quantities of bovine parathyroid hormone (bPTH) labeled with carrier-free ^{125}I to a specific activity of 1300 Ci/mmol is described. A restructured and simplified apparatus was used for electrolytic iodination, making it feasible to use reaction volumes of 100 to 200 ml. The miniaturized setup requires only a small platinum crucible connected via an agar-KCl salt bridge to a saturated KCl solution, a battery to drive the reaction, and a voltmeter to monitor the potential difference between the reference-saturated KCl solution (via a calomel electrode) and the platinum crucible. The [^{125}I]-labeled bPTH elutes as a single species when chromatographed on a Biogel P-10 column equilibrated in 3 M guanidine HCl-2.3 M formic acid, and it retains full biologic activity when bioassayed *in vivo*. It is evident that bPTH labeled to a high specific activity with ^{125}I does not suffer in regard to its biological potency.

11 TITLE: Steady non-ionic countergradient transport through membranes by coupled diffusion (UR-3490-1463)

AUTHORS: R. H. Notter, Y. M. Tam and S. Min

PUBLICATION: *AIChE J.*, (in press)

SUMMARY: The generation of non-ionic countergradient transport through membranes by coupled diffusion effects is analyzed by both experimental and theoretical means. Experiments on a well-characterized binary solution, ethanol in water, are carried out with a membrane wedge interferometer at 25°C . The membrane used is a cellophane dialyzer membrane and the results show that over a wide range of concentrations it is possible to generate net mass transfer of the

less permeable component ethanol against its concentration gradient. No net temperature or pressure driving forces are present in the countergradient transport system and no energy expenditure or membrane-bound carrier is involved. Only a concentration gradient driving force across the membrane is required, together with a difference in membrane diffusion or solubility coefficients for the transporting species.

The experiments are supplemented by a theoretical analysis of an idealized membrane separating two binary bulk solutions. The analysis is based on the widely used Fick's Law approach and allows a prediction of the conditions under which non-ionic countergradient transport can be generated from direct diffusional coupling effects in a membrane transport system. A comparison of theoretical and experimental results shows good agreement between observed and predicted countergradient transport characteristics.

|| TITLE: Studies of mycoplasma and mycoplasmavirus DNA (UR-3490-1437)

AUTHOR: J. A. Nowak (Supervised by J. Maniloff)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The mycoplasmas are a diverse group of prokaryotes which have as their distinctive characteristics small cell size, relatively small genomes (0.5 to 1.0×10^9 daltons), and complete lack of cell wall. Within the past decade, four types of mycoplasmaviruses have been isolated which can infect certain mycoplasma strains. One of these is a spiroplasmavirus and is specific for *Spiroplasma citri*. The others, mycoplasmavirus Groups 1, 2, and 3 are specific for *Acholeplasma laidlawii*. This thesis describes some of the properties of a Group 1 and a Group 2 mycoplasmavirus. In addition, some properties of the host cell, *A. laidlawii*, have been studied using the viruses as probes.

Mycoplasmavirus MVL51, a Group 1 virus, was reported to be a non-lytic, bullet-shaped, single-stranded DNA virus. Electron microscope observations confirm that the MVL51 genome is a single-stranded circular DNA molecule. Contour length measurements show that the MVL51 genome is 0.69 times the length of phage fd single-stranded DNA and that the double-stranded replicative form of MVL51 is 0.71 times the length of phage M13 double-stranded replicative form DNA. From these measurements it is calculated that the MVL51 single-stranded DNA genome contains about 4,500 nucleotides and has a molecular weight of 1.5×10^6 .

Mycoplasmavirus MVL2, a Group 2 virus, is a non-lytic enveloped virus which apparently matures by budding from its host cell. These studies show that the MVL2 genome is a superhelical covalently-closed circular, double-stranded DNA molecule. Contour length measurements indicate that the MVL2 DNA genome contains 11.8 kilobase pairs and has a molecular weight of 7.8×10^6 . Ethidium bromide dye titration experiments show that the MVL2 DNA has a superhelix density ($\sigma_{0.260} = 0.073$) that is slightly greater than that of ϕ x174 RFI, but not as great as that for PM2 DNA. The superhelical MVL2 DNA molecule contains non-base paired regions as judged by its susceptibility to nicking by the *N. crassa* single-strand specific endonuclease. A restriction enzyme cleavage map of MVL2 DNA has also been constructed.

In addition, studies are presented describing the effect of novobiocin, an inhibitor of DNA gyrase in *E. coli*, on *A. laidlawii* cells and on the replication of MVL51 DNA. Novobiocin, at a concentration of 10 $\mu\text{g/ml}$, reversibly inhibits *A. laidlawii* growth. The drug is seen to inhibit DNA and RNA synthesis but has only a slight effect on protein synthesis. Since MVL51 DNA normally forms a superhelical replicative intermediate in infected cells, it was thought that the drug would inhibit MVL51 replication if it were inhibiting a gyrase activity. Novobiocin does not inhibit MVL51 progeny virus production unless treatment begins before infection. The nature of the replicative intermediates formed in the presence of the drug is abnormal, as seen by sedimentation in sucrose gradients. Predominantly one DNA species is made which, although shown not to be a covalently closed circle, cosediments in neutral sucrose gradients with the superhelical replicative form (RFI). It is concluded that, except for a very early event, MVL51 DNA replication and transcription can occur in a novobiocin insensitive manner in a drug-sensitive host cell.

The drug is seen to have a second effect on *A. laidlawii* cells that has not been previously recognized. Novobiocin treatment of *A. laidlawii* cells promotes the stability of *A. laidlawii* nucleoids after cell lysis with the non-ionic detergent Brij-58. The cause of the effect is not understood but some preliminary experiments and electron micrographs characterizing these *A. laidlawii* nucleoids are described.

A variant of the host cell is also described which is unable to replicate infecting MVL51 DNA beyond the conversion of the infecting single strand to double-stranded replicative forms, as determined by sedimentation of infected cell lysates in sucrose gradients. The variant, *A. laidlawii* JA1-REP⁻, can still support the growth of Group 2 and Group 3 mycoplasmaviruses.

114 TITLE: Physical characterization of the superhelical DNA genome of an enveloped mycoplasmavirus (UR-3490-1426)

AUTHORS: J. A. Nowak and J. Maniloff

PUBLICATION: J. Virol., (in press)

SUMMARY: Mycoplasmavirus MVL2 is a nonlytic enveloped virion containing DNA. This DNA has been shown to be a double-stranded circular superhelical molecule of 11.8 kilobase pairs (7.8×10^6 daltons). The superhelix density is greater than that of ϕX174 RFI but less than that of PM2 phage DNA. A physical map of the MVL2 genome has been obtained using restriction endonucleases.

115 TITLE: Electron microscopy of single-stranded mycoplasmavirus DNA (UR-3490-1429)

AUTHORS: J. A. Nowak, J. Maniloff and J. Das

PUBLICATION: FEMS Microbiol. Letters, 4: 59-61 (1978)

SUMMARY: Mycoplasmavirus MVL51 virions are unenveloped bullet-shaped particles, about 14 nm by 80 nm, with helical symmetry. Studies of the effect of various specific nucleases on viral DNA infectivity showed that the MVL51 genome is circular single-stranded DNA. Viral replication involves two double-stranded DNA replicative forms: RFI, a covalently closed double-stranded circular derivative of the viral DNA, and RFII, a relaxed form of RFI.

Previous sedimentation studies of the MVL51 viral single-stranded DNA, in this laboratory, indicated the genome size was about $2 \cdot 10^6$ daltons. Since smaller DNA forms are sometimes seen in cell lysates, it was decided to reevaluate the viral genome size by electron microscopy. Measurement of double-stranded viral RF DNA by electron microscopy allows a more accurate determination of the molecular weight than was possible by the earlier sedimentation studies.

116 TITLE: Neutropenia (UR-3490-1184)

AUTHORS: J. P. Olson and M. A. Lichtman

PUBLICATION: Chapt. 5 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 105-120 (1978)

SUMMARY: This chapter discusses the diagnosis and management of human diseases that result in an isolated reduction in blood neutrophils.

117 TITLE: Yeast UAA suppressors effective in ψ^+ strains. I. Serine inserting suppressors (UR-3490-1410)

AUTHORS: B. Ono, J. W. Stewart and F. Sherman

PUBLICATION: *J. Mol. Biol.*, (in press)

SUMMARY: Over 200 revertants that suppressed three or more UAA markers were isolated in a haploid strain of yeast, *Saccharomyces cerevisiae*, containing the ψ^+ cytoplasmic determinant which increases the efficiency of action of certain suppressors. These revertants were grouped into five classes on the basis of suppression of four nutritional markers, the canavanine-resistant marker, *can1-100*, and the *cyc1-72* marker which contains a defined UAA mutant codon corresponding to position 66 in iso-1-cytochrome c. Genetic analysis indicated that these five classes of revertants resulted from the interaction of suppressors which had characteristic efficiencies of suppression and genetic modifiers that affected these efficiencies. After taking the genetic modifiers into consideration, these suppressors could be assigned to three major groups on the basis of their pattern of suppression and their efficiency of action. Further genetic tests indicated that 40% of the suppressors were highly efficient and were allelic to one or another of the known tyrosine-inserting suppressors, that 50% of the suppressors were relatively efficient and were allelic to one or another of the two serine-inserting suppressors *SUP16* and *SUP17*, and that 1% of the suppressors were inefficient and were allelic to the *SUP26* suppressor. The *SUP16* suppressors were shown to be allelic to the previously characterized suppressor *SUQ5* whose locus is on the right arm of chromosome XVI. This location and the pattern of suppression suggests that the *SUP16* locus may be identical to the previously described *SUP15* locus. Genetic analysis established that the *SUP17* locus is on the left arm of chromosome IX, between the *his6* and *lys11* markers. Examination of the degree of suppression of the *ade2-1* marker suggested that the *SUP16* suppressors were slightly more efficient than the *SUP17* suppressors and that the *SUP17* suppressor may be composed of two subclasses with slightly different efficiencies of action. In addition, it was found that the efficiencies of action of the *SUP16* and *SUP17* suppressors appeared enhanced in the ρ^- strains compared to ρ^+ strains. The examination of four different strains having various efficiencies of suppression revealed that the *SUP16* and *SUP17*

suppressors cause insertion of serine in iso-1-cytochrome *c* at the UAA site of the *cyc1-72* mutant. It is suggested that the gene products of the *SUP16* and *SUP17* loci are redundant forms of the same serine tRNA.

118 **TITLE:** Factors influencing paper chromatographic analysis of technetium-99m phosphorus compounds: concise communication (UR-3490-1445)

AUTHORS: A. Owunwanne, D. A. Weber and R. E. O'Mara

PUBLICATION: *J. Nucl. Med.*, 19: 534-537 (1978)

SUMMARY: A single-paper chromatographic system has been developed, capable of resolving Tc-99m dioxides, [^{99m}Tc] pertechnetate and Tc-99m phosphorus compounds. The best separations are obtained with CM82 paper developed in 0.5 M NaCl, and 3MM or ashless No. 40 paper developed in 1 M sodium acetate buffer. In these systems, ^{99m}TcO₂ remains at the origin, while ^{99m}TcO₄- and Tc-99m phosphorus compounds move with R_f values of 0.56 to 0.75 and 0.80 to 1.0, respectively.

119 **TITLE:** Phenotypic suppression of nonsense mutants in yeast (UR-3490-1451)

AUTHORS: E. Palmer, J. Wilhelm and F. Sherman

PUBLICATION: *Nature*, (in press)

SUMMARY: Streptomycin, an aminoglycoside antibiotic, can reverse the mutant phenotypes of numerous nonsense and missense mutations in *Escherichia coli* and in bacteriophage T4. This phenomenon has been denoted "phenotypic suppression" since the mutant phenotype returns after removal of the drug.

The most likely explanation for phenotypic suppression is that streptomycin promotes mistranslation *in vivo*, and that acceptable amino acids are inserted into the growing polypeptide chain at the site of the mutant codon. Consistent with this view is the observation that streptomycin causes *E. coli* ribosomes to mistranslate RNA *in vitro*.

Interestingly, streptomycin and neomycin were found to have no effect in stimulating ribosomes from eukaryotic cells to mistranslate RNA *in vitro*. Recently, however, Wilhelm and colleagues have demonstrated that a subclass of the aminoglycoside antibiotics does stimulate eukaryotic ribosomes to misread RNA. The highly active molecules are distinguished in that they contain the drug fragment paromamine (or 3' deoxyparomamine). In order to extend this finding, we have examined the capacity of various aminoglycosides to phenotypically suppress mutations in a eukaryotic organism, specifically the yeast, *Saccharomyces cerevisiae*.

120 **TITLE:** Variation of phenotypic suppression due to the ψ^+ and ψ^- extrachromosomal determinants in yeast (UR-3490-1482)

AUTHORS: E. Palmer, J. Wilhelm and F. Sherman

PUBLICATION: *J. Mol. Biol.*, (in press)

SUMMARY: Paromomycin, an aminoglycoside antibiotic, can phenotypically suppress nonsense mutations in the yeast *Saccharomyces cerevisiae*. We report here that the extrachromosomal

determinant, ψ^+ , enhances this phenotypic suppression of all three nonsense mutations, UAG, UAA, and UGA, by three- to seven-fold.

121
TITLE: Pulmonary tissue volume in dogs during pulmonary edema (UR-3490-1215)

AUTHORS: B. T. Peterson, M. F. Petrini, R. W. Hyde and B. F. Schreiner

PUBLICATION: *J. Appl. Physiol.*, 44: 782-795 (1978)

SUMMARY: Pulmonary tissue volume (V_t) and pulmonary capillary blood flow (Q_c) were measured in anesthetized dogs by analyzing end-expiratory concentrations of dimethyl ether (DME), acetylene (C_2H_2), and sulfur hexafluoride during a 30-s rebreathing maneuver. V_t was compared to the postmortem lung weight of control dogs and dogs with hemodynamic and nonhemodynamic (alloxan) pulmonary edema. Q_c was compared to the cardiac output measured by dye dilution. A 100-ml increase in alveolar volume (V_A) in the range of 1 to 2 liters results in a 9 ± 3 ml increase in V_t . V_t measured at a V_A of 1.9 liters measured $114 \pm 18\%$ of the postmortem lung weight in 20 control dogs and in six dogs with moderate edema (lung weight $< 250\%$ of predicted). V_t measured only $53 \pm 14\%$ of the lung weight in 11 dogs with more severe edema. DME and C_2H_2 gave the same mean values of V_t , but the reproducibility of a series of three to seven measurements was greater with DME (coefficient of variation was 5% with DME and 8% C_2H_2). Q_c measured $96 \pm 15\%$ of the cardiac output during the rebreathing maneuver but the maneuver caused a 4% to 40% fall in the cardiac output. These data show that V_t determined by rebreathing DME is between 86% and 135% of the lung weight in dogs with pulmonary edema until the lung weight is greater than 250% of the predicted value.

122
TITLE: Lung tissue volume and blood flow by rebreathing: theory (UR-3490-1214)

AUTHORS: M. F. Petrini, B. T. Peterson and R. W. Hyde

PUBLICATION: *J. Appl. Physiol.*, 44: 795-802 (1978)

SUMMARY: Rebreathing determinations of pulmonary tissue volume (V_t) and pulmonary capillary blood flow (Q_c) are supplanting breath-holding methods because of the shorter time for data collection and better reproducibility. However, rebreathing methods have errors due to dead space (V_D), volume rebreathed (V_E), rebreathing rate (RR), as well as from uneven distribution between V_t , Q_c , V_E , and alveolar volume (V_A). These errors were studied by calculating V_t and Q_c from a normal lung model with dimensions: $V_t = 600$ ml, $Q_c = 6$ l/min, $V_E = 2,000$ ml, residual volume = 2,000 ml, $V_D = 200$ ml, and $RR = 30$ /min. RR as slow as 10/min and V_D of 200 ml caused less than a 4% error in V_t and Q_c . Increases in V_D to 1,000 ml overestimated V_t by 31% and underestimated Q_c by 19% but a simple correction for the decreased effective V_A with the first breath reduced these errors to 8% and 13%, respectively. More rapid RR and larger V_E always decreased errors due to V_D . The uneven distribution reported in normal man due to gravitational forces caused a 4% error in V_t and a 1% error in Q_c . Lung models constructed from reported data for uneven distribution in severe obstructive lung diseases showed large errors in V_t (-13% to +46%) and smaller errors in Q_c (-1% to -18%). Models of severe restrictive diseases generally gave marked

underestimates of V_t (-3% to -64%). These data indicate that estimates of V_t and Q_c have acceptable accuracy in normal man and subjects with moderate degree of uneven distribution, but large errors develop with more severe forms of lung disease.

³
1 TITLE: Characteristics of amino acid transport in the isolated small intestinal epithelial cell
(UR-3490-1459)

AUTHOR: A. L. Picone (Supervised by G. A. Kimmich)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1977)

ABSTRACT OF THESIS: The amino acid transport characteristics of isolated chick intestinal epithelial cells were studied using radioisotope techniques. Ultimately, the purpose of the project was to identify a transport mechanism that was consistent with the observed characteristics.

A technique for rapid sample handling was developed in order to measure initial rates of valine influx and efflux. The technique represents a modified version of an earlier protocol after experimental evaluation indicated a number of limitations for the earlier procedures.

The influx and efflux of L-valine are consistent with function of a single saturable transport system which is sodium dependent. Both the kinetic parameters (the Michaelis-Menton constant and the maximal velocity of transport) which describe the saturable process depend on the level of Na in the suspending medium. Intracellular valine stimulates the unidirectional influx of valine, although extracellular valine was not shown unequivocally to stimulate valine efflux rates. By the same token, high levels of intracellular Na inhibited the unidirectional influx of valine, but high levels of extracellular Na could not be shown unequivocally to inhibit the rate of valine efflux. However, under certain conditions, extracellular Na or valine did modify the observed efflux of cellular valine. Based on these observations, a transport model is proposed which also can account for a number of ancillary observations.

The Na-dependent influx of 3-OMG was found to inhibit the observed Na-dependent accumulation of valine in a nonuniform manner (that is, a temporally increasing degree of inhibition of accumulation from 0% to 6% at initial time intervals up to $\approx$ 30% at the steady state). The interaction between the two transport processes was abolished in the presence of abnormally high levels of intracellular Na. Explanation of the interaction in terms of a multi-functional carrier for both species is unlikely. Instead, a localized perturbation in an intracellular Na microenvironment due to 3-OMG-dependent Na influx, is more consistent with the data. Elevation of Na in this microenvironment results in a trans-inhibition of valine influx. The interaction was, furthermore, relegated to mucosal border of the intestinal epithelial cell.

The results presented are consistent with the concept that the transmembrane electrochemical gradient for Na furnishes the driving force for active nonelectrolyte transport in the intestinal epithelial cell. The contribution of membrane potential to the transport process was not established by this investigation. However, the results were at least in part consistent with this concept. There is no necessity for invoking a direct input of metabolic energy in order to explain the results presented.

124
TITLE: Concentration distributions of free and attached Rn and Tn decay products in laminar aerosol flow in a cylindrical tube (UR-3490-1270)

AUTHORS: J. Porstendörfer and T. T. Mercer

PUBLICATION: *J. Aerosol Sci.*, 9: 283-290 (1978)

SUMMARY: The problem of the steady state diffusion of radon decay products in laminar aerosol flow through a cylindrical tube is presented. Neglecting axial diffusion and assuming constant aerosol concentration in the tube, the concentration distribution, the flux and the transmission of the free and attached radioactive atoms were calculated, taking into consideration the formation and attachment of the decay products. The first five eigenvalues E_n and the corresponding coefficients for different attachment rates X were computed. These results can be used to determine experimentally the diffusion coefficients of Rn and Tn decay products or small ions and their rates of attachment to aerosols.

125
TITLE: Influence of electric charge and humidity upon the diffusion coefficient of radon decay products (UR-3490-1299)

AUTHORS: J. Porstendörfer and T. T. Mercer

PUBLICATION: *Health Phys.*, (in press)

SUMMARY: The diffusion coefficient of freshly formed Tn decay products was measured as a function of relative humidity and electrical charge. Positively charged decay products under very dry air conditions ($RH < 2\%$) have a diffusion coefficient of only $(4.8 \pm 0.3) \cdot 10^{-2} \text{ cm}^2/\text{s}$ in contrast to higher relative humidities ($RH: 30\% \text{ to } 90\%$), at which we measured a value of $(6.8 \pm 0.4) \cdot 10^{-2} \text{ cm}^2/\text{s}$. For neutral ThB atoms we could find no influence of water vapour. Their diffusion coefficient is always $(6.7 \pm 0.4) \cdot 10^{-2} \text{ cm}^2/\text{s}$.

126
TITLE: Influence of nuclei concentration and humidity upon the attachment rate of atoms in the atmosphere (UR-3490-1339)

AUTHORS: J. Porstendörfer and T. T. Mercer

PUBLICATION: *Atmos. Environ.*, 12: 2223-2228 (1978)

SUMMARY: The attachment rate of atoms and ions to the atmospheric aerosol indoors and outdoors was studied by means of the Tn (^{220}Rn) decay products, which have a diffusion coefficient $D = 0.068 \text{ cm}^2 \text{ s}^{-1}$ and a sticking probability $S = 1$. In a nuclei concentration range between $0.6 - 7 \times 10^4 \text{ particles cm}^{-3}$ the attachment rates were $0.009 - 0.05 \text{ s}^{-1}$ (relative humidity: 30% to 50%) corresponding to a half-life of attachment 77 to 14 seconds. The change of the average nuclei size with humidity could be determined by measuring the attachment rate for different water vapour concentrations. By changing the humidity from 20% to about 100%, the average particle size increases up to a factor of 2.1.

² TITLE: Particle size dependence of a condensation nuclei counter (UR-3490-1257)

AUTHORS: J. Porstendörfer and S. C. Soderholm

PUBLICATION: *Atmos. Environ.*, 12: 1805-1806 (1978) *Short Communication*

SUMMARY: The influence of the particle size on the concentration indicated by a condensation nuclei counter (Model Rich 100, Environment One Corp.) was determined experimentally. The particle size dependence of this device was measured using fairly monodisperse silver particles and an absolute photographic condensation nuclei counter. The absolute calibration factor of the condensation nuclei counter also changed when the particle size of an aerosol containing atmospheric and Bunsen nuclei was changed.

⁴
² TITLE: Pathways of DNA repair in yeast (UR-3490-1333)

AUTHORS: L. Prakash and S. Prakash

PUBLICATION: In *DNA Repair Mechanisms*, Ed. by P. C. Hanawalt, E. C. Friedberg and C. F. Fox. (Proc. Symp., February 1978, Keystone, Colorado). Academic Press, New York, pp. 413-416 (1978)

SUMMARY: The RAD1 excision-repair pathway of yeast consists of three additional genes, RAD7, RAD14 and MMS19, all of which are shown to be defective in excision of pyrimidine dimers. In addition, two genes, MMS3 and CDC8 are discussed in terms of their effect on IV-induced mutations.

²
² TITLE: Divalent cation binding to phospholipid vesicles: dependence on temperature and lipid fluidity (UR-3490-1418)

AUTHORS: J. S. Puskin and T. Martin

PUBLICATION: *Biochim. Biophys. Acta*, (in press)

SUMMARY: Mn²⁺ binding to vesicles prepared from several different species of anionic phospholipids was determined as a function of temperature by electron paramagnetic resonance (EPR). The Mn affinities of phosphatidylserine (PS), cardiolipin and egg yolk phosphatidylglycerol all increased monotonically with temperature.

Vesicles prepared from hydrogenated and natural (bovine) PS were monitored with respect to hydrocarbon chain fluidity as well as Mn binding. Contrary to expectations based on surface potential considerations, the affinity of PS for divalent cations was apparently not lowered in going from the gel state to the liquid crystalline state of the bilayer. The results are instead consistent with an enhancement in cation affinity with increased lipid fluidity.

Dipalmitoyl phosphatidylglycerol vesicle fluidity and Mn binding were also studied with EPR. A large reduction in the measured Mn affinity accompanied melting of the phospholipid but observed hysteresis in the temperature dependence of the binding render uncertain any simple explanation based on changes in surface potential. Supplementary light scattering data indicated that aggregates of these vesicles were formed below the phase transition temperature, stabilized in part by Mn bridging between bilayers.

130
TITLE: Properties of a persistent viral infection: possible lysogeny by an enveloped nonlytic mycoplasma virus (UR-3490-1427)

AUTHORS: R. M. Putzrath and J. Maniloff

PUBLICATION: *J. Virol.*, 28: 254-261 (1978)

SUMMARY: MVL2, an enveloped double-stranded DNA mycoplasma virus, causes a nonlytic infection of *Acholeplasma laidlawii* leading to the establishment of a persistent infection. Persistently infected clones were found to be resistant to superinfection by homologous virus but could be infected by heterologous virus. Cells in a persistently infected culture had the potential to produce virus and transmitted this potential as a stable heritable trait. Mitomycin C and UV light induced an increase in infectious centers in persistently infected cultures.

131
TITLE: Parathyroid hormone stimulation of collagenase secretion from isolated bone cells (UR-3490-1118)

AUTHORS: J. E. Puzas and J. S. Brand

PUBLICATION: *Endocrinol.*, (in press)

SUMMARY: This report describes the development of a new culture assay for studying the secretion of collagenase by isolated bone cells.

The assay involves preparing viable isolated bone cells from fetal rat calvaria and culturing them in a ^{14}C -glycine labeled collagen matrix providing conditions similar to the environment in whole calvaria *in vivo*. Collagenase released by the cells is secreted directly into the radioactive substrate and can be easily assayed. The effect of hormones and other metabolic modifiers on collagenase secretion and possibly synthesis can be studied.

Parathyroid hormone in this system causes a reproducible stimulation of collagenase secretion at early times leading to an increase in collagen matrix degradation. The sustained effect of parathyroid hormone on collagen degradation is most probably due to enhanced collagenase synthesis and can be inhibited by puromycin.

An observation is also made regarding the susceptibility of the parathyroid hormone receptor to nonspecific protease activity as was previously seen in skeletal and renal tissue.

132
TITLE: Renal effects of renal X-irradiation and induced autoallergic glomerulonephritis (UR-3490-1371)

AUTHORS: D. S. Rappaport and G. W. Casarett

PUBLICATIONS: *Radiation Res.*, (in press)

SUMMARY: This study was conducted to determine what, if any, influence a single large X-ray exposure of kidney has on the development and course of an experimental autoallergic glomerulonephritis (EAG) in rats. EAG was induced in female Sprague Dawley rats by immunization with *B. pertussis* vaccine and homogenate of homologous kidney tissue and Freund's complete adjuvant. Progressive arteriolonephrosclerosis (ANS) was observed in right (irradiated) kidneys following unilateral renal irradiation (1500 rad). Rats were either immunized, sham-immunized, irradiated, sham-irradiated, or both immunized and irradiated. Light and immunofluorescent

microscopic observation, urine protein content and kidney weights were evaluated. In immunized-irradiated animals the effects of irradiation and immunization were largely additive. Immunization did not considerably influence the development and course of ANS and irradiation did not considerably influence the development and course of EAG.

3
13 TITLE: The effects of adrenalectomy, adrenal regeneration and renal irradiation on blood pressure (UR-3490-1373)

AUTHORS: M. Rosenblum and G. W. Casarett

PUBLICATION: *Radiation Res.*, (in press)

SUMMARY: Adrenalectomized, adrenal-enucleated, and adrenal-intact rats were sham-irradiated or received an X-ray dose of 1100 rad bilaterally to temporarily exteriorized kidneys. Systolic blood pressures were measured at 10, 25, 40, 60, and 80 days after irradiation. At 100 days after irradiation the rats were sacrificed for gross pathologic examination and renal histopathologic studies of the kidneys. Adrenalectomy alone caused a significant drop in blood pressure which persisted throughout the experiment; adrenal regeneration in adrenal enucleated rats or in those "adrenalectomized" rats in which adrenal tissue regenerated, caused a significant increase in systolic blood pressure after 80 days postirradiation. Irradiation of adrenal-intact, adrenal-regenerating or adrenalectomized rats did not cause significant elevation of blood pressure in comparison with that of the corresponding nonirradiated controls. Those rats showing subtle renal histological changes usually showed somewhat higher blood pressures than those rats showing no renal histological changes; a few rats which became severely hypertensive showed considerable histopathological changes in kidneys and other organs.

134 TITLE: Isolation of UV-sensitive and temperature sensitive conditionally lethal mutants and adaptation of the chromosome mediated gene transfer system in a haploid cell line derived from the frog *Rana pipiens* (UR/3490/LCP-11)

AUTHOR: B. S. Rosenstein (Supervised by B. M. Ohlsson-Wilhelm and C. W. Lawrence)

PUBLICATION: *Ph.D. Thesis, University of Rochester School of Medicine and Dentistry* (1978)

ABSTRACT OF THESIS: This study was carried out to examine the DNA repair pathways present in animal cells through the isolation of mutant cell lines sensitive to UV light. In addition, the chromosome-mediated gene transfer system was investigated as to its mechanism and possible relationship with a pathway involved in DNA repair. As an extension of the work carried out in the isolation of UV-sensitive cell lines, an enrichment scheme was developed for the isolation of temperature-sensitive conditionally lethal mutants.

The cell line chosen for these studies was derived from the frog *Rana pipiens* and was selected primarily because it is the only cultured cell line currently available that is haploid. It is likely that most mutants deficient in some aspect of DNA repair and sensitive to UV light would display a recessive phenotype. It was therefore expected that a greater variety of these mutants would be obtained at a much higher frequency in the haploid frog cell line as compared to the diploid cell lines in use.

It was discovered as part of this work that the fluorescent dye, Hoechst 33258, potentiated the killing of 5-bromodeoxyuridine (BUdR)-labelled cells by long wavelength UV light with only very low levels of the thymidine in the DNA substituted with this base analogue. This property was employed in the development of an enrichment scheme for the isolation of UV-sensitive clones based upon a deficiency in repair replication.

Through this work five clones were isolated that expressed greater sensitivity to UV light as compared to the parental cell line. One of these clones proved to be more sensitive when tested at 27.5° C than when tested at 20° C and thus displayed a temperature-sensitive phenotype. It was observed that three of these clones were deficient in their ability to carry out repair replication while the two other clones also exhibited a defect most likely associated with DNA synthesis. No alteration in postreplication repair or mutagenesis was observed in these UV-sensitive cell lines.

The chromosome-mediated gene transfer system was adapted to the ICR 2A cell line and transfer of the TT⁺, TK⁺, and oua^{res} phenotypes was carried out. The notation TT⁺ indicates the presence of a thymidine-specific transport system, TK⁺ denotes production of the deoxypyrimidine kinase, and oua^{res} indicates an ability to grow in medium containing 5 X 10⁻⁶ M ouabain. It appeared through these studies that the integration of the transferred piece of genetic material was not restricted to the homologous site of the particular gene in the recipient cell but may have occurred at several locations. In addition, the use of the UV-sensitive mutants and UV- or mitomycin C-treated cells as recipients in chromosome transfer experiments did not appear to alter the transfer frequency. This suggests that the enzyme systems altered in the UV-sensitive clones or involved in sister chromatid exchange production are not associated with the chromosome transfer or integration process.

In the final portion of this work the enrichment scheme used to isolate UV-sensitive mutants was modified for use in the isolation of a temperature-sensitive conditionally lethal mutant. The method that was developed was designed so that some of the difficulties encountered in previous work in the use of BUdR light-induced killing for the isolation of these mutants were overcome.

135 **TITLE:** Isolation of UV-sensitive clones from a haploid frog cell line (UR-3490-1560)

AUTHORS: B. Rosenstein and B. M. Ohlsson-Wilhelm

PUBLICATION: *Somatic Cell Genetics*, (in press)

SUMMARY: An isolation procedure has been developed which yielded five clones of haploid frog cells which are sensitive to ultraviolet light. This procedure employed a conventional mutagenesis, followed by time for phenotypic expression and then an enrichment for UV-sensitive mutants. The enrichment relies upon the uptake of bromodeoxyuridine (BrdU) by repairing cells following UV-induced damage, rendering repair-proficient cells differentially sensitive to photolysis by back light. The photolysis is potentiated by use of the bisbenzimidazole dye Hoechst 33258. The enriched population was screened for radiation-sensitive isolates resulting in 5 sensitives from 96 tested. No mutants were obtained from 300 isolates tested from a population which had not undergone enrichment.

6
13 TITLE: A rapid method for separating small vesicles from suspension (UR-3490-1509)

AUTHORS: R. N. Rosier, T. E. Gunter, D. A. Tucker and K. K. Gunter

PUBLICATION: *Anal. Biochem.*, (in press)

SUMMARY: Techniques for rapidly aggregating suspensions of small vesicles made either of natural biological membrane or of phospholipid or phospholipid-protein mixtures by addition of one of the basic polypeptides, polylysine or protamine, have been investigated. Either filtration or centrifugation may be used to rapidly (15 to 30 sec.) and completely (over 98%) separate the vesicular aggregate from the suspending medium.

At low values of the polylysine to vesicle weight ratio, aggregation is observed to increase with increasing polylysine concentration. At high values of this same ratio, aggregation decreases with increasing polylysine concentration. With protamine, like polylysine, aggregation increases with protamine concentration at low values of the weight ratio. At high values of the ratio, aggregation induced by protamine does not rapidly decrease with increasing protamine concentration as it does with polylysine. Explanations are given for these observations.

While leakage induced by polylysine may be troublesome under some conditions with phospholipid vesicles or reconstituted systems, protamine aggregation has been found to induce much less leakage than polylysine aggregation. The leakage rate induced by protamine was not found to be significantly different from the control leakage rate for the first few minutes after addition of protamine under any of the conditions tested. Since this provides ample time for filtration, the protamine aggregation-filtration technique seems to be the method of choice for separation of many types of small vesicles from the suspending medium.

^
7 TITLE: Role of the liver in regulating somatomedin activity: hormonal effects on the synthesis and release of insulin-like growth factor and its carrier protein by the isolated perfused rat liver (UR-3490-1305)

AUTHORS: D. A. Schlach, U. E. Heinrich, C. J. Johnson, B. Craznin and L. L. Miller

PUBLICATION: *Endocrinol.*, (in press)

SUMMARY: Recent evidence has indicated that the somatomedin (SM), nonsuppressible insulin-like activity (NSILA), circulates largely bound to its carrier protein (CP). There is evidence that NSILA is synthesized in and released by the rat liver and that these functions are hormone dependent. Employing the isolated rat liver perfusion technique, release of the CP of NSILA has been measured by a competitive protein-binding assay described herein. The net cumulative NSILA CP release from the livers of seven normal rats, relative to the donor body surface area, was found to be 5.0 ± 0.9 mg/300 cm² at the end of a 12-hour perfusion. The pattern of CP release is considerably different from that of NSILA, suggesting that each is regulated by separate control mechanisms. The addition of neither bovine GH, ovine prolactin nor insulin to the perfusions of normal livers altered the net CP release. However, puromycin significantly decreased but did not completely block CP release in the presence of bovine GH (3.1 ± 0.5 mg/300 cm² at 12 hours).

Hypophysectomy of donor rats caused a marked decrease in CP release from their isolated perfused livers. When partial hormone supplementation (bovine GH, T₃, cortisol or insulin) was

added to the perfusions of seven hypox rat livers, significantly less CP was released at 12 hours (1.8 ± 0.2 mg/300 cm²) than from normal livers. Full supplementation (all four hormones) of the liver perfusions of eight hypox rats without and three with prior hormone replacement therapy did not restore CP release (2.2 ± 0.2 mg/300 cm²) to normal. These data indicate that NSILA CP is released and probably also synthesized by the isolated perfused rat liver. Moreover, the hormonal regulation of these functions is similar but not identical to that previously shown for NSILA.

138

TITLE: Surgical considerations in hematologic patients (UR-3490-1219)

AUTHORS: S. I. Schwartz and M. A. Lichtman

PUBLICATION: Chapt. 20 in *Hematology for Practitioners*, Ed. by M. A. Lichtman. Little, Brown and Co., Boston, pp. 421-436 (1978)

SUMMARY: This chapter describes the special circumstances which may pertain when surgery is performed on patients with hematologic disorders. In addition, special attention is given to the role of splenectomy for the treatment of blood disorders.

139

TITLE: Primary-site and second-site revertants of missense mutants of the evolutionarily invariant tryptophan 64 in iso-1-cytochrome *c* from yeast (UR-3490-1438)

AUTHORS: M. E. Schweingruber, J. W. Stewart and F. Sherman

PUBLICATION: *J. Biol. Chem.*, (in press)

SUMMARY: The three missense mutants *cyc1-132*, *cyc1-166*, and *cyc1-189* in the yeast *Saccharomyces cerevisiae* contain nonfunctional and thermolabile iso-1-cytochromes *c* and have different replacements of the tryptophan at position 64 which corresponds to the invariant tryptophan residue found in cytochromes *c* from all eucaryotic species. The *cyc1-166* and *cyc1-189* mutants contain single replacements of, respectively, serine 64 and cysteine 64, while the *cyc1-132* mutant contains a double replacement of glycine 64 and alanine 65 instead of the normal tryptophan 64 and aspartic acid 65. Apparently the *cyc1-132* mutant arose by a double A·T → C·G transversion of two nearby sites. Intragenic revertants having at least partially functional iso-1-cytochromes *c* arose from these three missense mutants by single amino acid replacements of either tryptophan, phenylalanine, tyrosine or leucine at position 64 or by second-site replacements in which the mutant residues at position 64 are retained and the normal serine 45 is replaced by phenylalanine 45. Specific activities of iso-1-cytochromes *c*, measured by growth of the strains on lactate medium, ranged from approximately 100% of normal for phenylalanine 64 to iso-1-cytochrome *c* to 25% for tyrosine 64 iso-1-cytochrome *c* to between 0% and 25% for leucine 64 iso-1-cytochrome *c*. Similarly for the second-site revertant proteins, specific activity ranged from approximately 100% for phenylalanine 45, cysteine 64 iso-1-cytochrome *c* to 25% for phenylalanine 45, serine 64 iso-1-cytochrome *c* to between 0% and 25% for phenylalanine 45, glycine 64, alanine 65 iso-1-cytochrome *c*. Growth-limiting specific activities near 0 were estimated for the three missense proteins, serine 64, cysteine 64, and glycine 64, alanine 65 iso-1-cytochromes *c*. These results demonstrate that the small residues of glycine, serine and cysteine at position 64 are incompatible with function while the large hydrophobic residues of phenylalanine, leucine and tyrosine are capable of restoring at least partial function.

The second-site revertants indicate that deleterious effects of the three missense mutants can be compensated by the introduction of phenylalanine 45 which may occupy space normally filled by tryptophan 64. Apparently the principal role of the invariant tryptophan is stabilization of the active protein structure by providing a large hydrophobic group inside the protein below the inner propionic acid.

74 TITLE: Increased ouabain-sensitive glycolysis of lymphocytes treated with phytohemagglutinin: relationship to potassium transport (UR-3490-1349)

AUTHORS: G. B. Segel, E. J. Androphy and M. A. Lichtman

PUBLICATION: *J. Cell. Physiol.*, 97: 407-412 (1978)

SUMMARY: An early increase in lymphocyte plasma membrane K^+ transport is essential for PHA-stimulated lymphocytes to divide. Little is known about the specific source and amount of energy required to support the increased transport by activated lymphocytes. Since ouabain, a cardiac glycoside, specifically inhibits the transport ATPase, we have measured the decrement in glycolysis and tricarboxylic acid cycle activity when untreated and PHA-treated lymphocytes were exposed to ouabain. This metabolic decrement represents the portion of metabolism associated with monovalent cation transport and closely related processes. Since TCA cycle activity accounted for only 0.2% of glucose consumption, aerobic glycolysis was the major source of energy, i.e., ATP, for increased transport. Approximately one-third of the total lactate production in both control and PHA-stimulated lymphocytes was ouabain sensitive. Ouabain-sensitive lactate production in control, $105 \mu\text{mol}/10^{10}$ cells/hour, increased 1.8-fold to $193 \mu\text{mol}/10^{10}$ cells/hour after PHA treatment. Active K^+ influx in similar cell populations increased from $40 \mu\text{mol}/10^{10}$ cells/hour to $74 \mu\text{mol}/10^{10}$ cells/hour (1.9-fold) after PHA treatment. The increment in ouabain-sensitive energy production and K^+ transport were closely correlated and, therefore, 0.38 moles of K^+ are transported for each mole of ATP generated in both control and PHA-treated cells. The increased requirement for transport-related energy is provided by increasing the ouabain-sensitive ATP production rather than altering the efficiency of ATP transduction.

141 TITLE: A model for the control of potassium transport in PHA-stimulated human blood lymphocytes (UR-3490-1484)

AUTHORS: G. B. Segel, W. Simon and M. A. Lichtman

PUBLICATION: *Proc. 12th Intern. Leukocyte Culture Conf.*, June 1978. Beer-sheba, Israel, (in press)

SUMMARY: This paper examines the relationship of potassium transport in human lymphocytes to the internal cation concentration. These findings are used to explain the alterations in monovalent cation transport that occur in lectin-stimulated human lymphocytes.

142
TITLE: Ionophorous properties of the 20,000-dalton fragment of $(Ca^{2+} + Mg^{2+})$ -ATPase in phosphatidylcholine: cholesterol membranes (UR-3490-1356)

AUTHOR: A. E. Shamoo

PUBLICATION: *J. Memb. Biol.*, 43: 227-242 (1978)

SUMMARY: The purified 20,000-dalton fragment of sarcoplasmic reticulum $(Ca^{2+} + Mg^{2+})$ -ATPase has been shown by us (A. E. Shamoo, T. E. Ryan, P. S. Stewart, D. H. MacLennan, 1976. *J. Biol. Chem.* 251:4147) to have Ca^{2+} -selective ionophoric activity. The Ca^{2+} -ionophoric fragment has been purified by either SDS-column chromatography or SDS-preparative gel electrophoresis. The Ca^{2+} -ionophoric fragment has been subjected to prolonged dialysis to insure the removal of bound SDS from the fragment. The selectivity sequence of this fragment in black lipid membranes (BLM) formed from either oxidized cholesterol or phosphatidylcholine/cholesterol is the same, $P_{Ba} > P_{Ca} > P_{Sr} > P_{Mg} > P_{Mn}$. This selectivity sequence is the same as that for the intact $(Ca^{2+} + Mg^{2+})$ -ATPase. Treatment of the fragment with cholate to absolutely insure the removal of bound SDS resulted in the fragment having a selectivity sequence as above except that $P_{Mn} > P_{Mg}$. This and other data indicate that the 20,000-dalton fragment is the site containing the Ca^{2+} -ionophoric activity of the $(Ca^{2+} + Mg^{2+})$ -ATPase.

143
TITLE: Reconstitution of the 20,000 dalton fragment of $Ca^{2+} + Mg^{2+}$ -ATPase in phosphatidylcholine vesicles (UR-3490-1474)

AUTHOR: A. E. Shamoo

PUBLICATION: *In Proc. Workshop on Physical-Chemical Aspects of Cell Surface Events in Cellular Regulation*, Ed. by C. DeLisi. Elsevier/North Holland Publishing Co., New York, (in press)

SUMMARY: We present evidence that the 20,000 dalton fragment of $(Ca^{2+} + Mg^{2+})$ -ATPase possesses Ca^{2+} -ionophorous properties in phosphatidylcholine vesicles as has been shown in black lipid membranes. Furthermore, we show that a 12,883 dalton CNBr fragment of the 20,000 dalton fragment possesses the Ca^{2+} -ionophorous characteristic.

144
TITLE: Ionophores and ion transport across natural membranes (UR-3490-1414)

AUTHORS: A. E. Shamoo and T. J. Murphy

PUBLICATION: *In Current Topics in Bioenergetics*, Ed. by D. R. Sanadi. Academic Press, New York, (in press)

SUMMARY: In order to achieve our goal in the description of the mechanism of ion transport, unfortunately we must disassemble the machinery for such transport. Once we have disassembled the machinery we are faced with the problem of ensuring that the disassembled pieces have the "real" assigned function. This can partially be achieved by using common characteristics between the pieces and the parent protein such as: common specificity and selectivity, common inhibitors, etc. We should be vigilant in using multiple methods and criteria to make the connection between the isolated pieces and the parent protein. Furthermore, we should continue to develop better and more efficient reconstituted systems in order to avoid large volumes of data where protein-induced BLM conductance

increase have nothing or little to do with the transport systems *in situ* and to avoid the misinterpretation of data as happened when it was erroneously concluded that Cl^- was actively transported by $\text{Na}^+ + \text{K}^+$ -ATPase. In the case of $\text{Ca}^{2+} + \text{Mg}^{2+}$ -ATPase, sufficient data so far are available to correlate well the properties of the reconstituted system with the *in situ* function and therefore it could serve as a model for future elucidation of transport mechanism.

The identification of ion transport site (ionophore) and the ATP hydrolytic enzyme provide the best lead yet to the study of energy transduction mechanism. It could provide the means by which one can study the spatial relationship between the ATP hydrolytic site and the ion transport site and correlate this with the functional state of the enzyme. It would be very useful if a system is developed where one can control the state of phosphorylation and dephosphorylation of the enzyme to study the relationship between the ionophoric site and ATP hydrolytic under such controlled states.

745 TITLE: Low molecular weight Ca^{2+} -carrier from inner mitochondrial membrane (UR-3490-1419)
AUTHORS: A. E. Shamoo, A. Y. Jeng and W. F. Tivol

PUBLICATION: In *Frontiers of Biological Membranes: Electrons to Tissues*, Ed. by A. Scarpa, F. Dutton and J. Leigh. Academic Press, New York, (in press)

SUMMARY: We have isolated a 3000 dalton molecular weight protein from calf heart inner mitochondrial membrane. The selectivity sequence of this protein determined by the organic solvent extraction experiment is Ca^{2+} , $\text{Sr}^{2+} > \text{Mn}^{2+} > \text{Mg}^{2+}$. Ruthenium red and lanthanum inhibit the protein-mediated extraction of Ca^{2+} into the organic solvent. We have named this protein "calciphorin" as an abbreviation for calcium ionophore protein. Further analysis of this protein has indicated that its N-terminal is blocked and the C-terminal is histidine.

746 TITLE: The genetic control of yeast iso-1- and iso-2-cytochrome *c* after 15 years (UR-3490-1345)
AUTHORS: F. Sherman and J. W. Stewart

PUBLICATION: In *Biochemistry and Genetics of Yeast. Pure and Applied Aspects*, Ed. by M. Bacila, B. L. Horecker and A. O. M. Stoppani. Academic Press, New York, pp. 273-316 (1978)

SUMMARY: The yeast *Saccharomyces cerevisiae* contains two distinct cytochromes *c*, iso-1-cytochrome *c* and iso-2-cytochrome *c* that differ in primary structure and that normally constitute, respectively, approximately 95% and 5% of the total complement of cytochrome *c* in aerobically-grown derepressed cells. Genetic analysis of strains containing mutationally-altered cytochromes *c* has established that the primary structure of iso-1-cytochrome *c* is determined by the *CYC1* gene which is situated on the right arm of chromosome X and that the primary structure of iso-2-cytochrome *c* is determined by the *CYC7* gene which is situated on the left arm of chromosome V. Mutations of the *cyc2* and *cyc3* loci can cause specific deficiencies of iso-1-cytochrome *c* and iso-2-cytochrome *c*; the *cyc2* and *cyc3* genes are unlinked to each other and to the structural genes *CYC1* and *CYC7* and their function and gene products are unknown. Mutation of other loci produce minor deficiencies that are not believed to be specifically related to cytochrome *c* synthesis.

Point-mutations and chromosomal aberrations adjacent to the *CYC7* structural gene can result in 20- to 30-fold increases of iso-2-cytochrome *c* probably by altering the controlling regions contiguous to the structural region of the gene. Overproduction of iso-2-cytochrome *c* can also result from mutations of numerous other loci whose functions are unknown. Since these mutants are sometimes associated with other diverse abnormalities, they do not appear to be simple regulatory mutants of iso-2-cytochrome *c*.

Extensive genetic and biochemical investigations of over 200 *cyc1* mutants resulted in the identification of numerous mutational lesions and nucleotide changes. Deficiencies of iso-1-cytochrome *c* result from UAA and UAG nonsense mutations, frameshift mutations, mutation of the AUG initiator codon, mutation in the leader sequence and from deletions that can extend into neighbor genes. Non-functional iso-1-cytochromes *c*, which occur at below normal levels, result from a variety of missense mutations and in rare instances from deletions. Functional or at least partially functional iso-1-cytochromes *c* from revertant strains can have numerous and diverse alterations including single amino acid replacements at evolutionarily variant and invariant sites, compensatory double amino acid replacements at two distant sites, stretches of contiguous replacements, tandem duplications and deletions in unessential regions, and shorter and longer forms due to abnormal initiation.

147
TITLE: Use of the iso-1-cytochrome *c* system for investigating nonsense mutants and suppressors in yeast (UR-3490-1417)

AUTHORS: F. Sherman, B. Ono and J. W. Stewart

PUBLICATION: In Nonsense Mutations and tRNA Suppressors, Ed. by J. E. Celis and J. D. Smith. Academic Press, London, (in press)

SUMMARY: *Cyc1* mutants containing defined UAA and UAG mutations in the gene determining iso-1-cytochrome *c* have been used to investigate nonsense suppressors whose activities are attributed to altered tRNAs in the yeast *Saccharomyces cerevisiae*. Suppressors acting on two or more nutritional markers have been the subject of numerous investigations and many of these suppressors have been characterized in respect to which nonsense codon is suppressed, which amino acid is inserted and the amounts of iso-1-cytochrome *c* in the suppressed *cyc1* mutants. The range of recoverable suppressors was expanded by using diploid as well as haploid strains, by using genetic factors that modified the expression of the suppressors and by using discriminating nutritional markers in the selection procedures. Genetic analysis was used to assign the suppressors to their respective loci. The following conclusions were reached in comprehensive studies designed to reveal the maximum number of loci that can yield suppressors with identical or similar patterns of suppression: there are eight loci that yield highly efficient UAA suppressors and all eight insert tyrosine; these same eight loci yield the only highly efficient UAG suppressors, which also insert tyrosine; there are two loci that yield moderately efficient UAA suppressors and both of these insert serine; there are five or probably six loci that yield low efficient UAA suppressors which all insert leucine. Examination of single representatives from two other groups of suppressors indicated that *SUP52*, a low efficiency UAG suppressor, inserts leucine, and that *SUP-RL1*, a recessive-lethal UAG suppressor, inserts serine. These UAA and UAG suppressors presumably arose by single base-pair changes. It appears as if the suppressors with a group originated from redundant

but unlinked genes that determine the same tRNA species and that are expressed at approximately the same level. The yeast UAG suppressors appear similar to the bacterial UAG suppressors; in one case a yeast and a bacterial UAG suppressor both were shown to have the same expected change at the anticodon. In contrast, yeast UAA suppressors differ from the bacterial ochre suppressors, which suppress both UAA and UAG codons. While it is unclear why yeast do not give rise to tRNA suppressors that act on both UAA and UAG codons, it is suggested that the restriction in the codon specificity of yeast UAA suppressors is due to modification of bases in the anticodon.

148
TITLE: Deletions of the iso-1-cytochrome *c* and adjacent genes of yeast: discovery of the *OSM1* gene controlling osmotic sensitivity (UR-3490-1262)

AUTHORS: A. Singh and F. Sherman

PUBLICATION: *Genetics*, 89: 653-665 (1978)

SUMMARY: Some of the deletions in the yeast *Saccharomyces cerevisiae* that encompass the *CYC1* gene, which determines iso-1-cytochrome *c*, extend into the *OSM1* gene, causing inhibition of growth on hypertonic media, and into the *RAD7* gene, causing sensitivity to UV light. Two deletions (*cyc1-363* and *cyc1-367*) encompass only the *CYC1* gene, two deletions (*cyc1-366* and *cyc1-368*) encompass the *CYC1* and *OSM1* genes, three deletions (*cyc1-1*, *cyc1-364* and *cyc1-365*) encompass the *CYC1*, *OSM1* and *RAD7* genes, while none of the deletions extend into the closely linked *SUP4* gene.

149
TITLE: Mutation of the non-Mendelian suppressor, ψ^+ , in yeast by hypertonic media (UR-3490-1432)

AUTHORS: A. Singh, C. Helms and F. Sherman

PUBLICATION: *Proc. Natl. Acad. Sci. USA*, (in press)

SUMMARY: The ψ^+ extrachromosomal determinant in the yeast *Saccharomyces cerevisiae* suppresses certain UAA markers and increases the efficiency of suppression of UAA suppressors and certain frameshift suppressors. While the exact nature of ψ^+ determinant is unknown, it is believed to be a self-replicating cytoplasmic factor affecting some component of the translational machinery. In this report we describe growth conditions for efficient mutation or elimination of the ψ^+ determinant. Incubation of ψ^+ cultures in hypertonic nutrient medium resulted in rapid conversion to a culture containing predominantly ψ^- cells during the growth cycle. The kinetics of ψ^+ to ψ^- conversion established that the occurrence of ψ^- cells was due to induction and not to selection of pre-existing ψ^- cells. The results suggest that the replication of the ψ^+ determinant is sensitive to hypertonic conditions.

152

TITLE: Parallel decrease of erythrocyte membrane deformability and spectrin solubility at low pH (UR-3490-1346)

AUTHORS: B. D. Smith and P. L. La Celle

PUBLICATION: *Blood*, (in press)

SUMMARY: Reduction of pH over the range 6.0 to 4.5 results in a decrease of erythrocyte deformability in parallel with the induced progressive sphericity of cells. At low deformation rates employed, increase of hemoglobin viscosity was not significant. A decrease of membrane elasticity was detected in cells when spherizing, the major determinant of cellular deformability, was prevented at pH 5.0 by hyperosmotic medium. The pronounced change of deformability and the reduced elasticity occurred at calculated intracellular pH values at which solubility *in vitro* of extracted erythrocyte spectrin is also markedly reduced. The parallel decrease of deformability and spectrin solubility supports the hypothesis that spectrin aggregation may contribute to regulation of erythrocyte deformability through effects on shape and membrane elastic characteristics.

151

TITLE: Fluoride as an ecopoison (UR-3490-1231)

AUTHOR: F. A. Smith

PUBLICATION: *Proc. NATO Workshop on Ecopoisons, August 1977, University of Surrey, Guildford, Surrey, England, Ed. by D. V. Parke, (in press)*

SUMMARY: The hazards associated with airborne contaminants in the workplace are defined in large part by the numbers of people at risk, and the amounts of materials being handled. At present, NIOSH recognizes about 130 job categories in which the worker may be exposed to inorganic fluorides including hydrogen fluoride (HF); these jobs are filled by approximately 372,000 workers. Moreover, HF production, as a measure of use, more than doubled (to 375,000 tons yearly) in the interval 1967-1974. Thus, direct hazards to man associated with airborne fluorides is indeed significant and investigations into the effects of airborne fluorides have ample justification for both practical and theoretical reasons. This paper describes the results obtained to date of studies of the effect of airborne particulate fluoride (fluorspar, calcium fluoride, CaF_2) and of HF in guinea pigs.

152

TITLE: The Sked Software System. Manual 3, Revision D (UR-3490-1476)

AUTHORS: A. G. Snapper and G. B. Inglis

PUBLICATION: *University of Rochester, Rochester, N. Y., (1978)*

SUMMARY: This manual describes a software system developed for data collection and control of behavioral experiments. The SUPERSKED system consists of a two-pass compiler, a run-time system, and a monitor program that can be used to control 12 independent procedures.

A full description of the SKED state notation language, plus a configuration guide for tailoring the software to individual laboratory needs are given in the manual.

157
TITLE: Drug interactions with DNA (UR-3490-1572)

AUTHOR: H. M. Sobell

PUBLICATION: *In Effects of Drugs on the Cell Nucleus. (Proc. Bristol-Myers Symp., November 1978, Houston, Texas) Academic Press, New York, (in press)*

SUMMARY: During the past few years, important advances have taken place in understanding the molecular basis of drug-DNA interactions. For the most part, these advances reflect the technique of X-ray crystallography to determine the three-dimensional structures of a large number of drug-nucleic acid crystalline complexes and additional supporting data concerning the binding of these drugs and dyes to DNA. This chapter reviews our current understanding of drug-DNA interactions and, in addition, describes concepts of the dynamic nature of DNA structure that gives rise to drug intercalation. The subject of drug intercalation into DNA may be related more broadly to understanding a large number of protein-DNA interactions, many of these occurring in the organization of DNA in chromatin within the cellular nucleus.

154
TITLE: Structural and energetic considerations of wave propagation in DNA (UR-3490-1472)

AUTHORS: H. M. Sobell, E. D. Lozansky and M. Lessen

PUBLICATION: *Proc. 43rd Cold Spring Harbor Symp. on DNA Replication and Genetic Recombination, June 1978, Cold Spring Harbor, N. Y., (in press)*

SUMMARY: An important dynamic aspect of DNA in solution is the presence of coupled motions in its structure that involve bending, stretching, unwinding, and shearing components. We have postulated these motions to arise from wave propagation in the polymer, excited through impulses generated by the random and continuous bombardment of DNA by solvent molecules along its length. This gives rise to travelling structural distortions in DNA that result in DNA breathing and in drug intercalation. These distortions can be thought of as premelting conformational changes in DNA and, in this respect, could have important implications in understanding the structure of DNA active in RNA transcription, DNA replication and genetic recombination.

In this paper, we further document the nature of these distortions and discuss their relationship to DNA breathing and to drug intercalation. A key intermediate in these processes is the multiply-kinked structure, β -kinked DNA. This structure has both B and A characteristics, and we postulate this structure to be a conformational intermediate in the B $\rightarrow$ A polymorphic transition. In addition, we discuss a class of intercalators known as the *bis* functional intercalators, molecules that have *two* intercalative chromophores separated by about 10.2 Å. These bifunctional intercalators appear to bind DNA in a neighbor exclusion mode and could, therefore, be probes to detect the migratory β -kinked DNA structure we have postulated.

We have already described the implications our theory has in understanding how energy is distributed along DNA to form localized premelted regions of DNA. These regions form as the result of phonon energy that originates in the structural genome DNA and could correspond to promoters. Here, we discuss this further and examine, in addition, the nature of the excitation force due to Brownian motion of solvent molecules that gives rise to wave motion in DNA. This force is temperature dependent and one would therefore expect the average energy density along

the DNA molecule to reflect this. As one raises the temperature of DNA in solution, additional localized regions of DNA premelting could arise. Events such as these could have important implications in understanding the mechanism of DNA melting.

155
TITLE: Crystallographic studies of drug-nucleic acid crystalline complexes and their biological implications (UR-3490-1374)

AUTHORS: H. M. Sobell, S. C. Jain, T. D. Sakore, B. S. Reddy, K. K. Bhandary and T. P. Seshadri

PUBLICATION: *Intern. Symp. on Biomolecular Structure, Conformation, Function and Evolution, January 1978, Madras, India, (in press)*

SUMMARY: It is now over a decade since Lerman proposed his intercalation hypothesis to explain the strong binding mode of the aminoacridines to DNA. A large body of evidence now supports this concept and it has become increasingly apparent that (in addition to the aminoacridines) a large number of additional drugs and dyes bind to DNA by intercalation. The technique of molecular cocrystallization as developed in our laboratory has provided an opportunity to obtain detailed stereochemical information about interactions between many of these drugs and nucleic acid components and this has led to unifying structural concepts in understanding a large number of drug-DNA interactions. This paper summarizes the results of our crystallographic studies of drug-nucleic acid crystalline complexes done in recent years. It also discusses their broader biological implications in further detail.

156
TITLE: Diffusion measurements of aerosols

AUTHOR: S. C. Soderholm (Supervised by T. T. Mercer)

PUBLICATION: *Ph.D. Thesis, Department of Physics and Astronomy, University of Rochester College of Arts and Science (1978)*

ABSTRACT OF THESIS: Diffusion measurements are often the appropriate "sizing" techniques for ultrafine particles (diameter smaller than about 0.1 micrometers). A review is given of the theoretical results and data analysis techniques which have been used in diffusion measurements of aerosols. Most measurements have consisted of determining the aerosol concentration downstream of each of several diffusion cells in a diffusion battery. New and accurate theoretical expressions for the penetration of circular tube and parallel plate diffusion cells are extracted from the literature.

Of the previously proposed data analysis techniques, the two resulting in an effective diffusion coefficient and a best-fit lognormal distribution are considered the most useful. A new computer-oriented least squares histogram data analysis technique which results in a "complete solution" can be applied to diffusion battery data consisting of at least five penetration values. An example is given.

The theory of a parallel rectangular plate diffusion collector is presented. This device is unusual in that the particles deposited in the diffusion cell are analyzed rather than those which passed through it. Many of the techniques for analyzing diffusion collector data are similar to the techniques for analyzing diffusion battery data. However, if the diffusion collector deposit is

analyzed by electron microscopy, the distribution of absolute number concentration versus diffusion coefficient can be obtained for the full aerosol or for any distinguishable class of particles in the aerosol.

The construction of a silver aerosol generator, the design of a diffusion collector, the assembling of an aerosol monitoring system, and the collection of data are detailed. Two samples analyzed in detail verify the theory of operation of the diffusion collector and reveal unexpected properties of the silver aerosol which could not have been positively demonstrated by previous diffusion measurement techniques.

5 TITLE: Tissue distribution of inhaled mercury vapor in acatalasemic mice (UR-3490-1196)

AUTHORS: Y. Sugata, S. Halbach, J. Allen and T. W. Clarkson

PUBLICATION: J. Environ. Sci & Health, Part C, (in press)

SUMMARY: Substantial differences were observed in the pattern of tissue deposition in normal versus acatalasemic mice after inhalation of radioactive mercury vapor. Liver deposition was approximately double and lung deposition approximately one-half the corresponding deposition in normal animals. These results lend further support to the idea that the hydrogen-peroxide catalase peroxidative pathway plays a role in the metabolism of inhaled mercury vapor.

5 TITLE: Effects of fluoroacetate on the testis of the rat (UR-3490-1119)

AUTHORS: J. L. Sullivan, F. A. Smith and R. H. Garman

PUBLICATION: J. Reproduc. Fertility, (in press)

SUMMARY: Biochemical and histological responses were investigated in testes, kidneys and livers of rats receiving NaFAc in the drinking water. Animals receiving 20, 6, or 2 ppm NaFAc in the drinking water were sacrificed daily through 7 days of treatment and at more widely spaced intervals in the succeeding 21 days. Little change was seen in kidney and liver weights, ATP and citrate concentrations, and morphology, suggesting that the FAc concentrations used were not sufficient to cause renal and hepatic changes. Testis weights and ATP concentrations in rats receiving 20 or 6 ppm were decreased, citrate concentrations were elevated in all three groups and morphological damage was seen in testes from all groups. Initial cellular changes common to all three dosage levels included altered appearance of the spermatids, decreased numbers of spermatids, and giant cell formation of spermatids and spermatocytes. At the two higher concentrations, damage progressed to marked seminiferous tubular atrophy but this stage did not develop at 2 ppm. Regeneration of the seminiferous tubules in the 2 ppm group was complete by 7 days post-treatment. At the higher concentrations, regeneration was not complete by post-treatment day 21. Spermatogenesis was abnormal in some instances during the regeneration period in these groups. The findings are consistent with impaired energy production via blockage of the Krebs cycle, and subsequent impairment of carbohydrate metabolism through the Embden-Meyerhof pathway.

TITLE: The role of the metabolism of parathyroid hormone (UR-3490-1469)

AUTHOR: A. P. Teitelbaum (Supervised by W. F. Neuman)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The heterogeneity of parathyroid hormone (PTH) in plasma has prompted investigations of the metabolism of PTH and its relationship to hormone action. The time course of tissue distribution and metabolism of electrolytically iodinated PTH (E-PTH) previously shown to retain biological activity was compared with that of inactive PTH iodinated with Chloramine-T (CT-PTH), the assumption being that observed differences would reflect biological specificities of metabolism. Labeled PTH (0.4 μ g) was injected in the saphenous veins of anesthetized rats which were sacrificed at 1, 3, 5, 10, and 20 minutes. Tissue extracts from kidney, liver, and serum were chromatographed on Bio-Gel P-10 in 3 M guanidine to separate intact PTH from its metabolites.

In the kidney, the initial rate of degradation of E-PTH was greater than that of CT-PTH, as indicated by the appearance of metabolites as well as the relative accumulations of intact hormone. This difference in degradation was maximal at 5 minutes when the amount of unmetabolized hormone expressed as a percentage of total radioactivity was 40% for E-PTH and 68% for CT-PTH. The amounts of intact PTH and its metabolites delivered to the kidney by the serum were similar for both preparations of hormone indicating that the time course of degradation is a reflection of the rate of PTH metabolism within the kidney itself. The filtration fraction of PTH is only 35% of the total kidney uptake, so that the difference in initial rates of metabolism may be due, in part, to receptor-specific hydrolysis on peritubular cell membranes, where PTH-responsive adenyl cyclase is located, which selectively act on biologically active PTH molecules.

Modification of PTH deposition and metabolism was attempted by varying the calcium levels in the serum by acute injections of calcium or EDTA. from 5-7 mg.%, clearance of PTH was retarded by about 20% indicating possible local regulation of PTH degradation. However, in a range of 9-15 mg.%, no change in deposition or metabolism of E-PTH was detected. Attempts at modification of the pharmacokinetic disposition of PTH either by parathyroidectomy or secondary hyperparathyroidism (induced by a low calcium diet) were unsuccessful. It is concluded that regulation of PTH metabolism by change in receptor number or affinity resulting from an alteration in hormonal status is unlikely.

PTH-responsive adenyl cyclase activity in isolated kidney cortex plasma membranes was measured and PTH metabolism was monitored simultaneously at 37° C for 15 minutes. When degradation was completely blocked by histone f₃ (1 mg/ml), adenyl cyclase activity was significantly increased over control suggesting that the effective PTH concentration was raised and that PTH metabolism is probably not an activation mechanism. In addition, when adenyl cyclase activity was negligible, as when ATP was excluded from the incubation, the rate of PTH degradation by the membranes was not significantly diminished. Consistent with the *in vivo* data was the observation that E-PTH is metabolized by these membranes at a greater rate than CT-PTH. Free-flow electrophoresis of kidney cortex plasma membranes separated basal lateral from brush border membranes for comparison of the metabolism of active and inactive hormone on the peritubular

and luminal sides of the tubule. Apparent specificity of PTH metabolism was not limited to basal lateral membranes but was exhibited by brush border membranes as well, although to a lesser extent.

The data demonstrate the existence of a receptor-specific metabolism at sites which are independent of PTH receptor mediated adenyl cyclase activity.

¹⁶⁰
TITLE: Isolation, separation, and characterization of epithelial and connective cells from rat palate (UR-3490-1524)

AUTHOR: V. P. Terranova (Supervised by J. S. Brand)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: The purpose of this research was to isolate, separate, and characterize cells from rat palate in order to establish a model for the study of periodontal disease at the cellular level. Epithelial and connective tissue cells were isolated from rat palate by sequential collagenase, hyaluronidase and trypsin digestion of the extracellular matrix. Differences between the two populations were noted with respect to total cell protein, total cell water, proline uptake and incorporation, percent collagen synthesized, effects of parathyroid hormone, metabolism of D-valine and cell density.

Basal epithelial cells were subsequently separated from the heterogeneous epithelial cell population on shallow linear density gradients by velocity centrifugation.

The type of collagen synthesized by the basal epithelial cells was compared to the type of collagen synthesized by the connective tissue cells by means of labeled amino acid incorporation ratios.

In comparing cells isolated from the epithelial and connective tissue it was found that the epithelial cells: 1) have $235 \pm 15 \mu\text{g}$ protein per 10^6 cells; 2) have $0.53 \pm 0.1 \mu\text{l}$ cell water per 10^6 cells; 3) incorporate 860 pM proline into protein during a 4-hour incubation; 4) contain a D-amino acid oxidase; 5) have a density of 1.086 g/cc; and 6) the basal layer of epithelial cells synthesize basement membrane or Type IV collagen. With the connective tissue cells it was found that they: 1) have $170 \pm 10 \mu\text{g}$ protein per 10^6 cells; 2) have $0.23 \pm 0.04 \mu\text{l}$ cell water per 10^6 cells; 3) incorporate 820 pM proline into protein during a 4-hour incubation; 4) contain a subpopulation of cells; periosteal cells, which respond to PTH; 5) have a density of 1.076 g/cc; and 6) synthesize Type I collagen.

From these studies it can be concluded that epithelial and connective tissue cells can be isolated from rat palate as viable and distinct populations with respect to the biochemical parameters examined. Furthermore, subpopulations can be separated and biochemically characterized.

161
TITLE: Biochemical studies of mouse brain tubulin: colchicine binding (DEAE-cellulose filter) assay and subunits (α and β) biosynthesis and degradation (in newborn brain) (UR-3490-1559)

AUTHORS: C-F. Tse (Supervised by R. A. Doherty)

PUBLICATION: Ph.D. Thesis, University of Rochester School of Medicine and Dentistry (1978)

ABSTRACT OF THESIS: In part I of this thesis a DEAE-cellulose filter assay, measuring [^3H]colchicine bound to colchicine binding protein (CBP) absorbed on filter discs, has been modified to include 1 M sucrose in the incubation medium for complexing colchicine to CBP in samples before applying the samples to filter discs (single point assay). Due to the much greater stability of colchicine binding capacity in the presence of 1 M sucrose, multiple time-point assays (time decay method) and least squares linear regression analysis, for obtaining initial binding capacity (zero-time of incubation), were not necessary for accurate determination of CBP in brain samples as shown by the agreement of results obtained using the two methods to measure CBP in C129F₁ hybrid mouse brain at different stages of development. In this study, the highest concentrations of CBP (mmoles colchicine bound per milligram total protein) were observed in the 160,000 g supernatant and pellet of newborn brain homogenate. The colchicine binding protein concentrations in these two fractions were approximately twice those observed in the earliest stage measured (13.5 days gestation) and in the 11-month-old adult.

Further studies of the modified filter assay documented that, after correction for a measured solid phase quenching of 14% introduced by filters in scintillation fluid, the filter assay has an overall counting efficiency of 27.3%, that DEAE-cellulose filters bind and retain all tubulin in the assay samples determined by comparing the total colchicine binding measured by filter assay with the total tubulin-bound colchicine eluted from DEAE-Sephadex A50 microcolumn in the presence of 1 M sucrose, from the same samples, and that, with 1 M sucrose in the incubation buffer and with molar ratios of colchicine to tubulin greater than 4, one molecule of colchicine binds, on the average, approximately one molecule of tubulin dimer, determined by Scatchard analysis. Therefore, millimoles of colchicine bound per milligram total protein in mouse brain 160,000 g supernatant, determined by the single point filter assay, can be used to calculate tubulin content (mg tubulin per mg total protein). With this technique tubulin content of brain supernatant was found to be 11.9% (S.E., 0.5) for newborn, and 7.15% (S.E., 0.28) for 11-month-old mice. These results were independently corroborated by quantitative densitometry of SDS-urea polyacrylamide electrophoresis gels, which yielded estimates for tubulin of 10.00% (S.E., 0.96) and 4.61% (S.E., 0.71) for newborn and 8-month-old brain supernatants. Quantitative densitometry was also used to measure mouse brain supernatant actin content, yielding estimates of 6.56% (S.E., 0.10) and 4.85% (S.E., 0.10) for these two stages, in agreement with published results. The modified filter assay provides a simple and reliable procedure for determining concentrations of soluble tubulin in biological samples and should have general utility in the study of tubulin biology.

In part II of this thesis *in vivo* synthesis and degradation rates of tubulin α and β subunits (and other polypeptides) of two-day mouse brain 100,000 g supernatant have been studied after intracerebral injection of [^3H]leucine. Quantitative changes of the ratio of tritium specific activities of tubulin α and β subunits ($\alpha_{\text{s.a.}}/\beta_{\text{s.a.}}$) with time have been determined, after partial

isolation of tubulin by DEAE-Sephadex A50 microcolumn chromatography and separation of the two subunits by SDS-urea polyacrylamide gel electrophoresis, by counting the radioactivity in gel slices containing the protein of interest coupled with quantitation of total protein by densitometric analysis. The pattern of change of $\alpha_{s.a.}/\beta_{s.a.}$ was biphasic. During the first phase the ratio decreased from 0.93 at 15 minutes to 0.76 at one hour; during the second phase the ratio increased continuously, reaching 0.94 by 24 hours after injection. An interpretation consistent with all the data in this study is that the α subunit is synthesized at a more rapid rate (~ 1.5 -fold) than the β subunit. The decrease of $\alpha_{s.a.}/\beta_{s.a.}$ during the first phase may indicate the existence of a mechanism for immediate degradation of newly synthesized free α subunits (and perhaps, to a lesser extent, also free β subunits). The increase of $\alpha_{s.a.}/\beta_{s.a.}$ during the second phase was the result of dilution of radioactive tubulin subunits synthesized during the first phase ($\alpha_{s.a.}/\beta_{s.a.} \sim 0.76$), which were also continuously being degraded, with radioactive tubulin subunits newly synthesized from remaining tritium-labeled amino acids at the injection site during the second phase ($\alpha_{s.a.}/\beta_{s.a.} \sim 1.5$).

Actin, α tubulin-like polypeptide and Polypeptide 12K (molecular weight, $\sim 12,000$) were determined to have *in vivo* synthesis rates 123%, 139%, and 20% that of β tubulin subunit, measured between 15 minutes and one hour after [^3H]leucine injection. These five polypeptides were observed to have apparent degradation half-times in the range of 5 to 8 hours, measured between 1 and 5 hours after [^3H]leucine injection.

✓
16 TITLE: An improved DEAE-cellulose filter assay for quantitation of colchicine-binding protein (during mouse brain development) (UR-3490-1303)

AUTHORS: C-F. Tse and R. A. Doherty

PUBLICATION: J. Neurochem., (in press)

SUMMARY: A DEAE-cellulose filter assay for colchicine binding protein (CBP) has been modified to include 1 M sucrose in the incubation medium (single-point assay). Due to the much greater stability of colchicine binding capacity under the conditions described, multiple time-point assays (time decay method) were not necessary for accurate determination of CBP in brain samples, as shown by the agreement of results obtained using the two methods to measure CBP in C129F₁ hybrid mouse brains at different stages of development. In this study, the highest concentrations of CBP (mmoles of colchicine bound per milligram of total protein) were observed in the 160,000 g supernatant and pellet of newborn brain homogenate. The CBP concentrations in these two fractions were approximately twice those observed in the earliest stage measured (13.5 days gestation) and in the 11-month-old adult. However, CBP concentration in terms of mmoles of colchicine bound per gram of brain wet weight reached a maximum during the first week after birth. Between 17.5 days gestation and the end of the first postnatal week, more CBP accumulated in the pellet fraction than in the supernatant.

163
TITLE: A simple procedure for obtaining large quantities of tubulin subunits from newborn mouse brain (UR-3490-1293)

AUTHORS: C-F. Tse and R. A. Doherty

PUBLICATION: *Biochim. Biophys. Acta*, 535: 85-89 (1978)

SUMMARY: A simple, efficient two-step procedure of DEAE-Sephadex A-50 column chromatography followed by hydroxyapatite column chromatography for purification of α - and β -tubulin subunits from newborn mouse brain is described. Stored frozen mouse brains can be used as a convenient starting material. Differential elution of α and β subunits from hydroxyapatite was achieved using a linear gradient of 0.2 to 0.3 M phosphate buffer containing 2 M urea, 0.1% sodium dodecyl sulphate and 1 mM dithiothreitol. 20 mg of α -tubulin (purity: > 85%) and 16 mg of β -tubulin (purity > 95%) completely separated from each other can be obtained in one experiment.

164
TITLE: Preparation of very high specific activity [^3H] methyl acetimidate for protein labeling (UR-3490-1276)

AUTHOR: T. Y. Toribara

PUBLICATION: *Intern. J. Appl. Radiation Isotopes*, 29: 597-598 (1978) Technical Note

SUMMARY: A system is described for carrying out the complete reaction, including opening of the high specific activity [^3H] acetonitrile, in an all-glass train completely isolated from the atmosphere. In addition, the distillation of each of the reagents into the reaction vessel constitutes an extra purification step for each of the reactants.

165
TITLE: The presence of ^{202}Pb in ^{203}Pb samples (UR-3490-1334)

AUTHORS: T. Y. Toribara and F. R. Gibb

PUBLICATION: *Intern. J. Appl. Radiation Isotopes*, 29: 759-760 (1978) Technical Note

SUMMARY: The presence of the long-lived radionuclide ^{202}Pb as an impurity in commercially available ^{203}Pb is demonstrated. A solvent-extraction technique is used to extract the ^{202}Tl daughter. The amount of the impurity is then determined by gamma-ray measurements on the 279 keV gamma-ray from ^{203}Pb and the 439-keV gamma-ray from the 12-day ^{202}Tl .

166
TITLE: Airway reactivity to nitrates in normal and mild asthmatic subjects (UR-3490-1358)

AUTHORS: M. J. Utell, A. J. Swinburne, R. W. Hyde, D. M. Speers, F. R. Gibb and P. E. Morrow

PUBLICATION: *J. Appl. Physiol.*, (in press)

SUMMARY: Epidemiological studies have reported increased symptoms in young asthmatics when atmospheric pollutants containing nitrates and sulfates are elevated. To determine whether inorganic nitrate pollutants cause increased airway reactivity in humans, ten normal volunteers and 11 mild asthmatics inhaled a sodium nitrate aerosol (NaNO_3) with an aerodynamic diameter of $0.46 \mu\text{m}$ at a concentration of $7000 \mu\text{g}/\text{m}^3$, a level 100 to 1000 times greater than reported urban levels for nitrates. A sodium chloride (NaCl) aerosol of similar characteristics served as a control. By double-blind randomization, each subject breathed NaCl or NaNO_3 for a 16-minute period

and again two to four hours later. Deposition studies showed 32% to 78% retention of the inhaled aerosol. Functional residual capacity, airway resistance, FEV, FEV₁, and maximum and partial expiratory flow rates at 60% and 40% of total lung capacity did not significantly change during or after exposure. All subjects remained asymptomatic. To establish whether aerosol exposure increased reactivity to a known bronchoconstrictor, subjects inhaled 0.025% to 1.0% carbachol following the 16-minute exposure. Although this also produced no significant change in pulmonary function, two asthmatics demonstrated mild potentiation of the carbachol bronchoconstrictor response after nitrate exposure. These results suggest that in normal subjects and mild asthmatics short term NaNO₃ exposure does not alter pulmonary function.

167
TITLE: Computers in nuclear medicine: introductory concepts (UR-3490-1444)

AUTHOR: D. A. Weber

PUBLICATION: *Seminars in Nucl. Med.*, VIII: 107-112 (1978)

SUMMARY: Computers play an important role in image and data processing in nuclear medicine. Applications extend from relatively simple mathematical processing of *in vitro* specimen assays to more sophisticated image reconstruction procedures for emission tomography. The basic concepts and terminology associated with computer applications in image and data processing in nuclear medicine are presented here.

168
TITLE: The agenda of behavioral toxicology (UR-3490-1382)

AUTHOR: B. Weiss

PUBLICATION: *In Advances in Pharmacology and Therapeutics*, Vol. 9, Ed. by Y. Cohen. (Proc. 7th Intern. Cong. of Pharmacology, July 1978, Paris, France) Pergamon Press, Oxford and New York, pp. 151-155 (1978)

SUMMARY: Behavioral toxicology is a new discipline distinguished from behavioral pharmacology by the same features that distinguish toxicology from pharmacology in general. Its domain encompasses the issues that now dominate the environmental health sciences: subtle adverse effects arising from long-term, low-level exposure to ambient contaminants. For behavior, these issues pose special problems because functional criteria are so much more amorphous than morphological criteria and even the latter represent a rather more debatable endpoint than death. Behavioral toxicologists, therefore, despite their diversity of background, are united by their common concern over the detection of incipient functional impairment, the experimental design problems fostered by chronic treatment, the difficulties interposed by longitudinal, lifetime observations, and, perhaps the most troublesome of all, the logic by which adverse functional effects are defined.

169
TITLE: Behavior as a sentry of metal toxicity (UR-3490-1478)

AUTHOR: B. Weiss

PUBLICATION: *Proc. European Commission Symp. on Metal Toxicity*, July 1978, Guildford, England. Pergamon Press, New York, (in press)

SUMMARY: Many of the toxic properties of metals are expressed as behavioral aberrations.

Some of these arise from direct actions on the central nervous system. Others arise from primary events elsewhere but still influence behavior. Toxicity may be expressed either as objectively measurable phenomena, such as ataxia, or as subjective complaints, such as depression. In neither instance is clinical medicine equipped to provide assessments of subtle, early indices of toxicity. Reviewers of visual disturbances, paresthesia, and mental retardation exemplify the potential contribution of psychology to the toxicology of metals.

170
TITLE: Environmental contaminants as origins of disordered behavior (UR-3490-1473)

AUTHOR: B. Weiss

PUBLICATION: *Proc. Workshop of Association for Children with Learning Disability, March 1978, Kansas City, Kansas, (in press)*

SUMMARY: Behavioral aberrations can arise from exposure to a wide array of substances. Heavy metals, such as mercury and lead, have been recognized since antiquity as nervous system poisons. More recently, food additives have been implicated as sources of behavioral disturbances. Young children seem particularly at risk both because their nervous system is incompletely developed and because they eliminate certain substances less readily. Better exposure estimates and testing procedures are both needed.

171
TITLE: Dyskinesias evoked in monkeys by weekly administration of haloperidol (UR-3490-1258)

AUTHORS: B. Weiss and S. Santelli

PUBLICATION: *Science*, 200: 799-801 (1978)

SUMMARY: In two cebus (*Cebus albifrons*) monkeys given weekly oral doses of 0.25 milligram of haloperidol per kilogram, movement disorders appeared 1 to 8 hours after drug administration following the tenth weekly dose. These disorders included oral movements, peculiar postures, writhing, and stretching. Such reactions faded in intensity after the next two doses. Increasing the dose to 0.5 milligram per kilogram has elicited the disorders reliably after each weekly dose for almost two years. Similar reactions also developed in a squirrel (*Saimiri sciurea*) treated weekly with haloperidol and in a third cebus monkey previously maintained for a year on a regimen of 0.25 milligram of haloperidol per kilogram on five days per week. These findings suggest an experimental model for determining the etiology of drug-induced movement disorders. They also suggest an unrecognized clinical problem.

172
TITLE: Biochemical endpoints of hormone action (UR-3490-1519)

AUTHORS: D. A. Young, M. L. Nicholson, W. A. Guyette, S. J. Giddings, S. L. Mendelsohn, S. K. Nordeen and R. T. Lyons

PUBLICATION: *In Glucocorticoid Action and Leukaemia, Ed. by P. A. Bell and N. M. Borthwick. (Proc. 6th Tenovus Intern. Workshop, April 1978, Cardiff, Wales) Alpha Omega Publishing Co., Cardiff, U. K., (in press)*

SUMMARY: The rapidly evolving metabolic effects of adrenal glucocorticoid hormones, such

as the hormonal inhibition of glucose transport and oxidative ATP production, and also the more slowly developing lethal actions, those measured by an increase in nuclear fragility, appear to be initiated by the synthesis of new messenger RNAs and proteins.

The chronic suppression of cell growth may be a consequence of the suppression of overall rates of protein synthesis (and probably RNA and DNA synthesis as well) that in turn may represent the cellular response to small changes in ratios of adenine nucleotides that are the consequence of the hormonal suppression of oxidative ATP production. The inhibition of glucose transport may also play a role here to prevent a compensatory increase in glycolytic ATP production.

Some other hormone actions, the decrease in the ability of cells to concentrate AIB and the increase in nuclear fragility, are related to and evolve separately from the hormonal inhibitions on energy production.

Cell killing is not the result of a suppression of protein biosynthesis, nor of hormone-induced increases in calcium uptake. While the mechanisms are unknown, the increase in nuclear fragility appears to be the earliest measure of their operation.

In tumor cells, resistance to the lethal actions of glucocorticoids may emerge by the selection of cells with hardier membranes, those that are better able to withstand the intracellular destruction set in motion by high levels of glucocorticoids.

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