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CENTRAL CHEMOSENSITIVITY

AND

THE MECHANISM OF EMESIS

by

Malgorzata Kondysar

A thesis submitted to the School of Graduate Studies of the University of Ottawa in partial fulfillment of the requirements for the degree, Master of Science, in the Department of Physiology, Faculty of Health Sciences.

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LIST OF ABBREVIATIONS

AP	Area Postrema
CTZ	Chemoreceptor Trigger Zone
VC	Vomiting Center
CSF	Cerebrospinal Fluid
BBB	Blood-Brain Barrier
NTS	Nucleus Tractus Solitarius
SG (SNG)	Subnucleus Gelatinosus
ASP	Area Subpostrema
DMV	Dorsal Motor Nucleus of the Vagus
CNS	Central Nervous System
APO	Apomorphine Hydrochloride
GABA	Gamma-Aminobutyric Acid
CCK	Cholecystokinine
iv	Intravenous
mg	milligrams
µg	micrograms
M	Moles
mM	millimoles
µM	micromoles
mA	milliampers
kg	kilogram
L	liter
ml	milliliter
g	gram

mOsm	miliosmoles
s	second
min	minute
cm	centimeter
mm	millimeter
°C	Celsius degree - temperature
%	Percent
No	Number
Na^+	Sodium ion
K^+	Potassium ion
H^+	Hydrogen ion
Mg^{++}	Magnesium ion
Ca^{++}	Calcium ion
PO_4^-	Phosphate ion
HCO_3^-	Bicarbonate ion
Cl^-	Chloride ion
NH_3	Ammonia
NH_4^+	Ammonium ion
pKa	Logarithm of the association constant, or the negative log of the dissociation constant
pH	Negative logarithm of the concentration of hydrogen ions relative to a 1 molar solution
pH_i	Negative log of the intracellular hydrogen ion concentration
pH_e	Negative log of the extracellular hydrogen ion concentration

pCO_2	Carbon dioxide partial pressure
pO_2	Oxygen partial pressure
BE	Base excess
tot.CO_2	Total carbon dioxide content
SAS	Statistical Analysis System
GLM	General Linear Model
APN	Area Postrema Normal (intact)
APX	Area Postrema Ablation
vs	versus
gav	gavage
ECF	Extracellular fluid
CBF	Cerebral blood flow
ICP	Intracranial pressure
ACh	Acetylcholine
α	Solubility, (mol/Liter) (µg/100ml)
p	Probability
PET	Positron Emission Tomography
hr	hour
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
OH^-	Hydroxyl ion
m^2	square meter

ABSTRACT

The effect of acute disturbances in acid-base parameters as potential factors initiating emesis was studied. A group of four adult beagle dogs was utilized for repeated testing. Ammonium chloride infusions (32 mM) were employed to achieve plasma acidification. Intravenous infusions or intra-gastric administration of ammonium chloride caused vomiting. Venous blood samples were taken at timed intervals for analysis of pH, blood gases and electrolytes. Significant changes in these parameters were correlated with emesis. Ablation of the area postrema, the putative site of central emetic chemoreceptors, prevented the emetic response to iv or intragastric ammonium chloride. The infusion of other solutions, ammonium bicarbonate, lactic acid, sodium lactate, sodium bicarbonate and sodium lactate followed immediately by sodium sulphate, was employed to investigate aspects of the emetic response to ammonium chloride. Emesis was seen in some animals exposed to ammonium bicarbonate and to the dual infusion of sodium lactate and sulphate. Direct stimulation of central emetic chemoreceptors by plasma ammonia was implicated. Although plasma pH was changed, significant changes were not seen in other acid-base factors, following infusion of cisplatin at a dose of body area 50 mg/m^2, a chemotherapeutic compound. However, extensive vomiting was observed. Area postrema ablation did not prevent cisplatin-induced vomiting. Cytotoxic changes and hypoxia induced by cisplatin are likely important in the emetic process. The involvement of receptor sites, perhaps located in the periphery, is suggested.

INTRODUCTION

1.0 EMESIS

Vomiting is a complex, highly coordinated motor response which may be initiated by a wide array of stimuli and which is associated with many clinical symptoms. The obvious physical evidence of vomiting is oral expulsion of gastric content. This expulsion requires changes in gastrointestinal muscle (a decrease in tone and increase in pyloric sphincter pressure) as well as the regulation of the somatic muscles of the abdomen, thorax and diaphragm (Borison and Wang, 1953). Retching is a laboured, rhythmic activity of the respiratory musculature, which is preparatory to, but not necessarily followed by vomiting. Retching, opening of the mouth and assumption of a typical posture, but without expulsion, strongly suggests vomiting. Although nausea and vomiting are common clinical symptoms, once the various control centres coordinating vomiting have been stimulated, the sequence of events leading to expulsion are relatively easy to identify (Wang, 1980). Numerous exogenous stimuli have been employed to study the physiology and the pathways leading to an emetic response. There is, however, comparatively little information concerning endogenous stimuli, which must be involved to explain this complex and common act.

2.0 A SHORT HISTORY OF THE STUDY OF THE MECHANISM OF EMESIS AND THE AREA POSTREMA

Investigations of the mechanism of vomiting started in the last century and have followed two main streams. First was the description of the morphology and role of the area postrema (AP). Subsequently, the emetic reflex was elucidated. The linkage of the area postrema and the emetic reflex was made by Wang and Bifison (1952), who postulated the existence of a Chemoreceptor Trigger Zone (CTZ) for vomiting and localized this critical tissue within the AP.

The first description of the gross anatomy and histology of the area postrema was published by Retzius in 1896. In 1906 Wilson identified nucleus postremus in humans. Wislocki and Putnam in 1920, gave a detailed description of blood supply to the AP and defined the blood-cerebrospinal fluid (CSF) communication in this region. In 1951 Borison and Brizzee defined the region within AP which exhibited chemosensitive properties and named this part the Chemoreceptor Trigger Zone. A detailed comparative histological study of man and other mammals was performed in 1957 by Ozawa. Duvernoy and Koritke in 1964, provided information concerning the complex vasculature of the AP.

PHYLOGENESIS: The origin of the area postrema in animals began at the developmental level of reptiles. The amphibians and lower vertebrates do not have a defined area postrema. Some species of birds possess this structure. All mammals

examined to date have an area postrema. However, the degree of specialization and organization of this tissue is species-dependent. Two important evolutional factors contributed to the development of the area postrema. The first was development of a true subarachnoidal space, to which cerebrospinal fluid (CSF) can flow. The second factor was the involution of the lateral line in the transition of water to land-dwelling animals. The evolutionary reconstruction of the hind-brain (location of the area postrema) led to the present spongiform appearance of the area postrema (Borison, 1984). The exceptional communication between blood vessels (from the pia mater) and CSF compartment is maintained through the perivascular sheaths. The blood-brain barrier in this region is incomplete (Brizzee and Klara, 1984). The AP persists as a bilateral structure (connected via tracts extending over the obex) in animals such dog, cat, ferret, cow, pig and in man, but it is of unilateral structure in animals such as the rodents (Borison, 1984).

3.0 MECHANISM OF VOMITING - CURRENT CONCEPTS

Borison and Wang differentiated and localized central and peripheral components of the emetic reflex (Borison and Wang, 1953). According to their theory, the central regulatory sites for emesis are in the dorsal portion of the medulla oblongata. They stated that the medullary emetic mechanism consists of two anatomically close, but functionally separable units: 1) a vomiting centre (VC) in the region of the fasciculus solitarius

and the underlying reticular formation, which is excited directly by visceral afferents; and 2) a CTZ located in the AP which is the site of emetic action of blood-borne agents. Polysynaptic afferents from the CTZ project to the reticular formation and this way communication between CTZ and vomiting center is established (Borison and Brizzee, 1951).

Electron microscopy has facilitated detailed study and precise description of the AP. The most informative studies were conducted by Leslie et al. in 1978 on the fine structure of the ventricular surface of the AP, with special references to supraependymal structures. The fine structure of the ependyma and intracellular junction in the AP was described in 1979 by Gotow and Hashimoto. The cellular morphology of the AP was demonstrated and described by Chernicky and associates in 1980. The ultrastructure of the subnucleus gelatinosus (SG) of the nucleus of the tractus solitarius (NTS) was presented in 1982 by Leslie et al. Other histological studies focussed on the neural structure of the AP with its afferent and efferent connections. Microscopic techniques were employed to investigate the neural pathways to and from the AP, VC and the periphery (Gwyn et al., 1978, 1979).

Specific blockers were used to assess involvement of various neurotransmitters within the AP (Leslie, 1985). Electrophysiological techniques were applied, using injections of neurotransmitters agonists, such as apomorphine hydrochloride, or of peptides: angiotensin II, arginine vasopressin and others (Wu et al., 1985). This type of investigation established the presence

of neurotransmitters and neuroactive substances in the region of the area postrema.

Borison utilized direct electrical stimulation (Wang and Borison, 1950) or radiochemical ablation (Wang and Borison, 1952) to localize the VC. The stimulation of gastrointestinal receptors was used in conjunction with electrode registration of myoelectric activity to localize central projections of gastric afferent vagal inputs (Harding and Leek, 1973). The electrical stimulation of the VC through implanted electrodes was re-examined by Miller and Wilson in 1983. This study, which included some work in Borison's laboratory, failed to induce vomiting and questions the existence of a discrete VC (Miller and Wilson, 1984). AP lesions accomplished by electrocautery abolished emesis due to chemical stimuli but not electrical stimulation (Wang and Borison, 1951). In 1985 Harding et al. reported that discrete lesioning of the area postrema abolished radiation-induced emesis in the dog.

The mechanism of vomiting must be approached from the point of view of its etiology. Hence, separate studies are conducted on mechanisms of emesis under different conditions and influences, including motion sickness, after radiation, chemotherapy-induced, postoperative, pregnancy-related, infantile, psychogenic, and other factors.

4.0 ANATOMY OF THE AREA POSTREMA

There are many similarities between the area postrema of human and animals, especially between mammals such as the dog, monkey and cat. These animals are among the few which exhibit a

complete emetic reflex. The closest similarity is found between the human and canine area postrema, especially with respect to their fine structure (Ozawa, 1957).

4.1 GROSS ANATOMY

4.1.1 Location and Vascularization

The area postrema lies on the medulla oblongata and is a part of the floor of the fourth ventricle. It protrudes into the fourth ventricle on each side of the midline, and therefore is in contact with cerebrospinal fluid. In rodents and lagomorphs the area postrema is a unilateral structure in the midline position overlying the central canal (Brizzee and Klara, 1984).

The area postrema is one of the circumventricular organs. Capillaries of these organs contain fenestrations which have the characteristics of an incomplete blood-brain barrier. Infiltration of the tissue by cerebrospinal fluid (CSF) is reduced by special junctions between ependymal cells. The spread of injected dye from the intraventricular space into the perivascular space (vascular and parenchymal basal lamina and lumen of the capillaries) indicates direct connections between the perivascular space and the subarachnoid space. The unique organization of the area postrema predisposes this organ to rapidly sense stimuli derived from blood or cerebrospinal fluid (Gotow et al., 1979).

Blood flow to the area postrema derives mainly from the posterior inferior cerebellar and posterior spinal arteries. Blood supply to the AP is independent of adjacent regions of the

medulla oblongata and the choroid plexus. Vessels of the AP are large and are organized in a network. Arteries arrive on the external (dorsolateral) surface and the veins drain from the internal (ventral) side (Brizzee et al., 1984, Duvernoy et al., 1964).

4.2 CYTOLOGY

Cytological observations of the area postrema (canine) revealed three distinct regions. These are a mantle zone nearest the ventricular surface, a central region - intermediate zone, and a junctional zone close to the medullary tegmentum (Chernicky et al., 1980).

The mantle zone contains bipolar neurons intermixed with glialoid cells. Both cells possess long ventrolateral processes. The intermediate zone connects both the mantle and junctional zones with numerous fine processes of astrocytes and stellate neurons. The outer junctional zone contains small stellate neurons with fine processes which project to adjacent areas, including the Nucleus Tractus Solitari (NTS). Cell structures of the area postrema include: ependymal cells, supraependymal cells, glial and neuronal cells.

4.2.1 Ependymal Cells

The distinctive characteristics of ependymal cells of the area postrema makes them different from those overlying adjacent structures. They are flattened cells with very few cilia, a moderate number of the microvilli, a well-developed Golgi apparatus, and prominent rough endoplasmic reticulum (Gotow, 1978). Another noticeable feature of these cells is the presence

of basal processes containing numerous dense vesicles or tubular formations which project to the perivascular basal lamina. A remarkable feature of ependymal cells is adherent junctions with neuronal axons which contain synaptic vesicles. The body of these neurons with their neuronal processes is encompassed by the ependyma and localized closely to the ventricular surface. They are also exposed directly to the perivascular spaces surrounding vessels of the AP.

4.2.2 Supraependymal Cells

Another important cell type of the AP is the supraependymal cells (Leslie et al., 1978). These cells protect the ventricular system and subarachnoid space against invading organisms. Morphologically, they resemble macrophages. Single cells contain small apical vacuoles, lysosomes, prominent Golgi apparatus and phagosome-like bodies. Microvilli are arrayed as tufts or as single units. Tufts are often placed closely to the superficial blood vessels which are surrounded by large perivascular spaces.

4.2.3 Glial Cells

Glial cells resembling astrocytes are the most numerous cells of the AP. A common feature of these cells is multiple cytopodia which terminate on the parenchymal basilar laminae of perivascular spaces (Brizzee et al., 1984).

4.2.4 Neuronal cells

Neurons of the area postrema are of a mature pleomorphic type, with an axon and branching dendrites. They are often adjacent to perivascular spaces with intervening glial processes.

The rostral half of the AP is rich in nerve terminals, closely related to the choroid plexus. The caudal part of the AP exhibits a few terminals deep in the parenchyma (Brizzee et al., 1984).

4.3 NEURONAL COMMUNICATION WITH THE AREA POSTREMA

4.3.1 Vagal projections

The largest nerve bundle leaving the AP projects to the NTS, which is generally described as possessing lateral and medial parts. The dorsomedial region of the NTS (in man) is termed Subnucleous Gelatinosis (SNG). Much of the SNG lies subjacent to the AP (Leslie et al., 1982). It also extends rostral to the AP to lie immediately subjacent to the floor of the fourth ventricle. A part of NTS called the Area Subpostrema (ASP), the most dorsal part of the NTS extends rostrally to the SNG. Considerable numbers of the vagal afferents arising from the stomach wall terminate in NTS and ASP (Leslie et al., 1982; Gwyn et al., 1979). There is no evidence demonstrating connections between AP and SNG. The AP is usually considered to have a role in chemoreception. However, it does receive some vagal afferents which are of gastrointestinal origin (Gwyn, 1979; Harding et al., 1973). The projection of vagal and sympathetic afferents to the VC was shown by Borison and Wang (1952). The connection still remains to be explored especially after the controversial study of Miller and Wilson (1984). The recent information on vagal projections and neuroactive substances in the dorsal vagal complex of the medulla oblongata was presented in 1982 by Leslie

et al. The major target of vagal sensory information is a distinct region in the dorsomedial medulla oblongata which incorporates most of the NTS, as well as the AP. These brainstem nuclei, together with the dorsal motor nucleus of the vagus nerve (DMV), constitute a region of the brain called the dorsal vagal complex (DVC). Most of the remaining vagal afferents fall into the nucleus ambiguous (ventral in the medulla oblongata) and the spinal trigeminal nucleus (lateral). NTS is a major afferent nucleus (for gastric and respiratory structures, cardiac projections, and baroreceptor information). The NTS is also the site of most sensory fibers of the facial and glossopharyngeal nerves (gustatory function). The NTS is in a position to influence many levels of autonomic and endocrine control, and sends efferent projections to many central nerve structures involved in these processes i.e., visceral function (Gwyn and Leslie, 1978).

The second large terminus of vagal afferents is in the AP. Some of the vagal afferents enter the medulla via the spinal trigeminal tract and terminate in the nuclei of that tract (lower pharynx, larynx, esophagus and a few fibers from the region of the ear).

4.3.2 Neuroactive Substances

Immunocytochemical techniques have provided most of the presently available knowledge concerning neuroactive substances in this region. This information was obtained mainly from animal studies and is still very fragmentary. Catecholamine, dopamine,

noradrenaline and adrenaline receptors have been associated closely with the NTS; regulation of blood pressure, gastric acid production, mucosal blood flow (Leslie, 1985).

One of the most effective emetic agents is apomorphine, a potent dopamine agonist. There is some evidence that a high concentration of the dopamine and α_2 adrenergic binding sites occurs within the AP, DMV, and NTS (Robertson and Leslie, 1985). The biogenic amine serotonin (5-hydroxytryptamine, 5-HT) is present in the DVC, AP and NTS, but little is known about the distribution of 5-HT receptors within the medulla oblongata. No muscarinic binding sites are reported to occur in the AP. Some cholinergic receptors were assumed to lie within the NTS.

Another large group of neuroactive substances which occurs naturally in the CNS is the oligopeptides. Their properties may be similar to neurotransmitters. Some of them have long-lasting effects on the post-synaptic membrane, in contrast to "classical" neurotransmitters. Neuropeptides require ribosomal involvement of the perikaryon or dendrite for their production (from precursor protein).

Endogenous opiates (endorphins) have been localized in the DMV and NTS. Neuronal somata and fibers immunoreactive for met-enkephalin have also been reported in the AP (Leslie, 1985). Other peptides associated with the brain opiate system were found in the AP, which suggests that large concentrations of opiate receptors are present in this structure. Borison and associates demonstrated that AP lesion abolished emesis produced by morphine

and apomorphine (Wang and Borison, 1952; Borison, 1953).

Substance P has been localized in the NTS in those areas which receive baro- and chemoreceptors via the vagus. It may also exist within DVC axons and varicosities which make synaptic contact with dendrites of intrinsic neurons of the AP. Substance P probably has some effect on the central control of blood pressure. Cholecystokinin, a gut and CNS peptide, has also been described in the AP (Leslie, 1985).

Some of the neuropeptides are more typically associated with the endocrine system. Angiotensin II specific receptors occur in high concentration in AP. Experiments with AP ablation have suggested that angiotensin II may act on the AP to facilitate sympathetic vasomotor output (Leslie, 1985; Wu et al., 1985).

Besides neuropeptides, some of the amino acids behave as neurotransmitters. One of them is gamma amino butyric acid (GABA), and has been identified in the NTS, DMV and AP. GABA is known to act as an inhibitory neurotransmitter in the DVS (Leslie, 1985). Glutamate, the precursor for GABA, has an excitatory function in the CNS and an affinity for NTS and DMV. The pancreatic hormone, insulin, has been shown to bind extensively in the AP and subnucleus gelatinosus (Leslie, 1985).

5.0 THE ROLE OF THE AREA POSTREMA

A role for the area postrema has been postulated in the regulation of water and food intake, blood pressure, and the sleep cycle (Borison, 1974). The significance of the area

postrema in the emetic mechanism relates to the sensory role of the CTZ as one of the central sites for stimuli derived from blood or cerebrospinal fluid. AP afferents also project to the vomiting center, an integrative site which if stimulated elicits the motor response of the emetic reflex. Although a discrete VC may not exist, a linkage of vomiting control nuclei has been proposed, and these receive input from the AP (Miller et al., 1984; Davis et al., 1986).

6.0 EMETIC REFLEX

6.1 SENSORY PATHWAYS

In addition to the central components of the sensory arc of the vomiting reflex, are the vestibular apparatus and the gastrointestinal tract. Activation of emesis can be initiated by different stimuli as has been documented by Borison and Wang (1953). Fig. 1 is a schematic presentation of possible types of receptors involved in initiation of vomiting.

6.2 CENTRAL REGULATORY SITES

6.2.1 Chemoreceptor Trigger Zone

A blood-borne factor has been postulated to trigger emesis at the chemoreceptor trigger zone (Wang and Borison, 1952). AP ablation studies have proved that animals become refractory to emesis induced by apomorphine, copper sulphate, enkephalins, intrathecal administration of nicotine (Borison and Wang, 1953), and to radiation-induced vomiting (Harding et al., 1985).

Presumably several types of receptors may be activated.

Figure 1 presents several types of putative receptors initiating emesis. Clinically relevant vomiting may occur in conjunction with various diseases, as listed in Table 1.

Although the stimuli produced are diverse, they may be associated with several common stages including changes in blood flow, oxygenation and local changes in the pH of tissues.

6.2.2 Vomiting Center

As Fig. 1 shows, the activation of the vomiting centre may occur directly from the gastrointestinal tract via vagal or sympathetic nerve fibers (Wang and Borison, 1952). Peripheral receptors of the gastric and intestinal mucosa seem to be chemically sensitive (Borison and Wang, 1953). The vestibular apparatus and proprioceptors are able to generate emetic stimuli with changes in posture and position. Other centres such as the cerebellum and cortex may provide stimuli for the VC (Wang, 1980). Further, the cortex might integrate impulses arising from other regions of the central nervous system (Wang, 1980). This is most likely in the case of learned vomiting and vomiting of psychogenic origin.

6.3 MOTOR PATHWAYS

Transmission from the central sites (VC) elicit motor responses which result in emesis. The motor signals are sent to target organs including the gastrointestinal tract, cardiovascular system, muscles of the head, chest and abdomen, as well as exocrine glands via somatic efferent fibers (Wang and Borison, 1952). Davis et al. (1986) have suggested that perhaps

various "centres" controlling the somatic aspects of vomiting are stimulated sequentially and result in an integrated response which we recognize as vomiting. These induce the series motor effects which are: licking, salivation, panting, coughing, assumption of the characteristic posture changes, retching and expulsion of gastric contents (Davis, 1986). While vomiting per se is a neatly delineated mechanical behaviour, the prodromes of vomiting are so varied as to defy general description (Davis et al. 1986).

7.0 THE ROLE OF VOMITING

7.1 WARNING SIGNAL

Vomiting appears in many diseases which are in essence changes in homeostasis. No consistent temporal relationship is evident, although vomiting may often be said to herald the onset of significant dearrangement or disease.

7.2 PROTECTION AGAINST TOXICITY

A major role of emesis is protection of the body against toxicity (Davis et al., 1986). Toxins may be introduced into the organism (drugs, chemicals, bacterial toxins), or produced within the body endogenously (toxic metabolites, acid-base disturbances). Expulsion of gastric content is one method to relieve the body of toxic material, as well as an amount of gastric and/or duodenal juice.

8.0 CONSEQUENCES OF VOMITING

Loss of gastric content during vomiting leads to removal of

hydrogen ions and chloride ions. Pronounced vomiting may involve duodenal content and result in the loss of bicarbonate and sodium ions. In both situations, the organism is depleted of certain ions and disturbances of acid-base, electrolytes and body fluids may follow. Repetitive loss of gastric juice alone produces alkalosis and hypokalemia, and this is the most prevalent consequence of vomiting (Wallace et al., 1968). Acidosis and hyperkalemia may develop during excessive vomiting, involving the removal of alkaline duodenal contents. Repetitive vomiting alone can lead to life-threatening distrubances in body fluid and acid-base balance. In addition to the systemic disease, these effects can lead to further deterioration of the general condition and worsen the disease. In the case of chemotherapy, emesis often limits the dose of drug and by this, the effectiveness of the treatment.

9.0 STUDY OBJECTIVES

The purpose of this study was to investigate the mechanism of vomiting at the central nervous system level, particularly the chemosensitivity of the CTZ. A chemical stimulus was chosen as the most appropriate to act on putative chemosensitive cells within the CTZ. Since the regulation of acid-base balance, electrolytes and metabolites, significantly contribute to homeostasis, disturbances in these variables were studied as probable direct stimulating factors (at the CTZ) for emesis. The variability in the chemical dearrangements produced by selected

treatments provided ample opportunity to study these aspects in association with observed symptoms.

The following hypotheses were tested:

1. Changes in acid-base, electrolytes and metabolites are significant emetic factors.

2. Ammonium compounds may be important in initiating emesis, possibly as an endogenous metabolite.

3. Changes in acid-base, electrolytes and endogenous metabolites activate central chemoreceptors in the chemoreceptor trigger zone.

In the first stage, studies were designed to produce specific disturbances in body homeostasis in the animal in vivo (acute and transient metabolic acidosis and alkalosis in the blood). The dog was selected as the most suitable animal model. Emesis was the end-point of each experiment, and an equal amount of emetic and nonemetic treatment was given. The venous blood was monitored closely for changes in biochemical parameters (blood acid-base, electrolytes and ammonia analysis) through repetitive sampling of conscious animals. Experimental treatments were selected in a particular order, which allowed sequential evaluation of their ionic composition. The investigation gradually focussed on ammonium chloride as a potent emetic.

Elimination procedures were used to define the physico-chemical characteristic of ammonium chloride responsible for the induction of vomiting.

The second part of the investigation included a comparison study between the central and peripheral sites of chemosensitive receptors. Ammonium chloride solutions were used as potent emetics. Two kinds of trials were considered. One differentiated between intravenous and intragastric routes of administration of ammonium chloride. Another distinguished between the response seen before and after surgical ablation of the area postrema in the same animals. In this part of the study, free ammonia in plasma was measured as a prospective induction factor for emesis.

The last part of the investigation was clinical application of the theory generated in this study. In order to investigate chemotherapy-induced emesis, the influence of the antineoplastic agent cisplatin on blood acid-base, electrolytes and free ammonia was assessed. In an acute trial all animals, AP intact and AP ablated, were infused with this drug.

METHODS

1.0 GENERAL

1.1 Animals

The experiments were carried out on adult, unanesthetized, beagle dogs: three males and three females. The animals ranged in weight from 10-12 kg. Four of the six dogs studied were used repeatedly in all trials. Two of the dogs were tested only with saline and an infusion of sodium lactate followed immediately by sodium sulphate.

1.2 Diet

The diet consisted of dry Purina Chow and water ad libitum. Animals were fasted over night (12-18 hrs), preceding experimental measurement of plasma ammonia levels.

1.3 Handling

The dogs were trained to stand quietly in a sling. For this purpose each animal was placed in the sling for increasing periods of time, and was considered to be trained when they would stand quitely for periods up to 1.5-2.0 hours.

1.4 Cannulation

Intravenous catheters were introduced into the cephalic vein and the saphenous vein of two limbs. Two types of catheters were used: a 14 gauge intravenous needle (Surfo iv catheter), with pass-through tubing (Intramedic nonradiopaque tubing, Clay Adams). The tubing was connected directly to the syringe (disposible type, Becton Dickinson Canada Inc.). This type of intravenous set allowed placement of catheters high in the limb,

which was beneficial when infusions containing irritants (such as lactic acid) were made. Another type of cannula was an indwelling 18 or 20 gauge catheter (Monoject, Div. of Sherwood Medical). Connection with the syringe was made by using a specially designed extention, which involved polyethylene tubing, a rubber ball and a polyethylene tip.

1.5 General experimental set-up

Solutions containing the chemical or the drug were infused into the vein at a constant rate of 0.135 ml/min (Sage Instruments, model 341A Infusion Pump). The total amount infused each time was 32 mM in a volume of 80 ml (3 mM/kg). An exception was lactic acid, which, due to its irritant properties, was diluted to 100 ml (32 mM). Thus the concentration of the solutions was 0.4 M, except for lactic acid which was 0.3 M (Fine, 1982). Mannitol was prepared at two osmolality levels, one 904 mOsm/L, and the second as a 674 mOsm/L solution. Gavages contained the same total amount of ammonium chloride (1.7 g) in two volumes - 20 ml or 40 ml of water (Martindale Pharmacopeia, 1982). All intravenous equipment as well as all solutions were sterile. Syringes and needles were of a sterile, disposible type or were sterilized by gas. Solutions were filtered through 0.22 micron filters (Millex GV Filters Millipore Co., Mississauga, Ont.).

1.6 Sampling and maintenance of the experiments

Animals were allowed to recover completely between experiments. Control blood samples were analyzed at the

beginning of the next treatment. Periodically (1/month), blood cell counts, hematocrit and hemoglobin levels were checked (Hematology Series Cell Counter 7000, Baker Instruments).

Infusions were administered to the animals through the cephalic vein and blood samples were drawn from the saphenous vein. The time interval between samples was 5 minutes for experiments with lactic acid and sodium lactate, and fifteen minutes with cisplatin. During all other trials, samples were taken every 10 minutes. The average duration of infusion was 1 hour for a single infusion and 1.5 hours for a double. The observation time extended from 0.5 hour to 1.5 hours after the end of the infusion. Cisplatin treatment required observation for up to 180 minutes.

1.7 Preparation of infusion solutions

Stock solutions were stored in the dark at 0-4°C, and used within one week. Drugs and chemicals were freshly prepared, filtered and warmed-up before infusion. The pH of the solutions was adjusted or controlled before administration. The chemicals were Certified A.C.S.: Chemical Company Standards.

1.8 Gavages

A guide tube was fashioned by removing the conical end from the sleeve normally used to package a Becton Dickson 60 ml disposible syringe. This was placed in the animal's mouth and extended from the back teeth to a point about 3 cm beyond the snout. An infant naso-gastric tube was inserted, through this guide tube down into the stomach. When it was clear that the

tube was in the stomach (by noting the absence of expired air exiting the tube), the free-end was attached to a 50 ml syringe and the gavage solution was injected.

2.0 SPECIFIC METHODS

2.1 Control tests

Control tests were undertaken in every case before initiating further experiments. Apomorphine hydrochloride was given in a single injection at a dose of 15 μg/kg (intravenously) to test for a positive emetic response. One hundred ml of 0.9% sodium chloride was infused intravenously over one hour as a control infusion. Fifteen percent sodium chloride 20 ml as a single gavage was administered to insure the presence of a gastric emetic response. Measurements of blood gas were performed before a new infusion was started to check whether animals compensated from the previous treatment.

2.2 Infusions

Table 2 presents a summary of the chemicals used in this study.

2.3 Gavages

Table 2 shows the composition of the gavages used in the study.

2.4 Cisplatin

Cisplatin was dissolved initially in 0.9% saline, then mixed with 5% dextrose and 20% manitol. The dose of cisplatin was adjusted to the animal's body surface area (50 mg/m^2; Drug

Information, 1986) and dextrose to the body weight (3.9 ml/kg). Mannitol 20% was administered in a total volume of 1.0 ml for smaller animals, and 2.0 ml for larger animals (0.12 ml/kg). These concentrations were chosen to reflect the doses typically employed in clinical medicine and required a reduction of the total fluid volume infused with cisplatin and a significant decrease in the dose of mannitol. The mixture was given to the animals as an intravenous drip over 60 minutes. The dose of Cisplatin (1. Platinol-AQ, Cisplatin Injection, Belleville, Ontario, Candiac Quebed; 2. Cisplatin Injection, David Bull Laboratories Ltd., Melbourne, Australia, Distr. Horner, Montreal, Canada) was 50 mg/m^2, calculated for the dogs on the basis of the doses for antineoplastic agents (Ettinger, 1975).

3.0 ANALYSIS

3.1 Blood gases, pH and bicarbonate

Blood samples were drawn into 1 ml plastic syringes pre-filled with 0.05 ml of Heparin (1,000 units/ml). Prechilled syringes were kept on ice and measurements of blood gas were done immediately after collection. Analysis of blood gas and calculation of the bicarbonate, base excess and total CO_2 was performed on a pH/Blood Gas Analyzer (No. 813, Instrumentation Laboratory).

3.2 Electrolytes: Na^+, K^+

Blood samples for Na^+ and K^+ determinations were taken after those for blood gas. Samples were collected in the vacutainers

(Becton Dickinson Canada Inc.), and serum was separated by centrifugation within 30 min (Clinical Centrifuge, International Equipment Co.). Analysis of serum Na^+ and K^+ levels was done using a flame photometer (Flame Photometer 443 Instrumentation Laboratories, Flame Photometer 480 Corning).

4.0 DETERMINATION OF AMMONIA LEVEL IN PLASMA

Ammonia levels in plasma were measured using micro-techniques modified from previously published methods (Attili et al., 1975).

4.1 The ammonia-sensitive electrode assembly (Figure 2).

The MI-740 Electrode kit consists of: 1) a glass pH electrode with external silver-silver chloride reference electrode; 2) replaceable membranes incorporated in plexiglass housings; 3) bottle of reference solution; 4) syringe with plastic tube for adding reference solution to the plexiglass housing; and, 5) a bottle of 10 M NaOH (ammonia free). The specifications of the ammonia electrode were as follows: Total length 6.3 cm; Lead length 2 mm; Body (Outer Diameter) 3 mm; Tip (Outer Diameter) 3 mm; Sensitivity 90%; Response Time 30 sec; Depth of Immersion 0.1 mm; Reference Electrode Type Ag-AgCl; Range 10^{-6} to 1 M (Microelectrodes Inc. Operating Instructions, 1985).

The ammonia electrode is a gas sensor which measures NH_3 in solution or humidified air. Ammonium ion (NH_4+) can also be

measured after conversion to ammonia by a pH adjustment with sodium hydroxide. The probe uses a glass electrode and a reference electrode mounted behind a gas-permeable membrane that separates the sample from a thin film of an internal solution pressed between the membrane and the surface of the glass electrode. Sample NH_3 diffuses across the membrane until the partial pressure of ammonia in the sample and in the film layer are equal. The NH_3 partial pressure is proportional to NH_3 concentration. Ammonia reacts with water in the internal solution to form ammonium ion and hydroxide ion. The resulting pH change is measured by the glass electrode (Orion Research, 1982 Handbook of Electrode Technology).

4.2 Reagents

Buffers were prepared on the basis of the recipe for "Titrisol" buffer (Attili et al, 1975), and listed below.

4.3 Calibration

Preparation of ammonia standards:

Ammonium chloride reference standard 100 ± 0.0005 mM/L (Orion Research Inc. No. 951006, Cambridge, Mass, USA) was taken in a volume 71.4 ml and diluted to 100 ml with distilled water (standard I).

Standard I was diluted with distilled water again:

1.0 ml taken up to 100.0 ml, to give the concentration of 10 mg of ammonia nitrogen/L (Standard II).

Standard II was diluted as follows:

2.0 ml with 8.0 ml

1.0 ml with 9.0 ml - of distilled water

0.5 ml with 9.5 ml

to give the final concentration of:

Standard III = 2.0 mg/L

Standard IV = 1.0 mg/L

Standard V = 0.5 mg/L

Standard V was diluted once more - 1.0 ml with 1.0 ml of water, to a concentration of 0.25 mg/L (Standard VI) (Cooke, 1983).

Five standards were used for calibration (II-VI). Equal 0.2 ml volumes of each standard were mixed in a tuberculin syringe with 0.4 ml of pH 10.4 buffer. The syringe was placed on the pump and the electrode was perfused with the solution at a rate of 0.04 ml/min (FIGURE. 4). The reading was taken after 8-10 min of stabilization. The result was expressed in millivolts on the electrometer (Radiometer Copenhagen, Figure 4), which measures and displays the voltage developed between the sensing electrode and the reference electrode placed in a solution.

4.4 Sampling and sample preparation

The following steps were followed to prepare the syringe for centrifugation and to insure that gaseous ammonia did not evaporate from the sample. Blood samples taken from fasted animals, were injected into prechilled tuberculin syringes (total 0.9 ml) (FIGURE. 2), and stored on ice. They were then centrifuged for 10 min at 2500 RPM and 0°C in the same syringe,

within 60 min of the time the sample was taken (IEC Centron-7R refrigerated centrifuge, International Equipment Co., Div. of Damon, USA). Following this, plasma from the syringes was placed into clean tuberculin syringes. A volume of 0.2 ml of plasma was mixed in this syringe with a pH 10.4 buffer, up to 0.6 ml volume. Samples ready for measurement were allowed to warm up slowly while calibration was performed.

The theoretical basis for the ammonia determination is as follows. Ammonia in aqueous solution dissociates according to a known equilibrium equation having a pKa of about 9.3 at 25°C. The $NH_3:NH_4^+$ ratio is proportional to the pH of the solution: the higher the pH, the higher the ratio. Since the method uses an electrode sensitive only to NH_3, it is necessary to work at a high pH. Ideally, readings should be taken at pH 12.0, because at this pH all the ammonia is in the un-ionized form as NH_3. Determination of plasma ammonia at such a high pH may, however, be complicated by ammonia radicals from many sources: urea, proteins, etc. Three types of buffers were prepared to bring the plasma pH to 10.4. A pH of 10.4 was used to maintain a high NH_3 content (95%) and to avoid excessive alkalization and errors as mentioned above (Attili, 1975; Davidson et al., 1980).

4.5 Modification of published methods

Originally, "Titrisol" buffer pH 10.0 (Merck & Co., Darmstadt, F.R.G.), and "Titrisol" pH 12.0 (Merck & Co.) were used (Attili et al., 1975). In this study, buffers were prepared in the laboratory. All proportions and concentrations were

identical with those in the commercial preparations, except a slightly larger amount of sodium hydroxide was used to bring the pH to 10.0 and 12.0. It was also necessary to design and construct a flow-through adapter to deliver samples to the electrode in an enclosed chamber, without losing gaseous ammonia to the atmosphere. The small size of the adapter allowed flushing of the tip of the electrode by the sample at a constant rate. The photograph and caption to Figure 2 illustrates these modifications.

4.6 Experimental assay

Buffered plasma (0.6 ml) was pumped from the syringe at a constant rate of 0.04 ml/min into a flow-through adapter. The tip of the ammonia electrode was immersed in the plasma thereby allowing gaseous ammonia to diffuse through the sensitive membrane. This initiated the rise in electrical current registered on the meter in millivolts. The infusion rate of 0.04 ml/min appeared to be optimal for equilibration of the ammonia concentration. The total time to assay each sample was 8-10 min. This time could be reduced (rate = 0.07 ml/min) when ammonia levels did not exceed the normal range.

4.7 Calculation

The ammonia concentration in the plasma was calculated from a comparison of the semilog plot of the sample readings with those achieved with standards (Hewlett Packard Calculator HP-97, Curve Fitting Program). The experimental data were expressed in µg/100 ml of ammonia concentration in plasma.

Conversion factors for ammonia concentration in plasma:

µg/100 ml to µmol/L is 0.5872 (as NH3)

(10-80 µg/100 ml = 5-50 µmol/L)

µmol/L x 1.703 = µg/100 ml (as NH3)

(Metric Commission Canada, 1985)

5.0 SURGICAL PROCEDURES

Selective, electrolytic lesions of the area postrema were prepared under sterile conditions. The surgery was performed by Dr. H. Hugenholtz, using previously proved techniques (Harding et al., 1985). The animals were anesthetized with halothane. Dura mater was transected at the craniocervical junction, and the cisterna magna was opened. The area postrema was visualized, and five to seven discrete electrolytic lesions were produced under direct visual control on each side along the longitudinal extent of the bilateral area postrema (using an anodal DC current 1.6 mA/10S and a concentric bipolar electrode SNE-100, Rhodes Medical). Recovery was complete within one week without complications.

6.0 HISTOLOGY

At the end of the cisplatin experiment, animals were anaesthetized with an iv dose of Somnotol. The two jugular veins were isolated in the neck, and the left carotid artery was dissected free for a length of 5 cm. A 19 ga needle and cannula

infusion set was introduced into the carotid and inserted about 5 cm towards the head. The jugular veins were severed and 250 ml of saline solution were infused to clear the head of blood. Two hundred and fifty ml of phosphate-buffered 10% formalin were then infused to begin fixation. The medulla was then dissected free and placed in formalin for 2-4 days. Following fixation, the tissue was embedded in paraffin and sectioned using a rotary microtome at 8 or 20 µm. The 8 µm sections were stained with haematoxylin and eosin and the 20 µm sections were stained with cresyl violet. Eighty sections were collected and stained. These represented a series encompassing the entire length of the AP. The sections were coded and examined utilizing a Zeiss Photomicroscope I.

RESULTS

The present study on the mechanism of vomiting includes both qualitative and quantitative assessments of the data. The presence or absence of vomiting was noted for each treatment on a "yes" or "no" basis. A "yes" rating required a full emetic response with expulsion of gastric contents. Other recorded symptoms included licking, salivation or retching, and these were included in the behavioral assessment. The latency period was measured and compared between treatments. Nonparametric and parametric (statistical) tests were used for the assessment of the numerical data. Statistical significance was assumed at a probability level of $p < 0.05$.

1.0 BEHAVIORAL STUDY

Table 3 presents the emetic response observed with each test solution. Ammonium chloride was infused intravenously or introduced into the stomach as a gavage (in 20 ml and 40 ml of water). The emetic response from iv and 20 ml gavage to each challenge was 100 percent and 50% to 40 ml gavage. Of the other treatments, only ammonium bicarbonate led to vomiting (in two of four animals). A dual infusion consisting of sodium lactate followed by sodium sulphate was given intravenously in order to assess whether immediate and opposite changes in acid-base balance were able to induce emesis. Emesis was observed in one of four subjects. Finally, the antineoplastic drug cisplatin was given intravenously to the animals and close measurement of blood constituents was performed. All four animals vomited intensively

despite two of them being AP ablated. No gender differences or effects of time-on-test were observed.

2.0 CONTROL SAMPLING

Control tests were undertaken before further treatments were started. Animals were pretested with the well-known emetic and dopamine agonist, apomorphine hydrochloride. Hypertonic saline was used as a standard test for activation of gastric receptors. This solution was prepared as 15% NaCl in 20 ml of water and given as a gavage. Isotonic saline (100 ml) was used as a control solution. The emetic response was 100% to apomorphine hydrochloride and 75% to hypertonic saline. Animals did not vomit to normal saline given intravenously.

The experiments listed below were conducted in this group of animals over a period of 14 months. Time for complete recovery was allowed between treatments. Measurement of the baseline parameters (pH, blood gases, bicarbonate, ammonia) were made before every trial.

Statistical comparison of the baseline data (time 1) was obtained using SAS Duncan test (multiple comparison of the means). These analyses confirmed that recoveries were complete and no seasonal drift in baseline values occurred. Only the starting pH was seen to be different in the series involving ammonium chloride gavage. All other variables were not significantly different.

3.0 EMETIC AND NONEMETIC TREATMENT

On the basis of the presence or absence of vomiting

(qualitative assessments) the treatments were divided into two major groups; those which led to vomiting and others which did not. The purpose of the quantitative assessment was to reveal significant changes in the blood constituents due to the treatment given over the period of time.

3.1 LATENCY PERIODS

Table 4 presents the time of infusion of solutions and the length of the observation period. Figure 5 presents the comparison of the latency periods for all solutions and drugs which led to vomiting. The shortest latency period was observed after intragastric administration of 15% saline in 20 ml of water. Vomiting occurred in 3 of 4 animals within 0.8-2.6 minutes after its introduction to the stomach. Apomorphine hydrochloride induced vomiting within 1.5-2.5 min after intravenous injection in all (4) subjects.

A longer latency period, 8.2-15.4 min, was observed following treatment with ammonium chloride (NH_4Cl, i.v. or gavage). Similar onset times were noted in spite of the use of different routes of administration and different concentration of solution. All four animals vomited to intravenous NH_4Cl and to a 20 ml gavage. One of the animals treated intravenously vomited in the 40th minute of the infusion. This same animal treated with a 40 ml gavage did not vomit. Another retched in 73rd minute after 40 ml gavage. A longer latency period was observed during infusion of ammonium bicarbonate. Two of four animals vomited beginning at 36.3 or 51.7 minutes from the beginning of the infusion.

All of the above emetic episodes happened during the

intravenous administration of the solutions or, in the case of gavage, soon after its application. Latency periods exceeding the infusion time were observed in two different trials. The first was after intravenous administration of the sodium lactate, followed immediately by sodium sulphate. One of the four animals vomited 55 min after the end of the treatment. In the experiment with the antineoplastic agent cisplatin, the intravenous drip was delivered in 60 min. Emesis was observed in all four animals, including the two which were area postrema ablated. The first episode of vomiting was observed 76-124 min after the end of the infusion period.

3.2 STATISTICAL ANALYSIS OF TIME EFFECTS

Table 5 compares the direction of the changes in acid-base parameters of the venous blood following infusion of solutions. Two kinds of statistical tests were applied to assess the degree of changes in blood parameters over time. When the total number of animals observed in a trial was four, repeated measurements were employed. The BMDP 2V program for repeated measurements with balanced design was chosen for the analysis of variance. One-way ANOVA BMDP2V.6 (one within subject, deleted grouping factor) was used for the time effect analysis. Friedman's ANOVA was used as a nonparametric test for this set of data. In addition, correlation between time as a quantitative factor and each response variable was measured by polynomial regression. Frequency distribution of all data, grouped by variable, was symmetrical (Frequencies, SPSSX).

Table 6 presents a summary of the variables which were

statistically significant ($p < 0.05$) in the time effect analysis, all treatments are included.

Three separate statistical analyses were conducted with the data. Due to the small sample size (n=4) in the presence of repeated measures in the same group of animals over a prolonged period of time, only descriptive statistics were possible. A one-way analysis of variance (excluded grouping factor) was compared with the result of Friedman's ANOVA (ranking of data), and a Regression analysis (correlation between time and the dependent variable) were employed. This was done to identify the variables which were most consistently changed and to increase confidence in these changes. The distribution of data (by variable) within each treatment (group) was symmetrical, despite the small sample size (Frequencies, SPSS-X). The preliminary assessment showed that the changes in pH were comparable with the result numerical analyses. The one-way Analysis of Variance (BMDP 2V.) was chosen to assess the changes produced by a particular treatment or infusion. The two-way ANOVA BMDP 2V. allowed an assessment of the treatments under the influence of time. A multiple comparison test (Duncan SAS) was chosen as a follow-up test to differentiate between control and treatment effects, and to conduct comparisons between treatments. All of these tests were selected as the most appropriate for an assessment of repeated measures within a small sample size (Marks, 1982). Raw data used to produce Figures 6 to 13 are found in Appendix I.

3.2.1 Nonemetics

Nonemetic treatments, although they did not lead to

vomiting, were associated with large changes in certain blood parameters, proved to be statistically significant. These include: lactic acid, sodium lactate, and sodium bicarbonate. Figures 6 and 6(a-d) show statistically significant changes in blood pH, base excess, gases and bicarbonate from the infusion of 3 nonemetics and control infusion.

Lactic acid produced a significant decrease in the pH of venous blood ($p < 0.05$). Significant changes were also seen in BE, HCO_3^- and total CO_2 (pCO_2). The duration of infusion was restricted to 30 min (total lactic acid infusion 32 mM). Preliminary experiments showed that after this time the various parameters returned to normal values despite continuous infusion (Gladden, 1983). The same variables were significantly changed in case of sodium lactate administration. The direction of response was opposite because sodium lactate caused a rise in blood pH.

Statistically significant changes in blood pH, BE, HCO_3 and total CO_2 were observed during treatment with sodium bicarbonate. The two different solutions of mannitol (674, 904 mOsm/L) were used. Mannitol 674 mOsm/L influenced the pH of blood (decrease) without significant changes in other parameters.

3.2.2 Emetics

Figures 7 and 7(a-d) present the response of venous blood constituents to treatments which caused vomiting. Ammonium chloride as an intravenous 0.4M solution caused a significant decrease in the blood pH, BE, HCO_3^- (and total CO_2). The same changes in venous blood, except changes in pH, were produced by the 0.8 M gavage in 40 ml of water. Other treatments (ammonium chloride 1.6M in 20 ml of water, and ammonium bicarbonate) did not produce significant changes in the blood parameters (pH, blood gases, bicarbonate), but initiated some vomiting.

3.3 EMETICS: INTERACTION BETWEEN TIME AND TREATMENT

A two-way Anova BMDP 2V.11 for repeated measurements was used to assess the degree of the interaction between time and treatment (balanced design, two within subject factors, no grouping factor). The result of the calculation is summarized in the Table 7. Only factors undergoing significant changes are listed;

R = a treatment effect,

S = a time effect,

RS = an interaction of treatment and time.

The treatments are grouped in five sets to analyse different

physiological problems. Saline 0.9% was the control solution in all sets.

Set I: In this grouping, the control solution was compared with other treatments which were expected to significantly influence blood parameters. Time trend analyses confirmed these expected effects.

The effect of time (R) on blood parameters revealed significance between treatments with respect to pH, BE and HCO_3^-. However, no treatment differences were found (S). There was a significant difference between treatments in respect to interaction between time and treatment (RS) in the following parameters; pH, BE, HCO_3^-.

Set II: This grouping gave information concerning significant differences between treatments, which varied with respect to osmolality, and chemical composition. These trials tested the influence of osmolality on the induction of emesis.

The time effect showed significant differences between treatments in pH, BE, HCO_3^- and total CO_2. A treatment effect was revealed for pH only. The interaction of time and treatment was different in this group of solutions for all four parameters: pH, BE, HCO_3^- and total CO_2.

Set III: This group of compounds compared the action of ammonium chloride given by two different routes. Also three different concentrations of ammonium chloride were used in this trial.

A time effect was seen for the pH changes only. A treatment effect was evident for BE, HCO_3^- and total CO_2. There was no difference in interaction of time and treatment.

Set IV,V: Comparisons were made to determine the differences between control and two emetics - ammonium chloride and cisplatin. The cisplatin data were divided between sets. In Set IV a comparison was made with the first part of cisplatin treatment, i.e., the infusion time.

Significant differences in the time effect were present between treatments in pH, BE and HCO_3^-. The same parameters were affected by a treatment effect. Interaction of time and treatment indicated differences between treatments in the same blood parameters.

In set V, the same treatments were compared with the later cisplatin data, which corresponded to the period from the end of the infusion period up to the beginning of emesis.

A time effect was seen for BE alone. The treatment effect was seen in the levels of BE, HCO_3^- and total CO_2. The interaction between time and treatment was significantly different with respect to pH and BE.

3.4 MULTIPLE COMPARISONS BETWEEN TREATMENTS (MEANS); DUNCAN TEST

Multiple comparisons of the means of each trial (equal number of subjects) were made to reveal significant differences between individual treatments. Duncan test (SAS General Linear

Model) was used as a follow-up test after analysis of variance. Consideration was given only to the treatments with significantly changed variables. The Duncan test in the SAS package was chosen as the most appropriate for a repeated measures design (Marks, 1982).

Table 8a and b contains the result of the Duncan tests.

Table 8a shows comparisons of control solution (Saline 0.9%) with the various treatments.

Significant differences are represented by the * symbol. A blank space zero means that no significant difference was found in the control vs treatment comparison. Significant differences were found in all parameters except:

- pO_2 in ammonium chloride intravenous
- pO_2 in ammonium chloride 20 ml gavage
- pH, pO_2, BE, HCO_3, total CO_2 in ammonium bicarbonate
- pO_2 in lactic acid
- pCO_2, pO_2 in sodium bicarbonate
- pH, BE, HCO_3^-, total CO_2 in mannitol 904 mOsm/L
- pCO_2, pO_2, BE, HCO_3^- & total CO_2 in mannitol 674 mOsm/L
- pH, pCO_2, pO_2, BE, HCO_3^- & total CO_2 in cisplatin

In Table 8b, the control solution (saline) was excluded. The treatments were compared, each to the other, on the basis of significance in a two-way ANOVA analysis. In Set I, sodium lactate and sodium bicarbonate were not different. All other treatments significantly varied with respect to pH, BE, HCO_3^- and total CO_2.

In Set II all treatments were significantly different, except for the two solutions of mannitol (BE, HCO_3^- and total CO_2).

In Set III all treatments produced significant differences in pH. No significant difference was found between intravenous ammonium chloride and 40 ml gavage, in BE, HCO_3^- and total CO_2. A 20 ml gavage produced significant differences relative to other treatments in all 4 parameters.

In Set IV and V all parameters were significantly different.

3.5 OSMOLALITY AND EMETIC TREATMENTS

The influence of osmolality of the infusate on vomiting was tested with several solutions. Mannitol of two different osmolarities was used. One solution (674 mOsm/L) was hypertonic to the blood, but hypotonic to ammonium chloride 0.4 M (733 mOsm/L). The second infusion (904 mOsm/L) was hypertonic to both blood and ammonium chloride 0.4 M. Sodium lactate was also compared as this ionic solution was hypertonic to blood (802 mOsm/L).

Significance of changes in blood pH, gases, and bicarbonate seen following these hypertonic infusions are presented in Table 6 (time effect).

4.0 BLOOD CONSTITUENTS AND STIMULATION OF EMESIS

These analyses focussed on the differences between the values of a blood parameter measured at the beginning (before treatment started) and at the time immediately preceeding emesis.

A statistical program - SAS ANOVA (GLM procedure) for repeated measures design (contrast to level 1) was used. Each time point was compared to the pretreatment (time 1) control level. Significantly changed variables were identified. The time during which these changes developed corresponded with the latency period for emesis.

Table 10 presents a summary of the changes in blood pH, gases, bicarbonate and ammonia during the latency period up to the first emetic episode.

Between emetic treatments, the most intense changes in the blood gases and bicarbonate occurred during the intravenous infusion of ammonium chloride and from the joint treatment of sodium lactate followed by sodium sulphate. Other infusions influenced only pH or had no effect. The ammonia level in the plasma rose during administration of all solutions containing ammonium chloride. The plasma ammonia level was not measured for ammonium bicarbonate. Dual infusion of sodium lactate-sulphate did not cause vomiting in three of the four animals. In these trials the plasma ammonia level remained unchanged. One animal vomited and a concident rise in the plasma ammonia was observed. No statistical assessment in this case is possible, but the norm for fasting blood ammonia level was exceeded.

5.0 SITE OF ACTION OF AMMONIUM CHLORIDE: INTRAVENOUS VS INTRAGASTRIC ROUTE OF ADMINISTRATION

The aim of this study was to localize the site of action of

ammonium chloride. In particular, the question was asked, "Does ammonium chloride activate chemoreceptors at the central nervous system level (Chemoreceptor Trigger Zone)?". For this purpose, two routes of administration of this chemical were tested and compared: one - intravenous, the second - intragastric.

Animals were treated with three different concentrations of ammonium chloride in water (total dose 1.71 g in each solution):

0.4 M in 80 ml of water as an intravenous infusion,

0.8 M in 40 ml of water as an intragastric gavage,

1.6 M in 20 ml of water as an intragastric gavage.

Blood pH, gases and bicarbonate were measured in the group of four animals. Comparisons were made between both routes of administration. The measurements included length of the latency periods and the absolute level of each blood parameter. The magnitude of the changes, the effect of time and treatment, the interaction between time and treatment and particular differences between treatments were listed previously in the Tables 6,7,8a,8b.

The following summary addresses the salient points in these analyses:

Time effect. Significant changes in blood pH, BE, HCO_3^- and total CO_2, occurred during the infusion of the ammonium chloride and gavage NH_4Cl in 40 ml (except pH). The direction of the changes was similar in both cases.

Interaction. No difference was found in the interaction of time and treatment, as compared between saline, intravenous

ammonium chloride, gavage in 20 ml, and gavage in 40 ml. (RS = nonsignificant).

Duncan test. Comparison to the 0.9% Saline was significantly different for intravenous ammonium chloride (pH, pCO_2, BE, HCO_3^- and total CO_2), for gavage 1.6 M in 20 ml (pH, pCO_2, BE, HCO_3^-, total CO_2), and for gavage 0.8 M in 40 ml (pH, pCO_2, pO_2, BE, HCO_3^-, total CO_2).

Comparison between each of the treatments provided significant differences in:

pH - all treatments varied

BE, HCO_3 and total CO_2 - varied for 20ml gavage.

6.0 ROLE OF CENTRAL CHEMORECEPTORS

Two of the four animals underwent surgery and selective lesions of the area postrema (AP) were produced. Two AP ablated animals were tested again with APO and 15% saline 20 ml gavage. An emetic response to APO persisted in 1 animal (latency 2.45 min). Both animals vomited to 15% saline gavage, the first at 1.28 min, and the second at 3.05 min. Blood gases and bicarbonate were measured in ablated animals for a second treatment with ammonium chloride (iv and 20 ml gavage). In addition, measurement of ammonia levels was performed. Only descriptive statistics were designed for this analysis since the responses of two (the same) animals was compared before and after AP ablation. Ammonia levels were assessed between two different pairs of subjects, two of them intact and two AP ablated.

6.1 APN vs APX; ACID-BASE STATUS OF THE VENOUS BLOOD

FIGURES 8 and 8(a-d), 9 and 9(a-d) and 10 and 10(a-d) present the time effect of the changes in blood parameters (pH, BE, HCO_3^-, total CO_2). Since ammonium chloride was used as an experimental treatment, only the significant variables determined by previous tests were taken into consideration.

The comparison between changes in APN vs APX animals focussed on the direction of changes, the similarity of response between each individual, the time of maximum change and the highest level of response.

The time trend of all treatments (intravenous and gavage) was in the same direction, and was associated with a decrease in measured blood parameters (pH, BE, HCO_3^-, total CO_2).

The response of AP ablated (APX) animals to intravenous treatment was altered when compared with animals with intact AP (intravenous treatment) and with AP ablated animals (gavage). The changes in APX animals to intravenous treatment seem to be intermediate in both the time to develop and the degree of change in blood parameters. Intravenous treatment in APX animals are faster than via the intravenous route in APN subjects, but slower than from gavage APX. The magnitude of changes developed by AP ablated animals due to intravenous treatments were intermediate to those seen in other trials (APN iv, APX gavage).

6.2 APN vs APX: AMMONIA LEVELS IN PLASMA

Ammonia levels in the plasma were measured in four different subjects, two of them intact and two of them AP ablated. Two ways of drug administration were tested: intravenous and gavage. Figures 11 and 11(a-c) present the time trends and quantitative changes in the ammonia level. The ammonia level increased more quickly in i.v. vs gavage treatment with ammonium chloride. There were no obvious differences between the AP intact and AP ablated animals with respect to a rise in ammonia level.

The comparison of the change in ammonia levels was limited because of the small number of subjects and considerable disturbances in the infusion rate in one of the APN trials (4). The assessment focussed on the range of ammonia (NH_3) levels in the plasma. The absolute measurements of NH_3 levels at the time of emesis are presented below.

TIME (min)	SUBJECT	µg/100ml	µmol/L
2.7	2	510	299.5
5.2	1	530	311.2
9.7	1	1100	645.9
9.9	1	1100	645.9
19.8	1	650	381.7
54.3	2	980	572.5

7.0 SUMMARY: AMMONIA AS AN EMETIC FACTOR

A rise in plasma ammonia occurred in all animals during administration of a solution containing ammonium chloride. An increase in free plasma ammonia was also observed during the infusion of some compounds not containing ammonium ions (sodium lactate - sodium sulphate). The emetic response associated with the rise in ammonia level in the plasma was 100% positive in the normal subjects (ammonium chloride).

The emetic response to ammonium chloride was absent in the area postrema ablated animals. In the same subjects postsurgical emesis was noticed following excessive drinking of water (one animal) and from apomorphine hydrochloride (one animal). Both AP ablated animals vomited to gavage with 15% saline.

8.0 SUMMARY: CISPLATIN - CHEMOTHERAPY ASSOCIATED VOMITING

The antineoplastic agent cisplatin was given to four animals (two area postrema intact and two ablated) to explore the cause of emesis associated with chemotherapy. The purpose of this last trial was to determine the relevance of the preceeding infusions to a specific clinical problem. Significant changes in pH of the venous blood were seen in the cisplatin-treated animals. This is shown in Table 6 (time effect) and in Figure 12. A comparison with saline and ammonium chloride revealed significant differences in the interaction between time and treatment among these solutions and cisplatin (Two-way ANOVA BMDP 2V.11). The comparison between treatments performed by the Duncan test SAS revealed no difference between control treatment (saline) and

cisplatin. Statistically significant differences were seen between ammonium chloride and cisplatin with respect to BE, HCO_3, and total CO_2.

Ammonia levels in plasma did not exceed normal limits in cisplatin-treated animals (Figure 13). At the starting point of vomiting, a rise in the ammonia level was seen in three of four subjects. However, no statistical significance was found.

The emetic response was similar and striking in all four animals (APN and APX). The number of emetic episodes ranged from 5-13. The latency period for vomiting was 138-184 minutes from the beginning of infusion (76-124 min after the end of the drip).

Physical findings indicated a stressful appearance of the animals. The oral mucosa of the three of four animals was very pale and greyish-blue in colour. No vascular refill was present. The 2 animals maintained for a further 24 hr prior to tissue sampling gradually improved and were symptomatically normal by the next day.

9.0 HISTOLOGY OF THE AP IN ABLATED ANIMALS

Paraffin blocks containing segments of medulla proved to be unusually difficult to cut. The tissue was very hard and tore easily. It is not known if this was due to an error in tissue fixation or processing or to some feature of cisplatin cross-linking. Analysis of cresyl violet stained sections showed that the electrolytic lesions were discrete and complete. No AP remnants were identified and no deep lesions, indicative of damage to underlying tissue and centres, were seen.

Figures 4a and 4b are representative light micrographs from the two APX animals. As seen in these figures, underlying tissues expecially the DMV and NTS are intact. As mentioned previously, functional capability of this important visceral afferent terminus (DMV) and integrative centre (NTS) was proved by the persistence of an emetic response to hypertonic saline gavage.

10.0 BLOOD ELECTROLYTES IN INDUCTION OF EMESIS

An aliquot of plasma was taken to measure the concentration of sodium (Na^+) and potassium (K^+) for each time point. Table 9 presents changes in Na^+ and K^+ levels which were statistically significant. SAS GLM procedure for repeated measures was employed to compare each time level to control (Time 1). An overall significance due to each treatment separately was detected for sodium lactate-sodium sulphate infusion, sodium bicarbonate and mannitol 904 mOsm/L. Comparison of each time level to baseline revealed significant differences also in treatments with ammonium chloride (intravenous, gavage 40 ml) and cisplatin. Potassium levels were seen to change significantly at times just prior and post-emesis in animals treated with ammonium chloride. Overall, cisplatin did not cause major disturbances in K^+ and Na^+ levels during the whole treatment. Nevertheless, it produced significant differences in Na^+ between time 1 and time 4 and time 5. Time 4 corresponds to the 45th minute of cisplatin infusion, and time 5 to the 60th (final) minute of treatment. Significant changes in the K^+ level started at time 3 (the 30th

minute of infusion) and lasted until the 45th min of observation. After 60 min, blood Na^+ and K^+ returned to pretreatment levels. Normal levels persisted for the remainder of the observation period, although some minor decreases in K^+ occurred at each emetic event. During treatment with cisplatin, both K^+ and Na^+ decreased. This is unlike the situation with other treatments. Sodium sulphate-sodium lactate infusion, or sodium bicarbonate treatment caused a gradual rise in Na^+ and a decrease in K^+. Mannitol (904 mOsm/L) infusion was associated only with a decrease in Na^+.

DISCUSSION

1.0 THE ROLE OF ACID-BASE DISTURBANCES IN THE INDUCTION OF VOMITING.

> "The term chemoreceptor is used to refer to those receptors in sense organs which are stimulated by a change in the chemical composition of the environment in which they are located. These include receptors for taste and smell as well as visceral receptors such as those sensitive to the changes in the plasma level of O_2, CO_2 and osmolality."
>
> Ganong, 1973

The aim of the present study was to confirm the existence of central chemosensitivity related to emesis, while focussing on disturbances in acid-base homeostasis. Experimental evidence on emesis and chemosensitivity was provided by Borison and Wang in their classical experiments in 1951-1952. They initiated emesis by intravenous administration of noxious substances, and prevented vomiting by ablation of area postrema. By way of peripheral denervation or intravenous stimulation vs. the intragastric route, they localized the action of some drugs and chemicals (such as APO) to the region of CTZ, located within the area postrema.

In this study, the experimental set-up was organized according to the methods used by investigators exploring central chemosensitivity and the control of respiration. No references were available relating emesis to central chemoreceptors besides pharmacological experiments involving stimulation and ablation of the area postrema by Borison and Wang (1952). Table 2 shows the treatments which were used in this study. Their sequence and constituents were chosen according to their specific physico-chemical properties. The primary goal of the investigation was to explore the role of blood pH in the induction of emesis. This assumption was formulated because Hydrogen ion (H^+) was known to be a major stimulant controlling respiration.

Ammonium chloride was chosen since it is a commonly used acidifying agent which is known to produce metabolic acidosis. Also, repetitive emetic events had been observed by Kucharczyk, Hetenyi and Paradis (unpublished data, 1985) following NH_4Cl infusion in experiments not related to this study. After a series of control infusions with 0.9% sodium chloride, the acidifying and emetic potential of ammonium chloride was confirmed in preliminary trials. These infusions resulted in changes in blood acid-base homeostasis associated with emesis in all cases. Intravenous injection of ammonium chloride produced a decrease in venous blood, pH, BE, and HCO_3^- (Figure 7 and 7(a-d)). Ammonium chloride was established as the reference emetic for further consideration.

The systematic analysis of the physico-chemical features of

NH_4Cl were performed as a second step in this study. A discriminant analysis was applied to eliminate nonemetic characteristics of NH_4Cl and to define the emetic feature. The infusion of lactic acid was chosen next to mimic the plasma acidosis induced by ammonium chloride. The lowering of blood pH was associated with a decrease in BE, HCO_3, pCO_2 and tot.CO_2 (Figures 6 and 6(a-d)). Emesis did not occur in response to lactic acid infusions. The next treatment, sodium lactate, was infused to explore whether emesis is initiated during increases in the pH of blood. In addition, the possibility that the accumulation of lactate created an emetic factor was investigated. Again, emesis was not observed. Blood pH increased, as well as BE, HCO_3 and tot.CO_2 during treatment with sodium lactate (FIGURES 6 and 6(a-d)). The above experiments led to the conclusion that changes in blood pH (either an increase or a decrease) are not essential in the induction of emesis.

An attempt was made to explore the role of Cl^- by infusion of HCl. However the necessary infusions were associated with local irritation and were discontinued. An infusion of sodium lactate could have some effect on blood chloride ions since the solution contained Na^+ and was hypertonic to the blood (802 mOsm/L). Only this indirect evidence permits the suggestion that Cl^- are not involved in the emetic response.

Following the experiments which addressed the question of pH, the involvement of blood bicarbonate was explored since bicarbonate was seen to decrease during infusion with ammonium

chloride. Lactic acid was used to lower blood bicarbonate and since vomiting did not occur, a decrease in blood bicarbonate was eliminated as an emetic factor. Sodium bicarbonate was administered then to check the effect of a rise in blood bicarbonate associated with the rise in pH, BE and tot.CO_2 (Figures 6 and 6(a-d)). The role of sodium was already explored by treatment with sodium lactate and appeared to be not significant in the initiation of emesis. Vomiting did not occur in response to intravenous treatment with sodium bicarbonate. This eliminated the rise in the blood bicarbonate as a possible emetic factor.

The problem regarding the action of NH_4^+ or NH_3 of the ammonium chloride solution, still remained unanswered. Another treatment, ammonium bicarbonate, was used to clarify the role of ammonium ion or ammonia in the induction of emesis. Ammonium bicarbonate had the same ammonium ion in its molecule as NH_4Cl. However, the bicarbonate ion has alkalizing properties, in contrast to the chloride ion. The intravenous infusion of ammonium bicarbonate caused some variations in blood pH. However, these were smaller than those due to NH_4Cl, and went in both directions. All other blood parameters did not change significantly. Emesis occurred in 50% of animals, comparing with 100% response following NH_4Cl. The latency period before the first emetic event was longer than that seen with ammonium chloride.

Finally, dual infusions of sodium lactate immediately

followed by an equal amount of sodium sulphate were administered. Changes in all blood parameters, pH, pCO_2, pO_2, BE, HCO_3^- and tot.CO_2 were significant, but only one of four animals vomited. The latency period was much longer than with previous treatments; vomiting occurred 55 min after the end of infusion. Table 5 presents a summary of the direction of changes in blood parameters due to various treatments.

Observations of ammonium bicarbonate effect led to conclusion that: 1. ammonium ion was of major importance, since there was no significant change in the blood parameters, especially when compared with other treatments; 2. bicarbonate level in the blood may be involved in the initiation of emesis in a secondary reaction, since substitution of Cl^- for HCO_3^- in conjunction with NH_4^+ prolonged the latency period prior to emesis; 3. the highly significant disturbances in the acid-base induced by infusion of sodium lactate followed by sodium sulphate evoked vomiting in one of the four subjects. It suggested that strong and fast variations in the blood pH, pCO_3, pO_2, bicarbonate and total CO_2 were not the primary stimulus for emesis.

The effect of iv administration of mannitol was analyzed because 0.4 M NH_4Cl was hypertonic. The total amount of mannitol infused was 11.1g in 80 ml of 904 mOsm/L solution, and 8.8g in 80 ml of 674 mOsm/L solution. Since the average weight of the animals was 11 kg, the dose was 0.8-1.0 g of mannitol/kg of body weight over 60 min. The dose required to evcke diuresis in a

renal test is 200 mg/kg, when given intravenously within 3-5 min (Martindale Pharmacopoeia, 1982). Reduction of increased intracranial pressure requires iv administration of 1.5-2g/kg body weight over 30-60 min (Martindale Pharmacopoeia). The total amount of mannitol given to the animals during every trial was sufficient to produce a renal response, but did not reach the level recommended to decrease intracranial pressure. This prediction is confirmed in part by the observation that behaviour and consciousness of the animals was not altered. The statistical analysis showed significance in the time effect of pH during infusion of mannitol 674 mOsm/L. All other parameters were not significantly changed. This suggests that blood parameters were slightly influenced by pH of the infusate. The osmolality of both solutions was hypertonic to the blood, the 904 mOsm/L mannitol was also hypertonic to the 0.4 M solution of ammonium chloride. All these treatments were infused into the same group of animals within the same time period, and at the same rate. Vomiting occurred only in response to NH_4Cl. This excludes hyperosmolarity of the ammonium chloride solution as a possible emesis producing factor. However, this does not constitute the final statement on the involvement of osmolality in the induction of emesis.

The statistical analyses of the results obtained during this study are presented in Tables 6,7,8a and8b. The significant changes in the blood parameters produced by each treatment are summarized in Table 6. Sodium lactate-sodium sulphate infusions

produced significant disturbances in all blood parameters. Lactic acid, sodium lactate and sodium bicarbonate significantly changed blood pH, BE, HCO_3^- and tot.CO_2. Mannitol 674 mOsm/L, ammonium bicarbonate and cisplatin influenced only pH of the blood, without major disturbances in other parameters (Figures 6 and 6a-d, 7 and 7a-d). Vomiting was noted in association with NH_4Cl iv and gavage, NH_4HCO_3, cisplatin and sodium lactate - sulphate infusion.

It is well known that ammonium chloride produces acidosis in the blood while NH_4^+ ion dissociates with Cl^-. Ammonia (NH_3) leaves the plasma and enters blood cells (Loeschcke and Sugioka, 1969). Molecules of NH_3 are highly soluble in lipids and their diffusion coefficient is high. NH_3 diffuses according to the pH gradient, from a compartment of higher (blood) to lower pH (muscle or CSF). The titration of the major extracellular buffer (bicarbonate) by Cl^- and H^+, causes a decrease in HCO_3^- in the blood. Blood constituents, pCO_2 and pO_2, were not factors in the present study, since changes seen with NH_4CL were not significant (Florez et al., 1967). Not all statistical tests applied in this study confirmed the significance of changes in tot.CO_2 following the intravenous infusion of NH_4Cl.

The acidosis in the blood due to lactic acid was caused by the high concentration of H^+ ions introduced by the intravenous route. Lactate is a small molecule which does not possess strong ionic properties. After 1.5-2 hrs of infusion, lactate

is metabolized to bicarbonate (Martindale Pharmacopoeia, 1982). The sodium lactate dissociated in the blood to Na^+ and lactate. In preliminary trials, both infusions of lactic acid and sodium lactate were compensated by blood buffers after 30 min of infusion. This is in agreement with the observation reported by Gladden (1983).

The sodium bicarbonate caused an increase in blood pH, BE and bicarbonate which lasted longer than those caused by lactate. The alkalosis was persistent for several hours after infusion. The slow exchange with Cl^- ions by the kidney compensated for the increased bicarbonate level in the blood. The acid-base disturbances produced in the blood by ammonium bicarbonate had characteristics of bicarbonate and ammonia actions. Small variations in blood parameters occurred but these were not statistically significant. Presumably, as with the effect seen with NH_4Cl, NH_3 diffused to the compartments exhibiting a pH lower than normal blood (Loeschcke and Sugioka, 1969)). This left bicarbonate in the blood. The pH gradient (blood-CSF) between compartments with lower pH and the blood became reduced. In contrast, while ammonia diffused from the blood during NH_4Cl treatment, the gradient of pH (blood-CSF) became reversed. Compartments of lower pH became alkaline, and the blood became acidotic. Both situations changed the pH (blood-CSF) gradient by NH_3 entering the compartment of lower than blood pH. This would explain why both treatments were associated with emesis. The reduction of the gradient during treatment with ammonium

bicarbonate may be the reason for the delay in the initiation of emesis. In this case, either the increasing level of NH_3 entering CSF itself, or decreasing blood-CSF pH gradient (alkalosis in both compartments, intracellular and extracellular) may be responsible for delayed emesis.

2.0 THE ROLE OF CHEMOSENSITIVITY IN THE MECHANISM OF RESPIRATION AND EMESIS:

The most accurate results regarding possible blood-CSF relationships during acid-base disturbances produced by the above treatments would be collected by direct measurements of CSF parameters. Monitoring of the CSF acid-base status was not possible in the present study, hence literature relevant to CSF parameters is presented below. The study summarized below mainly concerns the problem of central chemosensitivity and CSF-blood, acid-base relationships influenced by treatments similar to those used in this study.

The study by Loeschcke and Sugioka (1969) is important to the topic of CTZ and experimental disturbances in acid-base parameters. Continuous measurements of the pH of the cisterna magna and the surface of the choroid plexus of the fourth ventricle were conducted. In addition, tidal volume, expiratory CO_2 partial pressure and arterial pressure were recorded. Transient and steady states were created by inhalation of CO_2, and the iv injection of HCl, $NaHCO_3$, NH_4Cl and ammonium carbonate $(NH_4)_2CO_3$. A surgical technique was developed to place a small

glass electrode on the surface of the lateral part of the choroid plexus of the fourth ventricle without damaging the surrounding tissue. The local pH was recorded continuously. In comparison experiments, the glass electrode was introduced into the cisterna magna. The data obtained during transient and steady states, are presented below. These should be viewed in comparison with the changes in venous blood parameters measured during the present study which used similar treatments.

PRESENT STUDY

	ENDTIDAL pCO_2	ARTERIAL pH	CSF pH	VENOUS
pCO_2	increased	decreased	pH CSF followed almost immediately, the changes in arterial pCO_2	not measured
HCl	transient increase	decreased	pH was constant or exhibited a decrease on the surface of the plexus	discontinued
NH_4Cl	early increase in respiration followed by depression	pH decreased (biphasically)	abrupt increase in pH	decrease
$(NH_4)_2CO_3$	initial increase in respiration then marked depression followed by diminished respiration	pH increased (bicarbonate)	abrupt increase in pH	NH_4HCO_3 variations, not significant in either direction
$NaHCO_3$	initial increase, then marked decrease	increased slowly but long lasting	decreased or constant	increased slowly, long lasting

The study of Loeschcke and Sugioka (1969) focussed on respiration. The present study explored chemoreception in the mechanism of vomiting. The following observations were made by Loeschcke and Sugioka (1969).

In contrast to ammonium bicarbonate, NH_4Cl initially increased respiration. This was followed by slight respiratory depression. Ammonium bicarbonate depressed respiration faster and much stronger. These changes were related to the reciprocal changes in arterial pH. NH_4Cl causes a decrease in arterial pH, while $(NH_4)_2CO_3$ raises it. It was concluded that the action of ammonia on a receptor is the most probable stimulating factor. The level of ammonia was not measured in their studies, but rapid penetration of ammonia into CSF was assumed. Since the solubility of α NH_3 is abnormally high (80 times α CO_2) the diffusion should be rapid, even in case of low NH_3 levels (Crone, 1965). According to Loeschcke and Sugioka (1969) ammonia also enters the cells of the brain. Distribution depends on the gradient in pH between brain tissue, and blood and CSF. The permeability of brain barriers to the NH_3 molecule (present in ammonium salts) generates bicarbonate in the CSF. One molecule of NH_3 generates one ion of HCO_3^-.

$$NH_3 + H_2CO_3 \rightleftharpoons NH_4^+ + HCO_3^-$$

Loeschcke and Sugioka (1969) concluded that all documented and inferred changes resulting from their study were inconclu-

sive, and did not allow them to state which chemoreceptor was activated - central or peripheral. The possibility exists that both were affected.

The effect of lactic acidosis and ketoacidosis on blood-CSF-brain relationships in man was studied by Marks and coworkers (1973). They focussed on the relationship of the CSF organic acid concentration to the CSF bicarbonate level, and to pH regulation of organic acidosis due to various diseases. The results of their study were as follows:

1. CSF (lumbar) organic acid concentration paralleled the increase in acid concentration in the blood, but at lower than plasma level.
2. CSF bicarbonate decreases as arterial bicarbonate decreases.
3. CSF bicarbonate - organic acid relationships were near equimolar (decrease in bicarbonate opposite to the increase in acid concentration).

This study demonstrated that efficient regulation of CSF pH is not maintained in the presence of a severe reduction of CSF bicarbonate concentration. This perhaps explains the absence of vomiting seen in the present study with lactic acid. Since CSF alkalization, not acidification, likely leads to vomiting.

3.0 CHEMOSENSITIVITY IN THE INDUCTION OF EMESIS:

The summary on page 59 compares the time course of the acid-base disturbances due to NH_4Cl, NH_4HCO_3, $(NH_4)_2CO_3$, $NaHCO_3$

and HCl in arterial blood, CSF and venous blood. The findings assessed as significant in this study are comparable with the results obtained by Loeschcke and Sugioka (1969). Although speculations regarding CSF acid-base disturbances cannot replace experimental measurements, the study of Loeschcke and Sugioka (1969), and Marks et al. (1973) can shed some light on the present investigations. With respect to established knowledge on central chemosensitivity, certain characteristics seem to be in common for both mechanisms, respiration and vomiting.

1. The direction of the changes in the arterial and venous blood were similar in such treatments as NH_4Cl, NH_4HCO_3 $(NH_4)_2CO_3$, $NaHCO_3$.
2. Ammonium chloride acidosis did not produce major changes in entidal pCO_2 (Loeschcke and Sugioka, 1969), or in pCO_2 and pO_2 of the venous blood.
3. Acidosis due to NH_4Cl had a stronger influence on respiration than acidosis produced by HCl. In the present experiment, NH_4Cl led to vomiting, lactic acidosis did not.
4. Sodium bicarbonate did not exert a significant effect on respiration and CSF pH, neither did it cause emesis.
5. Ammonium carbonate influenced respiration, and ammonium bicarbonate evoked emesis in some animals.
6. The initial increase of respiration by NH_4Cl was different than the response pattern from $(NH_4)_2CO_3$, which was characterized by marked depression of respiration. With respect to emesis, NH_4Cl caused vomiting in 8-15 min from

the beginning of infusion, while NH_4HCO_3 was effective after 36-51 min from the start point.

7. The occurrence of emesis, induced by NH_4Cl and NH_4HCO_3, despite difference in changes in acid-base of the blood, suggests NH_3 as an emetic factor. Loeschcke and Katsaros (1959) proposed NH_3 as a substance stimulating respiratory chemoreceptors in a manner similar to H^+. They considered the possibility that NH_3 enters the receptor cells and changes the H^+ ion gradient from inside to outside in the same direction, as extracellular H^+ would do.

8. The low incidence of emesis in chronic steady state diseases indicates the transient character of emetic stimulation. This agrees with the statement of Loeschcke and Katsaros (1959), that receptor cells respond to variations to the pH gradient rather than to absolute changes of H^+ concentration on either side.

9. The area on the ventral medulla defined as a site of respiratory central chemoreceptors is called glia spongiosa because of its anatomical appearance. The CTZ in AP is extremely spongiform in its structure, and facilitates contact between blood-CSF and extracellular fluid (ECF).

10. In the chemosensitive areas of the ventral medulla, the majority of the cells were activated by H^+. In brain slices of the dorsal surface of the medulla oblongata, the same type of cellular responses were observed, but here the

majority of cells was inhibited by H^+ (Shams et al., 1982). Therefore vomiting and ventilation are mutually exclusive events.

11. The application of ACh to the AP caused inhibition of ventilation. Acid had no effect. The application of ACh to the rostral chemosensitive areas produced an increase in ventilation (Mitchell et al., 1963a), again suggesting opposite effects for ventilation and vomiting.

4.0 PERIPHERAL VS CENTRAL CHEMOSENSITIVITY IN THE INDUCTION OF EMESIS

This section is devoted to the differentiation between peripheral vs. central chemoreceptors in emesis induced by ammonium chloride. Ammonium chloride given intravenously produced a significant decrease in the blood pH, BE and HCO_3^- (Figure 7 and 7(a-d)). The emesis associated with these changes can be induced by stimulation of peripheral chemoreceptors (aortic, carotid, gastric) as well as putative receptors in the CTZ. The second part of study was designed to analyze two routes of administration of NH_4Cl in order to localize the site of action of ammonium salts.

Two different gavage solutions; 0.8M NH_4Cl in 40 ml of water, and 1.6M NH_4Cl in 20 ml were administered intragastrically to the same group of animals. Gavage with 20 ml caused vomiting in all four animals. Gavage with 40 ml induced emesis in two animals and retching in a third.

The gavage 40 ml, like intravenous NH_4Cl, produced changes in blood pH, BE and HCO_3^-. Changes in these blood parameters revealed no significant differences between treatments, with respect to interaction and between treatment differences (Figures 8 and 8a-d, 9 and 9a-d). Both were the same magnitude and caused significant changes in blood acid-base. The direction of changes in blood variables was the same for iv and 40 ml gavage NH_4Cl. Gavage with NH_4Cl 20 ml did not produce any significant changes in acid-base parameters of blood. Vomiting occurred in all three types of treatment with approximately the same latency period (with the exception of two cases) regardless of the different routes of administration of ammonium chloride. This suggests that ammonium chloride given as a gavage acts on CTZ the same way as an intravenous administration. NH_3 diffuses rapidly from the stomach to the bloodstream and is carried to central chemoreceptor as a blood-borne substance. Treatment with an intragastric gavage of 15% saline in the same subjects produced emesis in three of four animals, within a much shorter period of time. This very short latency is indicative of vomiting induced directly by visceral irritation (Figure 5).

As a next step two of four animals had their AP surgically ablated. After complete recovery, intravenous and intragastric treatment with NH_4Cl was repeated in these animals. Two AP intact subjects had repeated intravenous treatment with ammonium chloride, since techniques to measure plasma ammonia were developed at this time and included as routine assays. The

results of this study showed that ablation of the AP abolished emesis when ammonium chloride was given intravenously. This observation strongly suggests that ammonium chloride acts at the central receptors to initiate emesis. One of the APX animals vomited (at 4.5 min) in response to a 20 ml gavage with NH_4Cl. At the time of emesis, the plasma NH_3 level rose to 245 µg/100 ml from a control level of 36 µg/100 ml. The same level and more, was achieved during the intravenous infusion of NH_4Cl. However, as outlined before, the animal did not vomit to iv NH_4Cl, post APX. The short latency seen here with a 20 ml gavage is more similar to that observed with hypertonic saline gavage (approximately 3 min), than it is to that achieved with an iv infusion or a 20 ml NH_4Cl gavage in APN animals (about 11 min). It is possible that in the case of the APX respondent, visceral receptors were primarily responsible for the emetic response. Harding et al. (1987) have reported that for some emetic stimuli, (i.e. irradiation) central and peripheral receptors contribute parallel emetic stimuli, although in their case the peripheral ones were less sensitive. The persistence of the emetic response to a hypertonic saline gavage in the APX animals indicates the discrete nature of the lesions and proves that emetic stimuli provided via the vagus from the periphery is intact. Perhaps in the APX respondent, the visceral route assumed more prominence and was sufficient to evoke emesis upon an irritating challenge with 20 ml NH_4Cl gavage.

The ammonia level in plasma showed a rapid and marked rise

regardless of the route of administration (Figure 11). The iv route differed slightly from gavage only in the time to achieve the maximum plasma level (Figures 11a-c). This difference was probably caused by the absorption time from the stomach. The rapid and significant rise in ammonia level from the gavage, and lack of changes in acid-base during this time in 20 ml NH_4Cl gavage, suggests that ammonia is the primary factor responsible for emesis, not changes in acid-base parameters of blood (Table 10). It does not exclude the possibility that gradient differences in pH and bicarbonate between blood and CSF (or ECF) are involved. This would create an emetic stimulus through changes in H^+ concentration directly. On the basis of this study, it is impossible to state whether NH_3 acts indirectly on receptors through changes in H^+ concentration within a H^+ sensitive cell ($NH_3 + H^+ \rightarrow NH_3^+$), or by direct influence on cells specifically sensitive to NH_3^+ (where changes in H^+ are intermediate). To answer this question, direct stimulation of the cells with NH_4^+ and H^+ ions, with concomittant registration of the cell action potential, would be required. The presence of ion-specific receptors within the AP seems to be probable since Adachi and Kobashi (1985) registered changes in activity of the AP neurons sensitive to Na^+ and glucose. Carpenter et al. (1986) recorded responses from AP neurons stimulated by insulin, apomorphine, leucine-enkephalin and glutamate. The stimulation by each substance was dose-dependent.

The comparison of the changes in acid-base in the same two

animals before and after surgery suggests some differences between responses of pH, BE and HCO_3^- (in intravenous routes only) before and after surgery (Figures 10 and 10a-d). The responses after surgery were less prominent. This could be caused by different buffering ability in these animals at the time of the experiment, perhaps resulting from differences in local HCO_3^- exchange between blood and CSF. The most likely explanation for the absence of emesis is that the AP contains central chemoreceptors (NH_3) which were destroyed along with some ion channels (HCO_3^-) during ablation, and these have a role in modulating the acid-base response.

The comparison of the latency periods between all emetics is presented in Figure 5. The shortest latency period was observed after treatment with 15% saline. Vomiting occurred within 0.8-3.0 min after gavage, and with one exception all animals responded. Because some of them were AP ablated, and the latency period was very short, the peripheral-gastric receptors were assumed to be stimulated by hyperosmotic concentrations of Na^+ or Cl^-. The next latency period encountered was within 1.5-2.5 min after intravenous admin'stration of apomorphine hydrochloride. All APN animals vomited, as did one of two APX animals. APO is a known dopaminergic agent and is recognized to act on dopamine receptors in the CTZ (Borison and Wang, 1953). The latency period due to treatment with ammonium chloride produced emesis within 8-15 min from the beginning of the infusion. Neither changes in the infusion rate nor different routes of

administration significantly changed this latency span. Two exceptions occurred, one when the latency period was changed to 40 and 73 min after iv and 40 ml gavage, respectively. These exceptions were likely due to differences in the animal's ability to reach a threshold level of NH_3, either in the CSF or in the cells due to higher dilution of NH_4Cl in 40 ml of water. The ammonium bicarbonate related latency period was longer because vomiting occurred between 36-51 min of infusion. The increased acidity of CSF due to increased bicarbonate in the blood can cause an increase in the total acid load in the CSF. This might bind NH_3 entering CSF, and for some time inhibit emesis. A latency period exceeding the time treatment was observed during infusion of sodium lactate followed by sodium sulphate. One of four animals vomited 55 min after the end of the last infusion. In this animal, a rise of NH_3 level in blood was probably secondary to absorption of NH_4^+ from the renal tubule. The longest latency period was observed after treatment with cisplatin in APN and APX animals. As discussed later, metabolic and other time-consuming events are necessary before emesis can occur in cisplatin-treated animals.

5.0 AMMONIA AS AN EMETIC FACTOR

5.1 METABOLISM OF AMMONIA

The metabolism of ammonia was described in a very concise manner by Powers and Meister in 1982. Ammonia is of central importance in the metabolism of nitrogen. It is a precursor of

nonessential amino acids, nucleic acids, and other nitrogenous compounds. It is also a product of protein and nucleic acid catabolism. The most important organ regulating ammonia metabolism is the liver. The steady state level of ammonia (NH_3 and NH_4^+) in the liver is 0.7 mM, and in plasma 0.07 mM. Free ammonia (NH_3) accounts for about 1%, at physiological pH (pK NH_3 = 9.25).

There are five major pathways of ammonia metabolism: a) release of nitrogen from amino acids, nucleic acid bases and amines in the form of ammonia or glutamate; b) deamination of glutamate through the action of glutamate dehydrogenase; c) conversion of ammonia to urea; d) conversion of urea to ammonia in the gastrointestinal tract by the action of bacterial urease; and, e) synthesis of glutamine (glutamine serves as a storage and transport form of ammonia).

The catabolism of protein leads in the first phase to an increased production of glutamate. Interestingly, glutamate is also a potent CNS excitatory neurotransmitter (Van Gelder, 1982). Glutamate is converted to ammonia by glutamate dehydrogenase and this constitutes the second pathway of ammonia metabolism.

The third significant source of hepatic ammonia is the intestinal flora, where 25% of urea degradation occurs. Urea diffuses from the liver into the bloodstream. The hydrolytic processes occur in the mucosal and juxtamucosal layer of the GI tract. Ammonia diffuses to the blood and is delivered to the liver, to be converted again to urea.

The fourth pathway of ammonia metabolism, urea synthesis, is closely controlled by enzymes and is responsible for the disposal of about 90% of surplus nitrogen in ureolitic organisms. Urea is formed from ammonia and CO_2 in a cycle involving ornithine, citrulline, argininosuccinate and arginine as carrier compounds. The activation of the cycle requires five enzymes. The role of the urea cycle is mainly nitrogen disposal and ammonia detoxification. Another probable role is in the maintanance of pH homeostasis, since one proton is released per turn of the urea cycle.

An equilibration between the storage of ammonia in the form of urea and the production of ammonia is essential in anabolic-catabolic reactions. The proper control of urea and NH_3 formation prevents ammonia toxicity and allows adequate synthesis of nitrogenous compounds. Coordinated changes in the quantity of urea cycle enzymes constitutes the slow control-response to metabolic disturbances. Urea is the major product of the metabolism of ammonia.

The second important product of ammonia metabolism and fifth metabolic pathway is glutamine which stores and transports ammonia. Glutamine is generated in the CNS during ammonia detoxification (Van Gelder, 1982). The conversion of glutamine to ammonia, and vice versa, is regulated by glutamine synthetase and favors glutamine synthesis. Glutamine is transported through the blood (20% of total amino acids) from the liver to the organs which can release ammonia on demand through the activity of

glutaminases. The formation of ammonia from glutamate is minor since the glutamate dehydrogenase effect on ammonia utilization is nonsignificant.

5.2 DIFFUSION OF AMMONIA INTO THE BRAIN

Lockwood et al., 1984, evaluated the diffusion of ammonia across the BBB in normal humans. They calculated concentrations of ammonia on the basis of CBF and the regional cerebral metabolic rate for ammonia obtained by position emission tomography (PET). This study showed that the permeability ratio of ammonia in gray-to-white matter was 0.37-1.0. They explained the lower permeability of the gray matter to ammonia on the basis of protection of neuronal cell bodies from the toxic effect of ammonia. They assumed that astrocytes mediated the differences in gray and white matter ammonia permeability since Martinez et al. (1977) showed that the enzymes necessary for brain ammonia metabolism are confined to astrocytes. The glia have root processes reaching the cerebral capillaries and they exhibit an intermediate ammonia permeability.

These findings are relevant to the mechanism of emesis. The AP contains astrocyte and astroblast-like cells in large amounts, and these are in close proximity to the blood vessels (Leslie, 1986). Their role is not explained yet. There are few neuronal cells in the AP (Gwyn and Leslie, 1986). This may be a protective advantage since the AP does not have a complete BBB and is exposed to the action of all blood-borne substances.

Cooper et al. (1979) showed that ammonia extraction by the

brain is proportional to the arterial ammonia concentration. The influence of the metabolites of ammonia on the CTZ should be excluded. Cooper et al. (1979) have shown that blood-borne ammonia is converted primarily to glutamine. This reaction occurred so fast that demonstration of the saturation or back-diffusion of the compound to the blood was impossible. Total flux of metabolites (glutamine and urea) was low. The rapid entrapment of ammonia after diffusion through the BBB and convertion to glutamate is a likely explanation for the observation that discontinuation of infusion containing ammonium chloride also ends emesis.

5.3 BLOOD AMMONIA LEVELS AND EMESIS

In the present study, two AP intact animals were infused with ammonium chloride and vomiting was observed in each. The ammonia level at the time of emesis is presented on page 46.

Within the range of 510-980 µg/100ml, emesis occurred twice in one of the animals, and some variations in ammonia level were noted (see Fig. 11a). These were likely caused by an irregular infusion rate, rather than the individual response of the subject. The rate of infusion changed three times during treatment. Therefore, the assessment focussed mainly on the range of changes in NH_3 levels. The second vomiting episode occurred following a slight increase in the infusion rate, after a steady state of infusion lasting 50 min. This perhaps suggests that besides an increase of the NH_3 level in the blood, the activation of emesis has a dynamic component beyond the absolute level of NH_3. The maximum rise in ammonia level in the present

trials was 1100 μg/100ml. No disturbances in consciousness were noted in the animals, although one of them had 4 episodes of emesis and started to present with "depression". The infusion in this case was discontinued at 19.9 min after the fourth emetic bout. The blood ammonia level at this time was 650 μg/100ml. This observation suggests that an ammonia level of 1100 μg/100ml closely precedes depression of the CNS as might be seen in hepatic coma. The conclusion of this experiment is that emesis is related to a certain range of NH_3 in the blood (about 290-1100 μg/100ml), and above this range depression of CNS occurs. Also, vomiting is induced by a transient increase in NH_3.

The relationship between ammonia-induced changes in plasma, CSF amino acid levels and the development of hepatic encephalopathy was studied by Schäfer et al., (1985). They measured plasma and CSF levels of ammonia and amino acids in dogs before and after portacaval shunt. Animals became comatose after 45-70 min (mean 64 min) of infusion with 10% ammonium acetate before portacaval shunt, and after 33-40 min (mean 37) of infusion following shunting. Ammonia acetate has a minor influence on blood pH. The levels of ammonia in the intact animals are listed below: (PCS - portacaval shunt, citation from Schäfer et al., 1985)

	BEFORE PCS	AFTER PCS	
	PLASMA pH=normal	PLASMA	CSF
Basal	83±18	189±63	94±41
Coma	1581±297	1984±229	423±11
Recovery	365±58	521±150	234±73

Analysis of the plasma levels of amino acids showed no correlation between glutamine concentration in CSF and signs of hepatic coma. Glutamine is the major product of cerebral ammonia detoxication. There was no correlation shown between the level of methionine, phenylalanine and tyrosine in hepatic coma. This experiment suggests that ammonia alone may be an important factor causing hepatic coma.

The typical symptoms observed by Schäfer et al. (1985) during trials were hypersalivation, retching, vomiting, hyperactive movements, stupor, convulsions and coma with no response to painful stimuli. In this study the first three symptoms were noted repetitively. The level of plasma ammonia at the comatose stage was 1581±294 μg/100ml (mentioned above). This indicates that the emesis observed in this study at an ammonia level in the range of 299-1100 μg/100ml preceeded the comatose state.

Another aspect of ammonia activity in hyperammonemia was described by Chodobski et al. (1986). They demonstrated that hyperammonemia is accompanied by an increase in intracranial pressure (ICP), CBF, and the CSF formation rate. The elevation of ICP seems to result from an increased rate of CSF production and cerebral vasodilatation. The rise in ICP was measured in cats when the ammonia level in arterial blood exceeded 400 μmol/L. The gradual but progressive increase in CBF was noted over a 2 hr period of observation. The increase in CBF reached a plateau when ammonia levels exceeded 500 μmol/L. The purpose of

the above study was to elucidate the increase in ICP in encephalopathies associated with liver failure and Rey's Syndrome. The changes in CBF and ICP developed slowly, and reached a plateau at the hyperammonemia steady state (Chodobski et al., 1986). This is in contrast with the data reported here where emesis was associated with a fast rise in arterial ammonia. Emesis appeared soon after the infusion started and stopped after withdrawal of ammonia treatment. This indicates that the rise in CSF formation rate and the increase in CBF and ICP, requires steady state hyperammonemia. In contrast, the induction of emesis requires a transient state, although the range for the NH_3 concentration in plasma is similar. The short lasting nature of hyperammonemia in NH_4Cl infusion implicates the activation of chemoreceptors. In contrast, increased ICP in steady state hyperammonemia can activate putative central baroreceptors or pressoreceptors, as well as chemoreceptors (variations in NH_3 level). Projectile vomiting is seen in the acute increase in ICP (head trauma), while it is rarely observed in increased ICP in hydrocephalus. This suggests that transient increases in ICP constitute an emetic stimulus, while prolonged steady states may have no effect on activation of baro- or pressoreceptors in the emetic reflex.

The effect of ammonium chloride on intra vs extracellular acid-base balance was studied by Rothe and Schimek (1984). Rats weighing 350-450 g were infused with NH_4Cl (0.3 mol/L) at a rate

of 3 mM/kg, over 20 min. This is comparable to procedures used in the present study. Measurements of arterial pH, pCO_2 were performed at time intervals for 6 hrs.

The calculations were made of "mean whole body" (intracellular) pH_i an overall estimate of the intracellular pH (complementary to arterial plasma pH). Three minutes after the end of the infusion, the maximal decrease in extracellular pH (pH_e) occurred. The pH_e slowly increased during the subsequent 4 hrs. The mean whole body pH_i continuously increased (faster in first 20 min), reaching a maximum of 0.082 pH units at the end of experiment. The ΔpCO_2 decreased gradually during the period of observation. A significant and constant reduction of extracellular bicarbonate was seen, but only a slightly decreased intracellular bicarbonate was observed. Therefore, NH_4Cl had an effect on extracellular, but not the intracellular buffer system.

Experiments on snail neurons in vitro (Thomas, 1974) showed that an increase in pH_i follows an increase in external NH_3 concentration. The influx of NH_3 intracellularly caused a subsequent H^+ ion uptake during the conversion of NH_3 to NH_4^+. This resulted in an increase in pH_i. The change in pH_i parallelled the influx of NH_3. Several other studies on different muscles, renal tubule and squid axon (Baron and De Weer, 1976) confirmed this observation. The hypothesis by Loeschcke (1963), Loeschcke and Sugioka (1969) and Loeschcke and Kastaros (1959) (about NH_3 entering the intracellular compartment after leaving blood) was proven to be true by these experiments. Ammonia has the ability to cross cell membranes and cause

intracellular alkalosis, which parallels the rise of NH_3 in plasma.

Carpenter et al. (1984) registered responses of neurons in the canine AP after systemic administration of various peptides in doses ranging from 0.03-0.35 mg/kg. Emetic responses were observed with angiotensin II, neurotensin, leucine-enkephalin, gastrin, vasoactive intestinal polypeptide (VIP), substance P, vasopressin, oxytocin, bombesin, thyrotropin-releasing hormone (TRH), and methionine-enkephalin. These responses were abolished by ablation of AP. The electrophysiological study of the neurons of AP showed that they were silent at rest. They were easily activated by glutamate, the well-known stimulant for CNS neurons. Other peptides evoked different potentials in the same neurons. Not all neurons responded to the same substances, which indicates localization. All cellular responses were of long latency and duration and exhibited remarkably low discharge frequencies. This corresponds well to the long and incremental character of the emetic reflex. On the basis of this study, Carpenter confirmed the role of the AP in the induction of emesis. He also proposed the existence of a species of ionic channels coupled to each receptor type or a common second messenger. This reinforces the physico-chemical approach to the activation of receptors, which was the subject of the present study.

6.0 BLOOD ELECTROLYTES AND EMESIS

There is no evidence in the literature to help explain the

correlation between an increase in plasma K^+ and the onset of emesis (Table 9). The 20 ml gavage data show that the increase in K^+ is not an absolute requirement prior to emesis. Potassium levels actually decreased (and Na^+ rose) in the dogs treated with sodium lactate and sodium sulphate, and one of these animals vomited. In the animals treated with cisplatin a decrease in both K^+ and Na^+ was seen. This was quickly reversed and the levels were normal 1 hr before the first emetic episode. Taken together, these data may suggest that transient changes in the extra- vs intracellular ionic concentration may contribute to the mechanism of emesis. However, the nature or direction of these changes permit no definitive or consistent conclusions to be drawn.

7.0 CISPLATIN INDUCED EMESIS

The last part of the present study was designed to test the emetic response to the antineoplastic agent cisplatin. This drug is known to cause delayed emesis in patients 1-4 hr after treatment. Emesis can persist for over 24 hrs, while nausea and anorexia may last up to 1 week. Cisplatin is more "emetogenic" than most chemotherapeutic compounds. Intense emesis may require a reduction in the dose of this drug, and less than optimal treatment results. Cisplatin is a water soluble metal coordination complex (diamminedichloro-platinum). The exact mechanism of action is unknown. After intravenous administration and an exchange of OH^- ion for Cl^- in the cisplatin molecule, the

modified molecule exhibits alkylating properties (Pharmacology Course Guide, 1986-87). These properties may cause cross-linking and interference with the function of DNA, and to a lesser extent RNA. Stimulation of the host immune system has also been suggested. The ability of this metabolite to bind proteins during the excretory (beta) phase is very high. The drug undergoes rapid nonenzymatic conversion to inactive metabolites. The half-life of the alpha phase is 25-49 min. The beta phase lasts 58-75 hr in normal subjects, but may last up to 240 hr in anuria. The inhibitory effect on DNA persists for several days. Cisplatin does not readily cross the BBB. Excretion is accomplished mainly by the kidney (27-43% after 5 days) and the agent is detectable in tissue 4 months or longer after administration.

During repetitive treatments cisplatin increases the level of blood urea nitrogen (BUN), serum creatine and serum uric acid (nephrotoxic effect), and decreases the level of creatine clearance, serum magnesium, serum calcium, phosphate and potassium concentration (USP-DI, 1986). Typically, cisplatin is administered as a single 50-75 mg/m^2 dose in 2 litres of 0.3-0.45% saline or 5% glucose, with 3.7 g of mannitol for intravenous infusion over 6-8 hr in man. The only available information on disturbances in acid-base and electrolytes associated with this agent refer mostly to the long-term complications of the primary disease or the anticancer therapy. Giaccone et al. (1985) evaluated disorders of serum electrolytes

and renal function during repeated treatment with cisplatin. In most of the cases cisplatin was given in combination with other antineoplastic agents. Significant decreases in serum level of K^+, Na^+, Mg^{++}, Ca^{++} were observed during chemotherapy. In catabolic stages, azotemia was detected and there was a tendency for potassium to rise in the period after treatment. Azotemia and electrolyte imbalance were reversible after adequate treatment.

In the present study, the tendency of free ammonia to rise was noted during the period of emesis. However, the level of NH_3 did not exceed the normal value for the dog or man. The blood pH was significantly changed with a decrease noted during the emetic period. Other parameters (blood acid-base) did not change significantly. The dose of the cisplatin given as a mixture with saline, glucose and mannitol was 50 mg/m^2. After a long latency period (76-124 min) this dose led to 5-12 emetic bouts in each animal. The changes in behaviour of three of four animals were marked. They exhibited a stressful appearance, a lack of interest in their surroundings, a very pale and gray-bluish color of the oral mucosa, with no vascular play or refill present. Strong emetic responses occurred in all four animals despite two of them being AP ablated. There were no differences in the emetic response of intact vs APX animals.

McCarthy and Borison (1984) reported cisplatin-induced emesis in the cat. There were several differences between their

work and the present study. The dose of cisplatin used by McCarthy and Borison (1984) was 3.0-10 mg/kg. The emetic effectiveness increased with doses in the range of 3.0-7.5 mg/kg, but decreased between 7.5-10 mg/kg. In the present study, the dose of cisplatin was calculated in milligrams per square meter. This method is more comparable with that used for antineoplastic treatment in humans. Fifty mg/m^2 in the beagles corresponds to 3 mg/kg. Also, to ensure adequate hydration, the drug was dissolved in a mixture isotonic to blood fluids, and mannitol was used to facilitate diuresis.

McCarthy and Borison (1983) reported that ablation of the AP abolished cisplatin-induced emesis in the cat. They postulated the involvement of the CTZ in the induction of emesis, but considered that it was not the primary site of action. The long latency period (71 min) does not indicate the primary involvement of CTZ. In the present study, the latency period was within a similar range, and emesis occurred in both AP ablated animals. One of them showed symptoms of malaise. Immediately after ablation, this animal vomited after drinking a large amount of water and in a later test was seen to exhibit short latency vomiting following a 20 ml gavage with NH_4Cl. This animal did not vomit to APO iv. The results in this animal suggest the presence of peripheral stimulation of emesis. The second animal (not exhibiting malaise) vomited only to APO iv. Both ablated animals vomited to gavage with 15% saline, but neither vomited to intravenous treatment with NH_4Cl. Histological studies confirmed complete and discrete ablation of the AP, with little damage to

surrounding tissue. The persistence of a post-lesion response to 15% saline gavage provides further proof that visceral afferent termini mediating this effect were not damaged during ablation. The persistence of the APO response in one APX animal cannot be explained. The present study suggests that cisplatin-induced emesis in the dog is not AP mediated. The long latency period indicates that some product of cisplatin action or its metabolite is responsible for emesis. The differences between the present studies and that of McCarthy and Borison (1983), may be attributed to species differences.

Gylys et al. (1979) suggested that cisplatin did not stimulate emesis at the CTZ. Their study was conducted in the dog and utilized a protocol similar to that employed here. The dose was 3 mg/kg iv. They proposed the involvement of peripheral mechanisms in cisplatin-induced emesis.

Harris and Cantwell (1986) suggested that the delay in the onset of emesis seen following the infusion of cytotoxic compounds can be explained by considering the biochemical site of action of the particular chemotherapeutic agent. In the present study, emesis occurred 138-184 min after the beginning of drug administration. This corresponds to the time of direct protein modification and synthesis. The trend toward an increase in NH_3 could be a consequence of interference with protein metabolism.

In addition to the change in NH_3 and pH in blood, disturbances in Na^+ and K^+ concentrations were detected (Table 9). The total change in the sodium and potassium level was not significant during the 240 min of observation. Comparison of

each level of observation to control values (before infusion) showed significant decreases in both K^+ and Na^+. The decrease in K^+ occurred first, at 30-45 min after the beginning of treatment. The decrease in Na^+ followed it at 45-60 min (the end of cisplatin infusion). Vomiting and malaise occurred 70-124 min later. After about 30 min the Na^+ and K^+ returned to pretreatment levels. A similar effect of cisplatin (decrease in Na^+, K^+, Ca^{++} and Mg^{++}) was described previously by Giaccone (1985). The concomittant decrease of Na^+ and K^+ in the blood, suggests impairment of the mechanisms maintaining the Na^+ and K^+ gradient between intra- and extracellular compartments. Membrane-bound Na^+-K^+-ATPase activity is a major mechanism for the control of transmembrane potential.

Changes in Na^+-K^+-ATPase activity and lipid peroxidation were observed in rat brain during reversible global ischemia (Goldberg et al., 1984). Weiss (1986) described Na^+-K^+ ATPase, glutamine synthetase, Ca^{++}-ATPase, and α-1-proteinase inhibitor as four proteins recently implicated in oxygen-metabolite-dependent damage. Since the animals treated with cisplatin revealed features of tissue hypoxia, although the venous oxygen level was within the normal range, it seems possible that cisplatin caused histotoxic hypoxia (Ganong, 1973). Dagani et al. (1984) reported that prolonged and intermittent hypoxia caused changes in enzymatic activity of the rat brain. Decreases in cytochrome oxidase and malate dehydrogenase were associated with a rise in glutamate dehydrogenase and lactate dehydrogenase in the rat medulla oblongata. These observations suggest that

future studies should investigate cisplatin-induced emesis on the basis of tissue toxicity, tissue hypoxia and altered oxygen utilization.

8.0 CONCLUSIONS

A chemosensitive mechanism in the initiation of emesis was confirmed. This was established by: studying changes in blood acid-base and other parameters during infusion with the emetic compounds ammonium chloride; studying responses to compounds which addressed various physico-chemical aspects of NH_4Cl; and retesting animals following ablation of the putative chemoreceptor trigger zone contained within the area postrema.

Ammonia dissolved in plasma and in intracellular fluids was identified as an important emetic stimulus. The role of ammonia in major metabolic pathways was considered. It was shown that in the presence of high plasma ammonia levels, transient increases are associated with vomiting. Ammonia is an important factor in anabolic-catabolic processes and in the manifestations of metabolic toxemia.

Evidence is presented that ammonia may be a direct stimulant of the emetic response following intracellular entry into receptor cells. It is speculated that the production of this compound may explain the presence of vomiting following a wide range of injury and disease states.

Area postrema ablation abolished emesis seen in response to intravenous infusion or intra-gastric administration of NH_4Cl.

No changes were seen in the homeostatic responses induced by these treatments following APX. Therefore, the AP was suggested as the site of central emetic chemoreceptors. Vomiting due to cisplatin infusion was not prevented by APX. This suggests the involvement of other chemoreceptors, perhaps peripheral or adjacent to AP, in the onset of emesis following treatment with this drug.

It is suggested that future studies directly assess the changes in intracellular pH associated with the infusion of ammonia-containing solutions, and during the vomiting response. CSF sampling should be employed to study changes in pH and other parameters in this compartment. The above experiments will perhaps help explain the activation of central chemoreceptors. Finally, the toxic effects of cisplatin in tissues associated with direct (such as decreases protein synthesis) and indirect (such as oxidative metabolism) consequences of the drug should be investigated to provide further insight into the emetic responses which follow infusion.

Table 1: Disorders associated with emesis are presented along with suggested underlying pathophysiological mechanisms and putative receptors involved in the vomiting response.

Cardiovascular diseases	Neurological diseases	Cerebrovascular disorders (disease)	Gastrointestinal disorders	Infectious diseases	Poisons	Other diseases (systemic disorders)	Psychiatric disorders
Myocardial Infarction	Acute intracranial hypertension (30)	Migraine (12)	Peptic ulcer (86)	GI infections	Exotoxins:	Cancer (76)	Anorexia (58)
Congestive Heart Failure	-head trauma	Transient ischemic attacks (42)	Motor disorders	Meningeal infec.	chemicals, drugs, chemotherapeutics, gases (70)	Renal failure	Depression
Cardiogenic Shock	-hydrocephalus (45)	Stroke (86)	Gastroenteritis	Sepsis		Hepatic failure	Bulimia (43)
Ischemic heart disease	Neoplasm		Hepatitis	Toxemia (2)	Endotoxins:	Diabetes mellitus	Anticipatory vomiting (43)
Hypertensive disease (86)	Epileptic equivalents (44)		Biliary tract disease		metabolites, acid-base disturbances	Endocrine (Addison disease)	
	Vestibular or middle ear disease: motion sickness		Pancreatitis		Electrolite imbalance (79)	Hyperthyroidism (86)	
	Meniere Disease		Vascular insufficiency (67)			Pregnancy (61)	
	eighth nerve tumor		Inflammatory bowel disease				
	Eye disorders -glaucoma (86)		Food allergy				
			Bowel dysfunction (84)				

RELATED PATHOPHYSIOLOGICAL MECHANISMS:
1. Changes in blood pressure and flow
2. Changes in cerebrospinal fluid pressure and composition
3. Release of neurotransmitters
4. Release of specific factors (peptides, enzymes) and metabolities
5. Disturbances in equilibrium of acid-base and electrolytes
6. Systemic introduction of poisonous substances (chemicals, drugs, toxins)

RECEPTORS:
1. pressoreceptors
2. baroreceptors
3. chemoreceptors
4. neurotransmitters
5. peptides:
   - gastrointestinal
   - vasoactive

Table 2: Summary of intravenous infusions and intragastric gavages. Chemicals were dissolved in distilled water up to 80 ml, except 0.3 M lactic acid which was diluted up to 100 ml with H_2O.

INTRAVENOUS TREATMENT		INTRAGASTRIC TREATMENT	
Ammonium chloride (1.71g)	0.4 M	Ammonium chloride	1.71 g/20ml (1.6 M)
Lactic acid	0.4/0.3 M	Ammonium chloride	1.71g/40ml (0.8 M)
Sodium lactate	0.4 M		
Sodium bicarbonate	0.4 M		
Ammonium bicarbonate	0.4 M		
Mannitol	674 mOsm/L		
Mannitol	903 mOsm/L		
Sodium sulphate	0.4 M		
Cisplatin solution 50 mg/m^2:			
0.9% Saline	41 ml		
5% Glucose	3.9 ml/kg		
20% Mannitol	0.12 ml/kg		

Table 3: Vomiting response vs treatment. Each solution contained 32 mM of compound dissolved in water. R = retching.

SOLUTION	RESPONDERS/ No. dogs
INTRAVENOUS:	
Ammonium chloride i.v. 0.4 M	$4/_4$
Lactic acid	$0/_4$
Sodium lactate	$0/_4$
Sodium bicarbonate	$0/_4$
Ammonium bicarbonate	$2/_4$
Mannitol	$0/_4$
Cisplatin	$4/_4$
GAVAGES:	
Ammonium chloride 1.6 M	$4/_4$
Ammonium chloride 0.8 M	$2/_4$, R $1/_4$
DUAL INFUSION:	
Sodium lactate & Sodium sulphate i.v.	$1/_4$

Table 4: Infusion period and observation time. Emesis = time of vomiting.

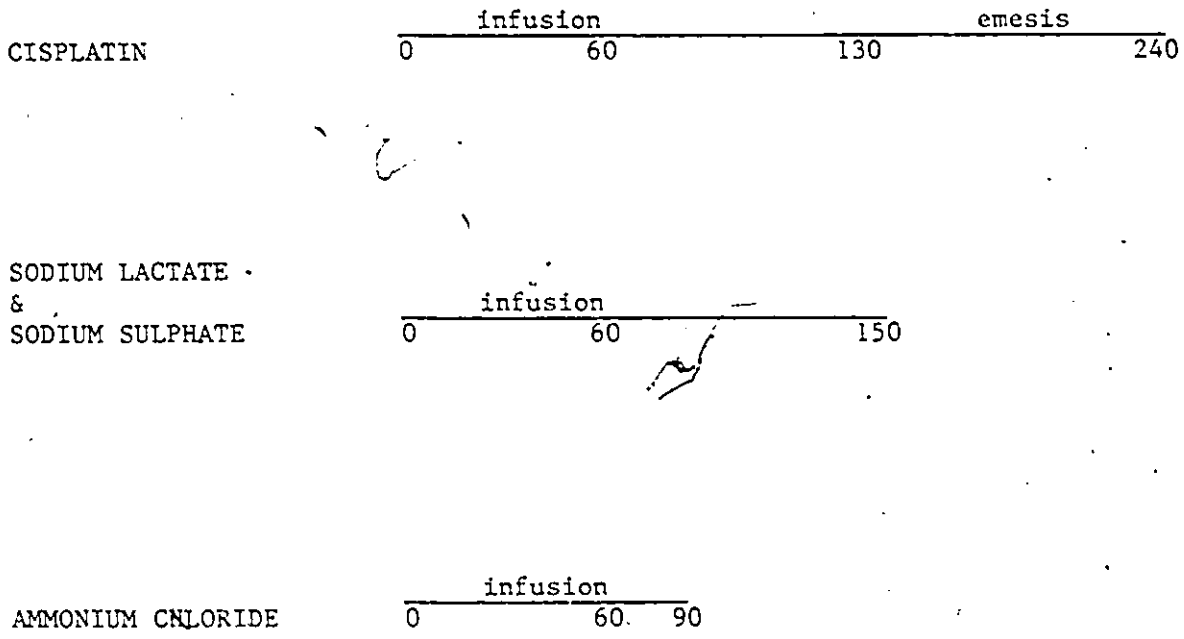


TABLE 5: Changes in pH and blood gases resulting from the administration of various treatments. Arrows present the direction of changes in these blood parameters. $X/_Y$ = the number of dogs vomited over the number of dogs tested. APN = normal area postrema. APX = area postrema previously ablated.
* = a descriptive assessment (n=2)

SOLUTION	EMETIC EFFECT	pH	pCO_2	pO_2	BE	HCO_3^-	tot.CO_2
Ammonium chloride i.v. APN	$4/_4$	↓	→	→	↓	↓	↓
Ammonium chloride i.v. APX	$0/_2$	* ↓	→	→	↓	↓	↓
Ammonium chloride gav.20ml APN	$4/_4$	→	→	→	→	→	→
Ammonium chloride gav.40ml APN	$2/_4$ $1/_4$ R	→	→	→	↓	↓	↓
Ammonium chloride gav.20ml APX	$0/_2$	* ↓	→	→	↓	↓	↓
Sodium lactate APN	$0/_4$	↑	↑	→	↑	↑	↑
Lactic acid APN	$0/_4$	↓	→	→	↓	↓	↓
Sodium bicarbonate APN	$0/_4$	↑	→	→	↑	↑	↑
Ammonium bicarbonate APN	$2/_4$	→	→	→	→	→	→
Sodium lactate & Sodium sulphate APN	$1/_4$	↑ ↓	↑ ↓	↑ ↓	↑ ↓	↑ ↓	↑ ↓

Table 6: Summary of statistical analyses time effect. The parameters listed below were changed significantly by the indicated treatments. Statistical significance ($p < 0.05$) was established by: an analysis of variance to assess changes with time (one-way ANOVA); a nonparametric test to rank these changes (Friedman's); a test of the correlation between dependent variable and time (regression).

TREATMENT	ONE-WAY ANOVA BMDP 2V	FRIEDMAN'S ANOVA	REGRESSION POLYNOMIAL
Saline 0.9%	pH	pH,BE	---
Ammonium chloride iv	pH,BE,HCO_3	pH,BE,HCO_3,$totCO_2$	pH,BE,HCO_3,$totCO_2$
Ammonium chloride gavage 20 ml	---	---	---
Ammonium chloride gavage 40 ml	BE,HCO_3,$totCO_2$	BE,HCO_3,$totCO_2$	BE,HCO_3,$totCO_2$
Ammonium bicarbonate	---	---	---
Lactic acid	pH	pH,pCO_2	pH,BE,HCO_3,$totCO_2$
Sodium lactate	pH,BE,HCO_3,$totCO_2$,pCO_2	pH,pCO_2,BE,$totCO_2$	pH,BE,HCO_3,$totCO_2$
Sodium bicarbonate	pH,BE,HCO_3,$totCO_2$	BE,HCO_3	pH,BE,HCO_3,$totCO_2$
Mannitol 904 mOsm/L	---	---	---
Mannitol 674 mOsm/L	pH	pH	---
Sodium lactate & Sodium sulphate	pH,BE,HCO_3,$totCO_2$	pH,pCO_2,pO_2,BE,HCO_3,$totCO_2$	pH,pCO_2,pO_2,BE,HCO_3,$totCO_2$
Cisplatin	---	pH	pH

TABLE 7: Summary of the results obtained from an interaction of time and treatment among groups of solutions, set up according to their physiological effects.
* = $p < 0.05$
[ ] = $p > 0.05$

Set	Treatments		pH	BE	HCO_3	tot.CO_2
I	Saline 0.9% Ammonium chlor.iv Ammonium bicarb. Lactic acid Sodium lactate Sodium bicarbonate	R	*	*	*	
		S				
		RS	*	*	*	
II	Saline 0.9% Ammonium Chlor.iv Sodium lactate Mannitol 904 mOsm/L Mannitol 674 "	R	*	*	*	*
		S	*			
		RS	*	*	*	*
III	Saline 0.9% Ammonium chlor.iv Ammonium chlor. gav.20 ml Ammonium chlor. gav.40 ml	R	*			
		S		*	*	*
		RS				
IV	Saline 0.9% Ammonium chlor.iv Cisplatin (0-75min.)	R	*	*	*	
		S	*	*	*	
		RS	*	*	*	
V	Saline 0.9% Ammonium chlor.iv Cisplatin (75-180 min.)	R		*		
		S		*	*	*
		RS	*	*		

Table 8a: Assessment of changes caused by various treatments. Asterisks indicate significant difference between 0.9% saline and treatment. * = <0.05 0 = p > 0.05

TREATMENT	pH	pCO_2	pO_2	BE	HCO_3	tot.CO_2
SALINE 0.9%						
Ammonium chloride iv	*	*	0	*	*	*
Ammonium chlor. gavage 20 ml	*	*	0	*	*	*
Ammonium chlor. gavage 40 ml	*	*	*	*	*	*
Ammonium bicarbonate	0	*	0	0	0	0
Lactic acid	*	*	0	*	*	*
Sodium lactate	*	*	*	*	*	*
Sodium bicarbonate	*	0	0	*	*	*
Mannitol 904 mOsm/L	0	*	*	0	0	0
Mannitol 674 mOsm/L	*	0	0	0	0	0
Cisplatin	0	0	0	0	0	0

TABLE 8b: Multiple comparisons of the means between treatments (each to the other by Duncan test). The asterisk indicates significant treatment effects ($p < 0.05$), the zero indicates non-significance.

SET	TREATMENT	pH		BE		HCO3		tot.CO2	
		p<0.05	p>0.05	p<0.05	p>0.05	p<0.05	p>0.05	p<0.05	p>0.05
I	Ammonium chlor. iv	*		*		*		*	
	Ammonium bicarb.	*		*		*		*	
	Lactic acid	*		*		*		*	
	Sodium lactate		o		o		o		o
	Sodium bicarb.		o		o		o		o
II	Ammonium chlor. iv	*		*		*		*	
	Sodium lactate	*		*		*		*	
	Mannitol (904)	*			o		o		o
	Mannitol (674)	*			o		o		o
III	Ammonium chlor. iv	*			o		o		o
	gavage 20 ml	*		*		*		*	
	gavage 40 ml	*			o		o		o
IV	Ammonium chloride	*		*		*		*	
	Cisplatin	*		*		*		*	

TABLE 9: The effect of time on blood electrolytes (Na^+, K^+)

TREATMENT	EMESIS TIME LEVEL	Na^+	K^+
Ammonium chloride iv	T2, T3 T5		T1 * T4
Ammonium chloride gavage 40 ml	T2, T6		T1 * T5, T6
Sodium Lactate Sodium Sulphate	T17	p<0.001; T1 * T7-T17	p<0.001; T1 * T2-T17
Cisplatin	T10, T12 T13	T1 * T4, T5	T1 * T3, T4
Sodium Bicarbonate	No Emesis	T1 * T5, T6	p<0.05 T1 * T5, T6, T7
Mannitol 904 mOsm/L	No Emesis	p<0.001 T1 * T2-T3	

Column 2 lists the time points at which emesis occurred for each treatment, i.e., T2 equals the second sample interval or 10 min after the beginning of infusion. These time intervals should be compared with those in the columns for Na^+ or K^+. When time intervals (T1, T4, etc.) appear in these columns, the level of the indicated ion was significantly different from control at that time. When $p<0.001$ or $p<0.05$ appears, the data set as a group was significantly different.

TABLE 10: Summary of the changes in blood acid-base parameters and plasma ammonia levels during the latency period before the first emetic episode. $X/_Y$ = number of animals exhibiting a change vs. the number tested.

TREATMENT	Ammonium chloride iv APN	Ammonium chlor. gavage 20 ml APN	Ammonium chlor. gavage 40 ml APN	Ammonium bicarbonate APN	Cisplatin APN	Cisplatin APX
BLOOD	BE, HCO_3^- $4/_4$	NONE $4/_4$	BE, HCO_3^- $1/_4$R	NONE $4/_4$	pH $1/_4$	
ACID-BASE	pH $1/_4$ tot.CO_2		NONE $2/_4$		NONE $3/_4$	
PLASMA AMMONIA	above normal level	above normal level	above normal level	not measured	within normal level, tending to increase at emetic start-point	

Fig. 1: Putative receptors involved in the initiation of emesis, with an indication of their input to central regulatory sites.

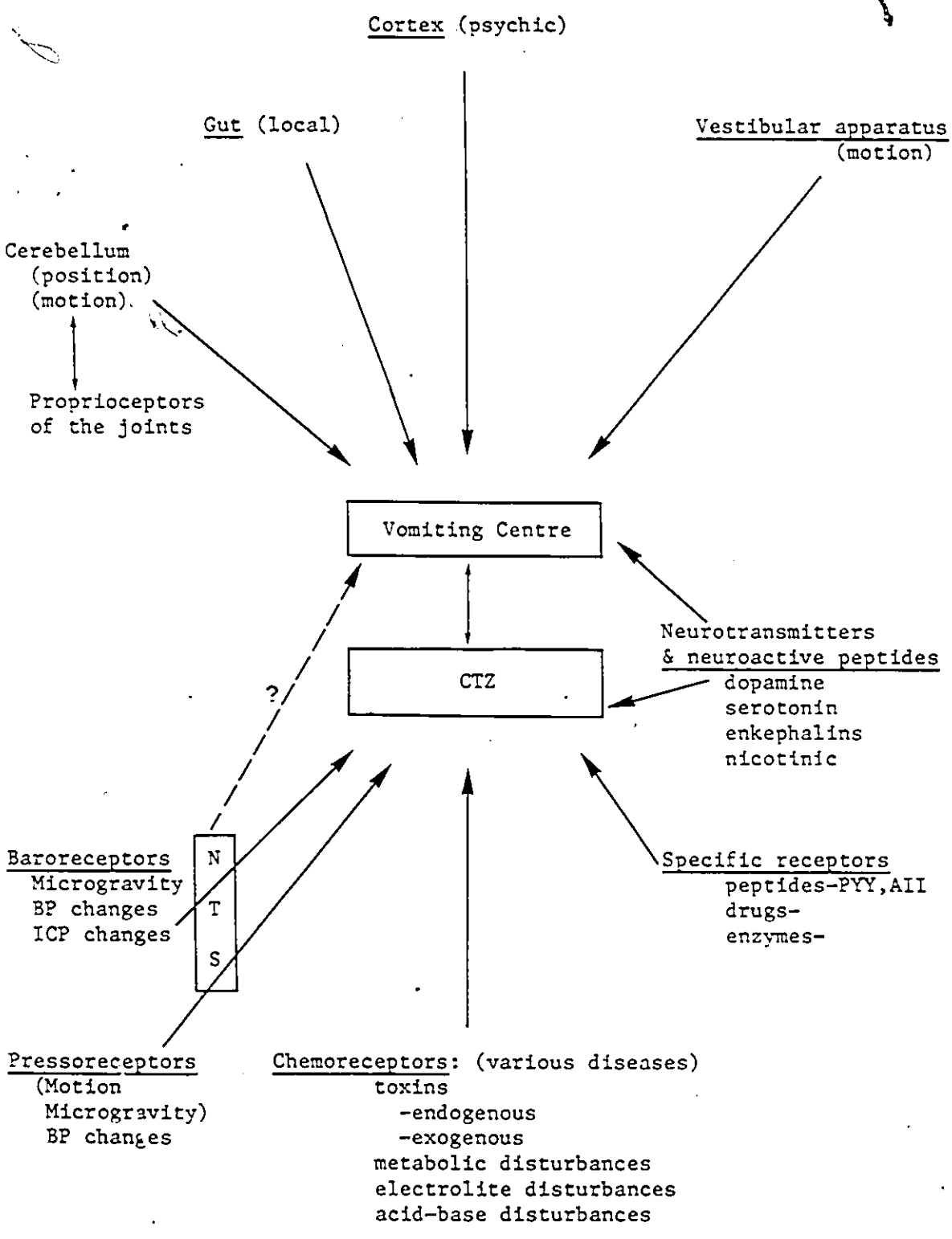


Figure 2a: Ammonia-sensing electrode assembly. Arrows indicate elements directly involved in the measurement of NH_3 in plasma. They are: a) gas-sensing ammonia microelectrode; b) mini-hood between electrode and flow-through adapter; c) flow-through adapter and chamber for tip of electrode; and, d) syringe containing buffered plasma sample. NH_3 sensing system lies on the surface of the infusion pump which injects syringe content to flow-through adapter.

Figure 2b: The ammonia assay set-up. Arrows point to: a) NH_3 sensing electrode; b) infusion pump; and, c) electrometer. The gas sensitive electrode has a membrane permeable to free ammonia. The infusion pump perfuses the flow-through adapter surrounding the tip of the ammonia electrode. The changes in NH_3 concentration around the reference electrode evokes an electrical current which is transmitted to the radiometer and is expressed in millivolts.

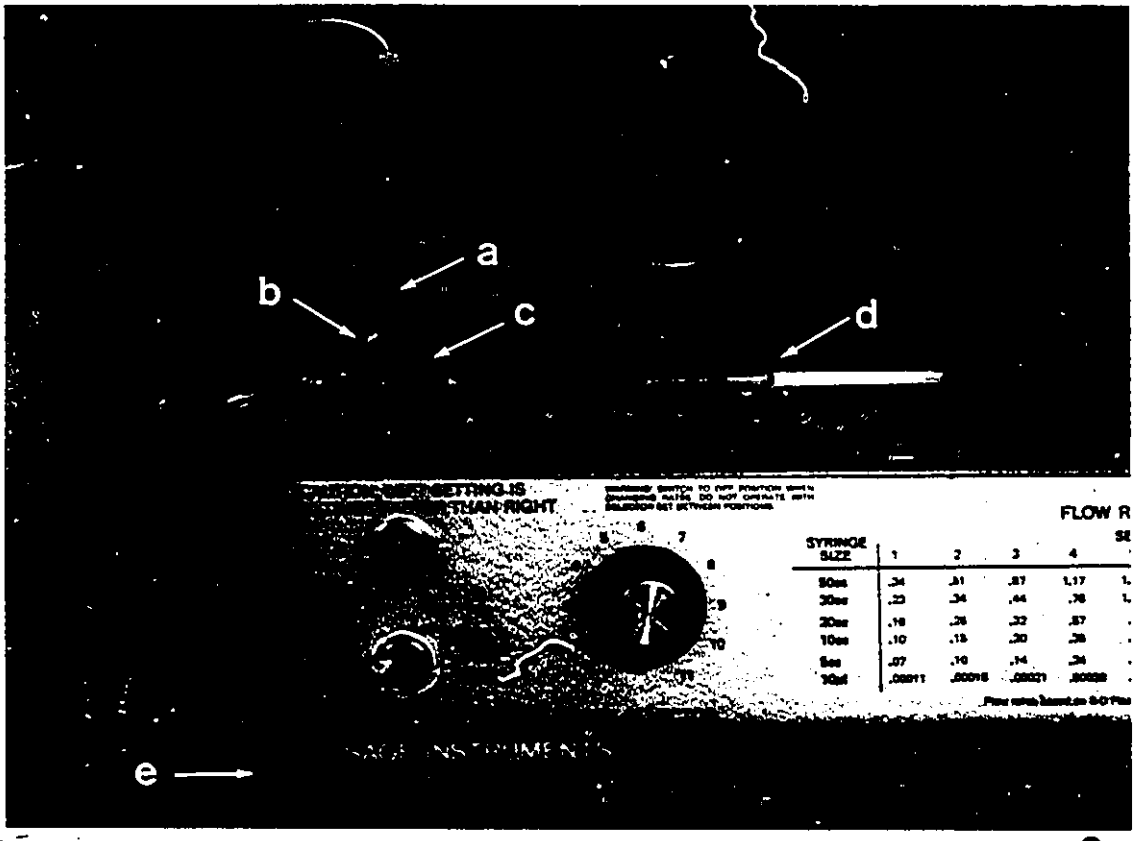


FIG. 2A

FIG. 2B

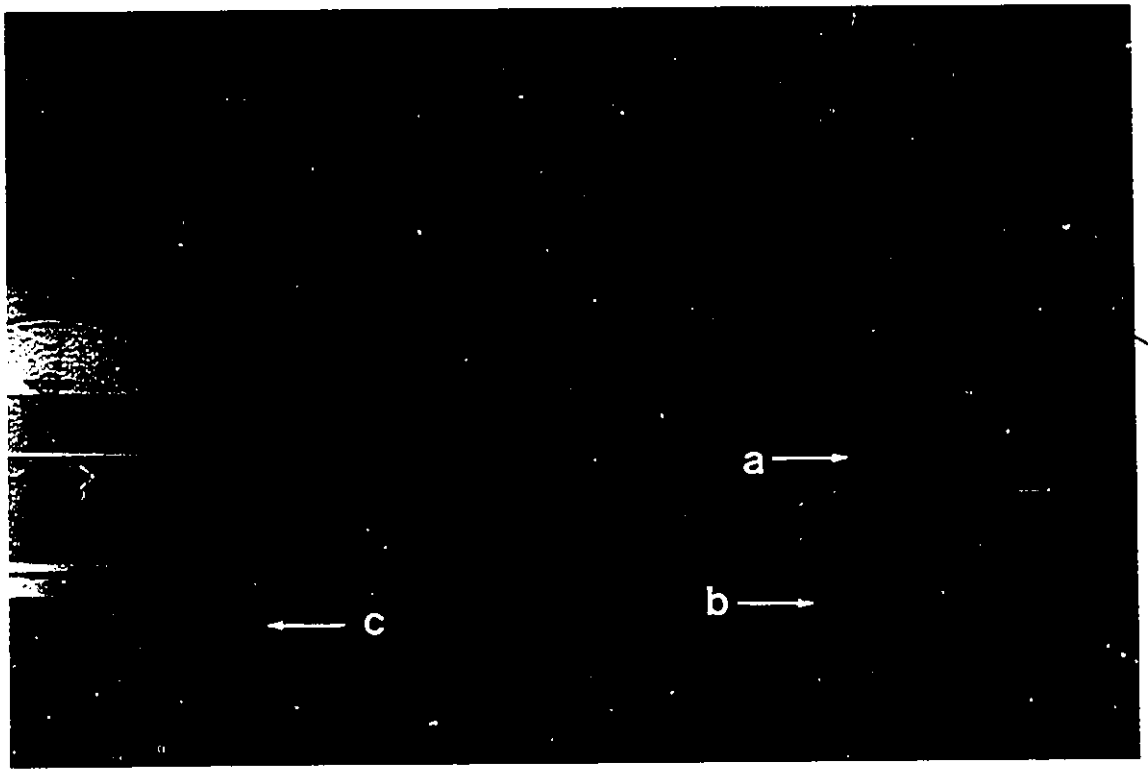
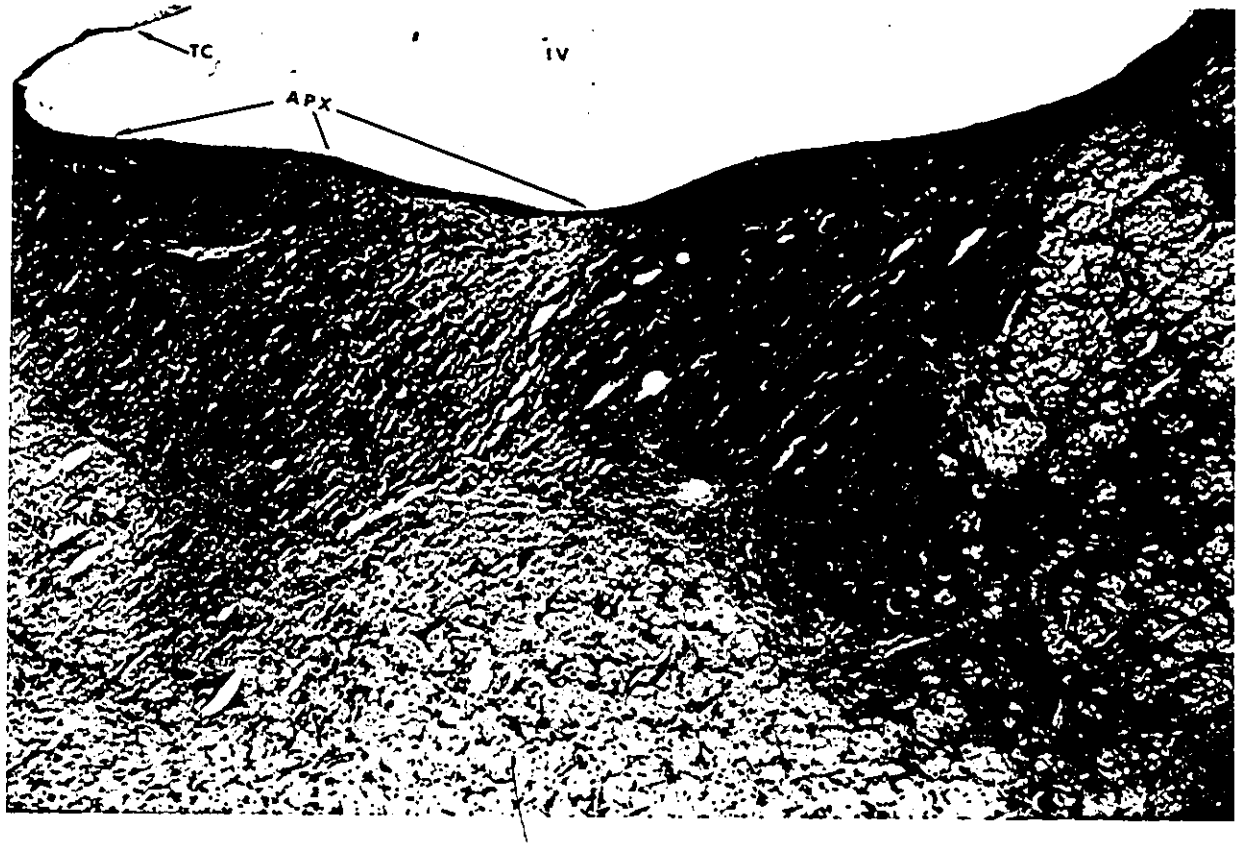


Figure 3: The ammonia-sample syringe. The important techniques of blood collection are indicated by arrows. The syringe is locked from both sides which immobilizes the piston. The sealed syringe allows centrifugation of the blood in the same syringe in the absence of air and prevents blood from releasing gaseous NH_3.

FIG.3

Figure 4a: Light microscopy cross section through the left side of the medulla depicting region of area postrema ablation in animal 1. IV, fourth ventricle, APX, region of area postrema ablation. TC, remnant of the taenia chorioidae, NTS, nucleus of the tractus solitarius, DMV, dorsal motor nucleus of the vagus. 20 µm section, cresyl violet stain.

Figure 4b: Light microscopy cross section through the left side of the medulla depicting region of area postrema ablation in animal 2. IV, fourth ventricle, APX, region of area postrema ablation. TC, remnant of the taenia chorioidae, NTS, nucleus of the tractus solitarius, DMV, dorsal motor nucleus of the vagus. 20 µm section, cresyl violet stain.


TC
IV
APX

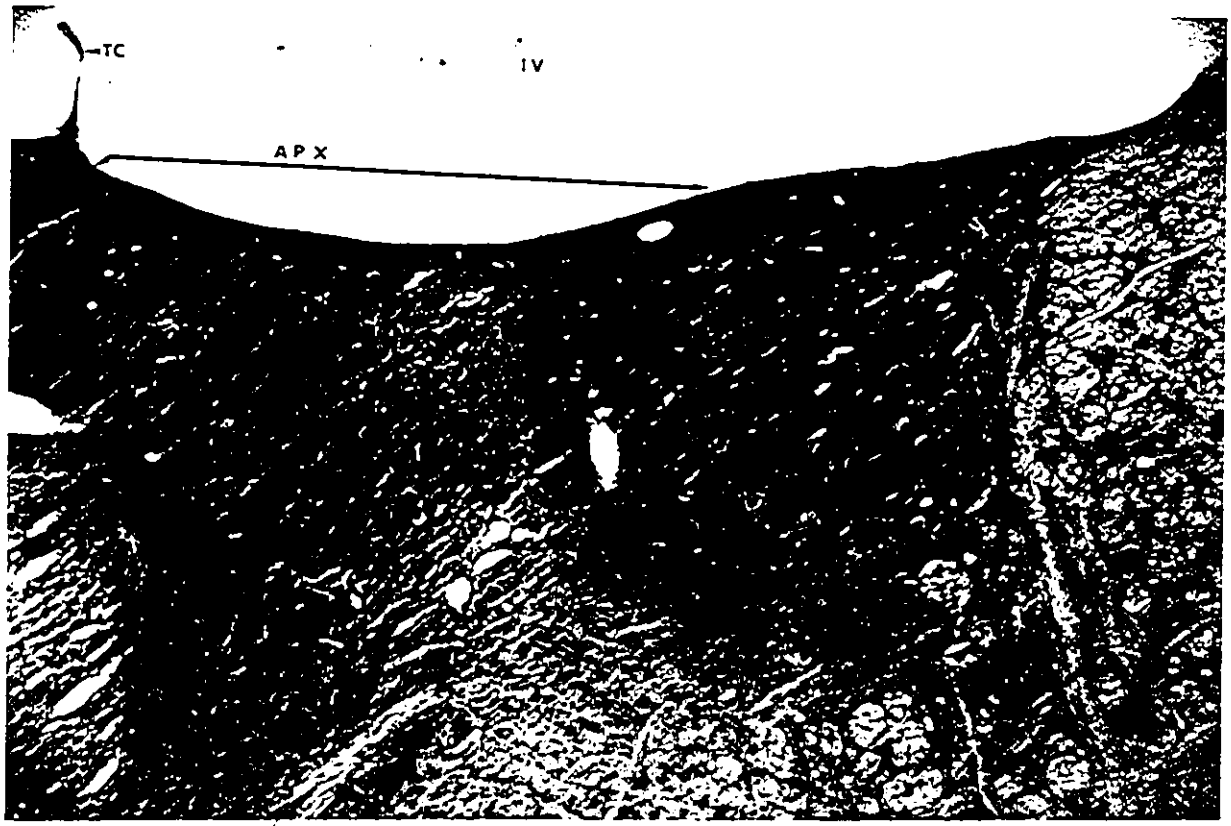

TC
IV
APX

Figure 5: Latency periods for emetic responses initiated by various treatments. Maximum and minimum time of response are presented as a range of the time vs treatments. Treatments were: 1) NH_4Cl iv; 2) NH_4Cl gav 20 ml; 3) NH_4Cl gav 40 ml; 4) NH_4HCO_3 iv; 5) cisplatin iv; 6) APO iv APN; 7) APO iv APX; 8) saline 15% APN; and, 9) saline 15% APX.

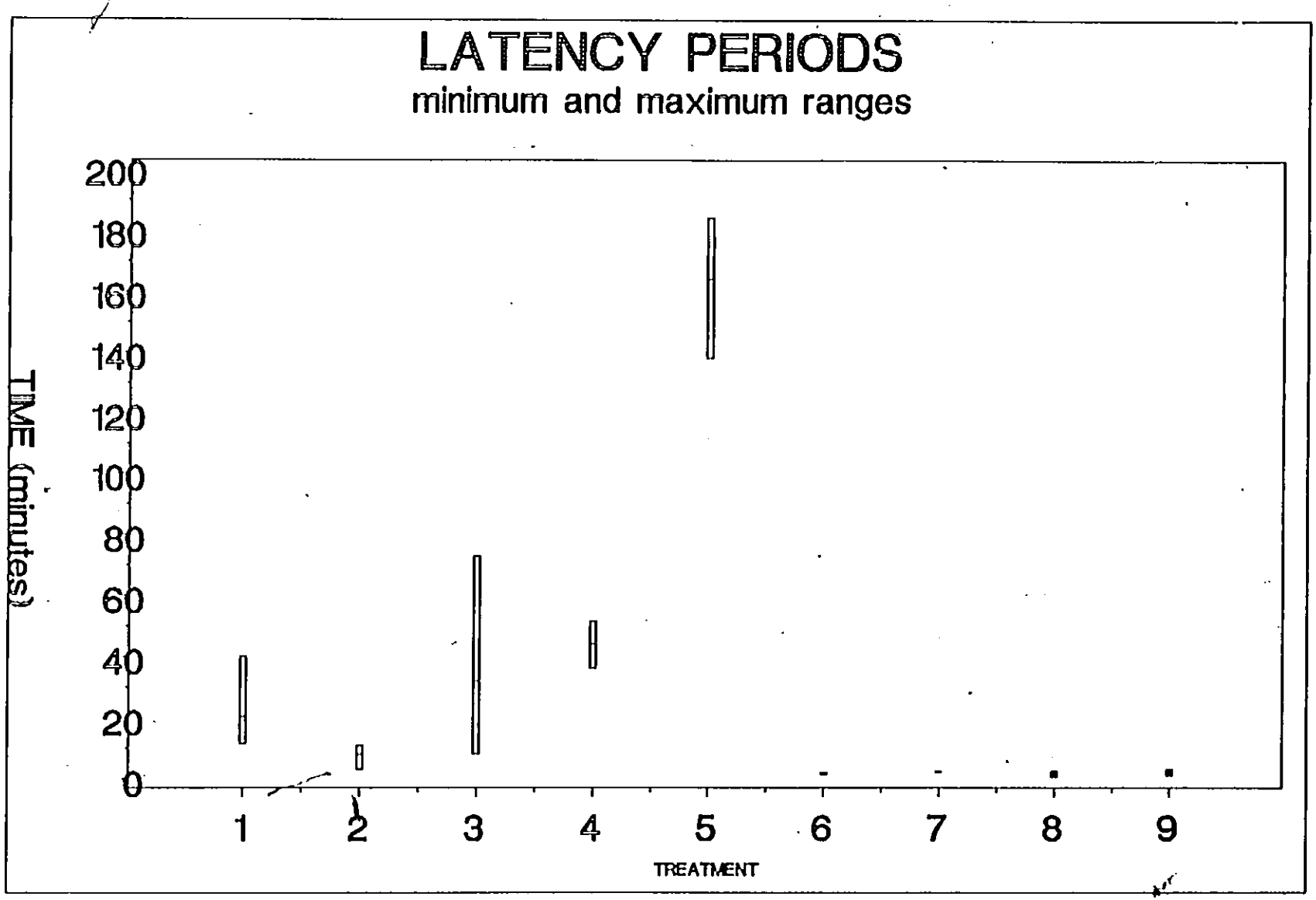
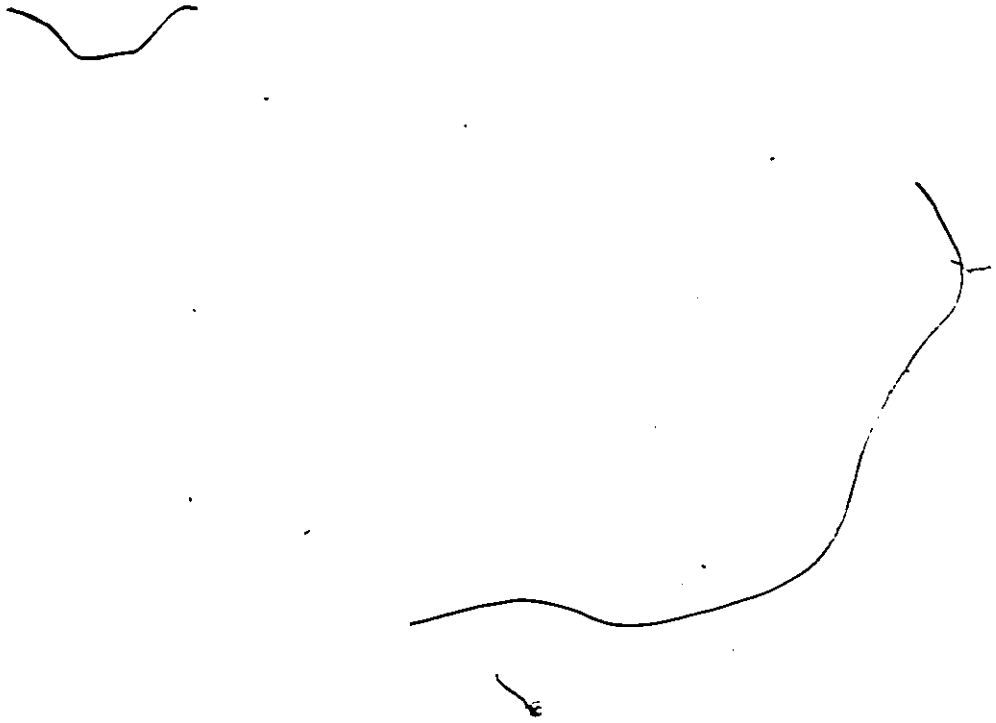
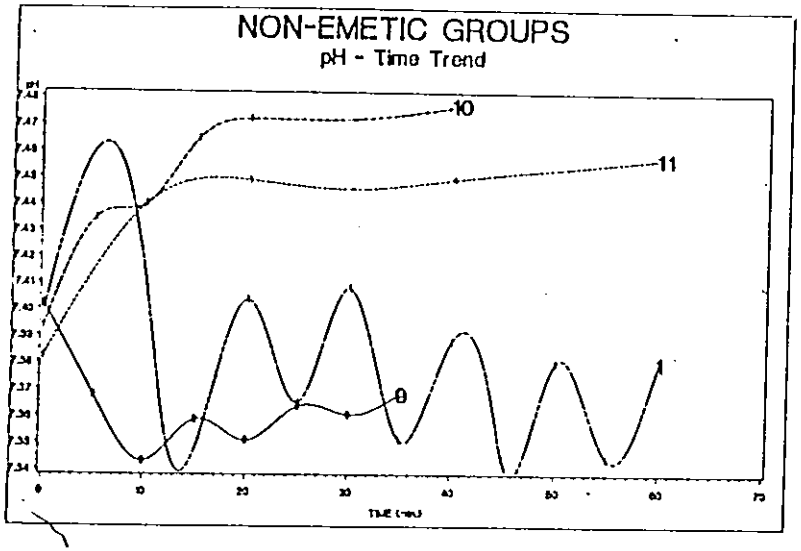
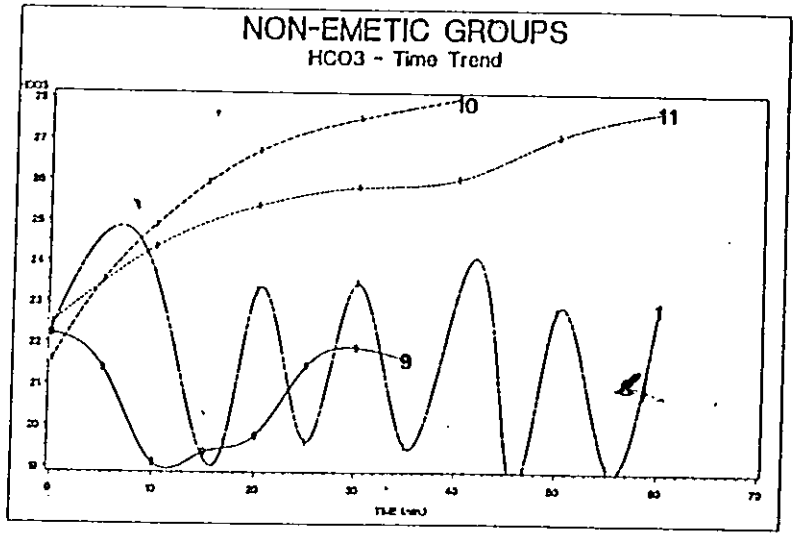
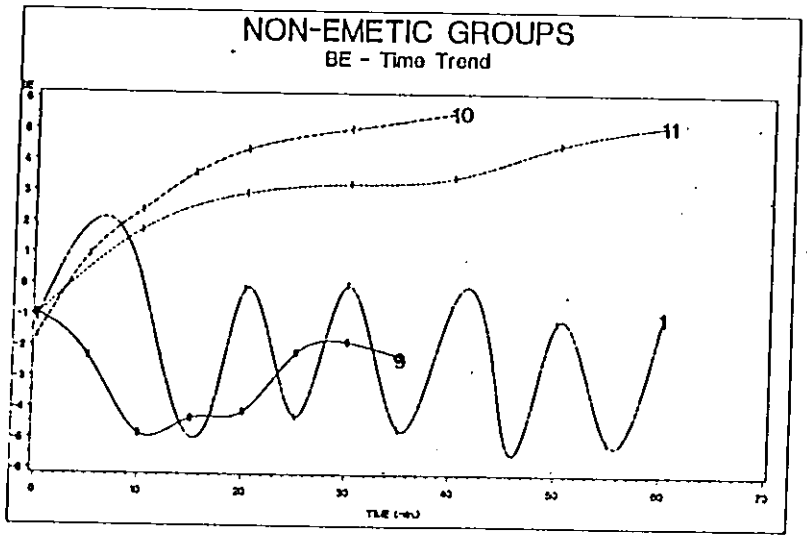

LATENCY PERIODS
minimum and maximum ranges
TIME (minutes)
200
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
TREATMENT

Figure 6: Composite figures presenting pooled data for acid-base changes seen following treatment with various nonemetics. See captions to figures 6a-d for details.




NON-EMETIC GROUPS
pH - Time Trend
10
11
9
1


NON-EMETIC GROUPS
HCO3 - Time Trend
10
11
9
1


NON-EMETIC GROUPS
BE - Time Trend
10
11
9
1

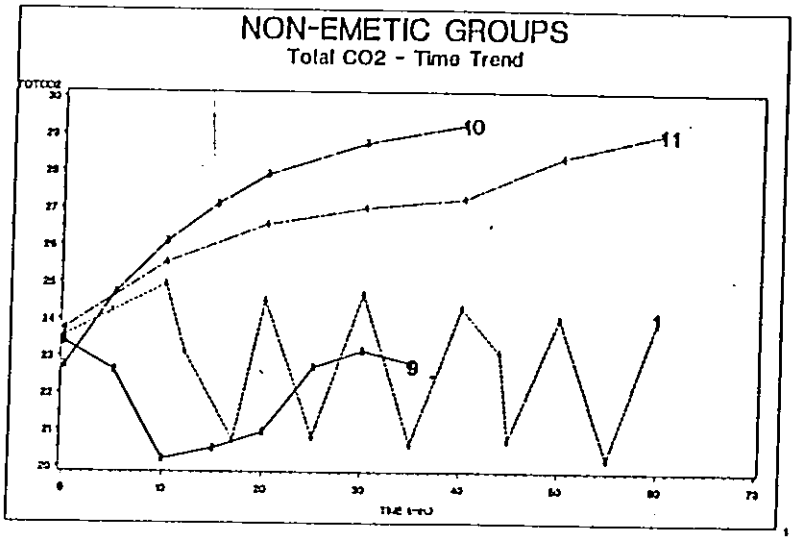

NON-EMETIC GROUPS
Total CO2 - Time Trend
10
11
9
1

Figure 6a: Changes in blood pH were significant during treatment with: 9) lactic acid; 10) sodium lactate; and 11) sodium bicarbonate (pooled data, n=4). Comparisons with control saline (1) showed all treatments were significantly different ($p<.05$). Comparison between treatments showed significant differences between lactic acid, sodium lactate, and sodium bicarbonate. No significant difference was found between sodium lactate and sodium bicarbonate treatments.

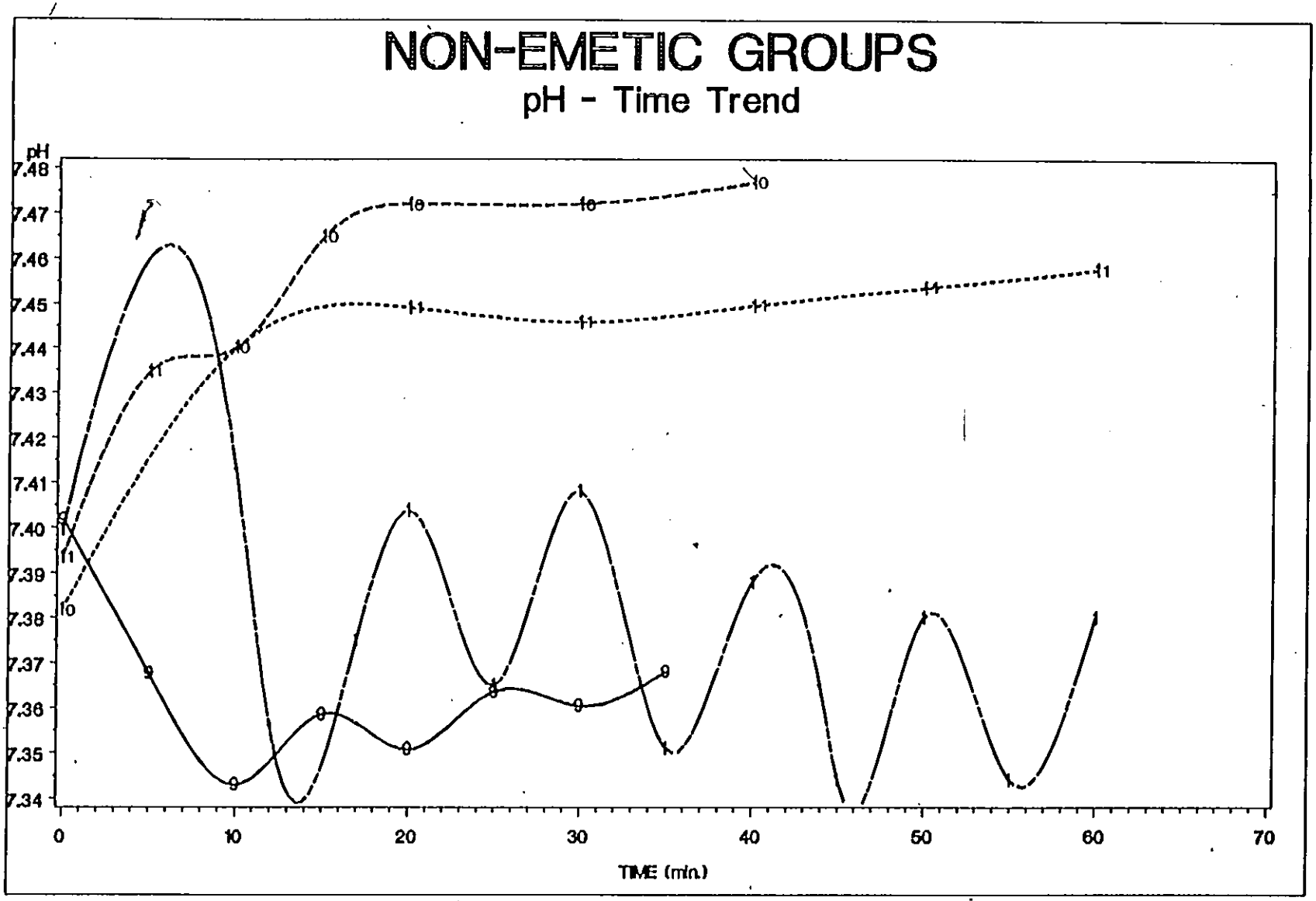

NON-EMETIC GROUPS
pH - Time Trend
pH
7.48
7.47
7.46
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.34
0
10
20
30
40
50
60
70
TIME (min)

Figure 6b: Changes in blood BE were significant during treatment with: 9) lactic acid; 10) sodium lactate; and 11) sodium bicarbonate (pooled data, n=4). Comparisons with control saline (1) showed all treatments were significantly different ($p<.05$). Comparison between treatments showed significant differences between lactic acid, sodium lactate, and sodium bicarbonate. No significant difference was found between sodium lactate and sodium bicarbonate treatments.

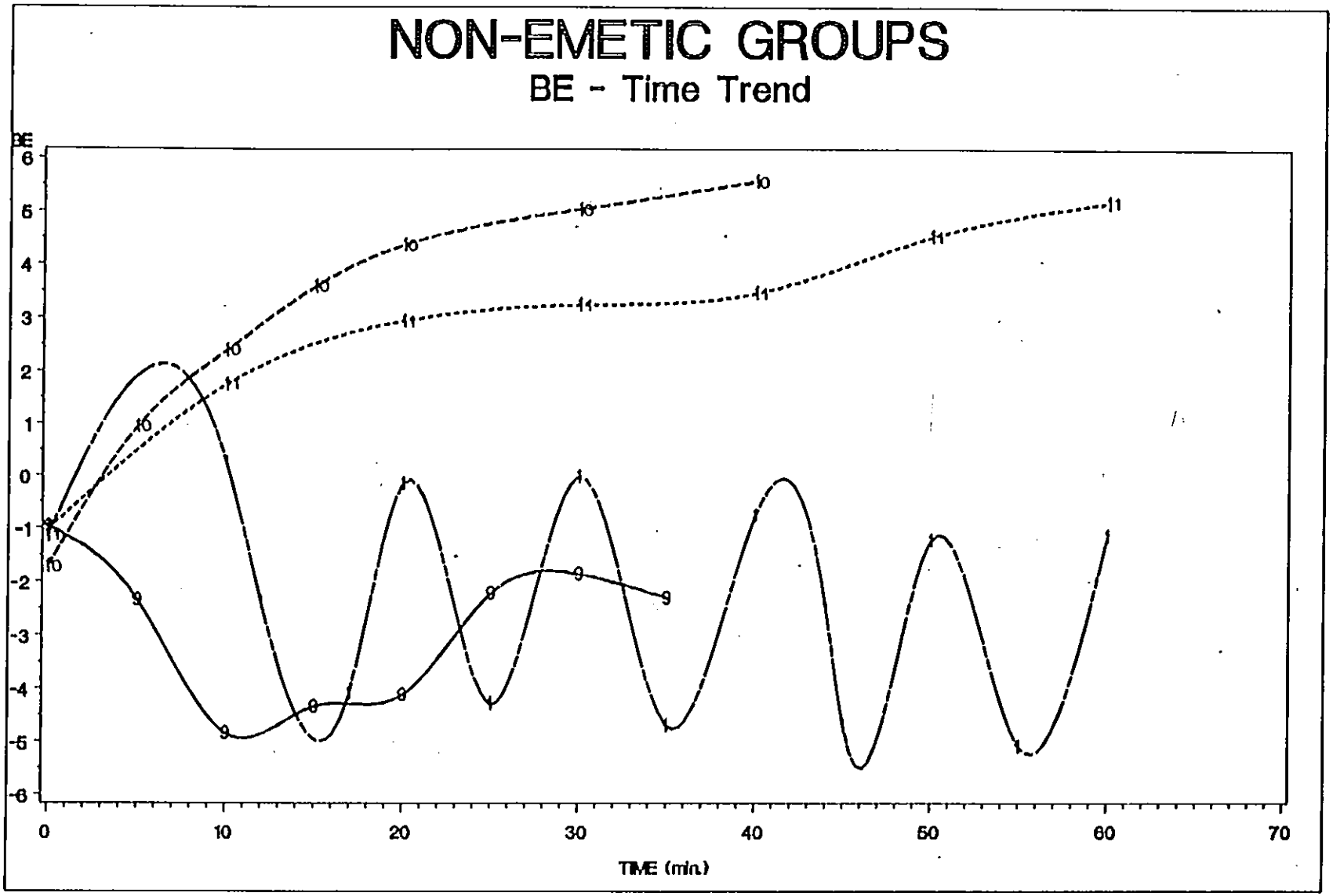

NON-EMETIC GROUPS
BE - Time Trend
BE
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
0
10
20
30
40
50
60
70
TIME (min)

Figure 6c: Changes in blood HCO_3^- were significant during treatment with: 9) lactic acid; 10) sodium lactate; and 11) sodium bicarbonate (pooled data, n=4). Comparisons with control saline (1) showed all treatments were significantly different ($p<.05$). Comparison between treatments showed significant differences between lactic acid, sodium lactate, and sodium bicarbonate. No significant difference was found between sodium lactate and sodium bicarbonate treatments.

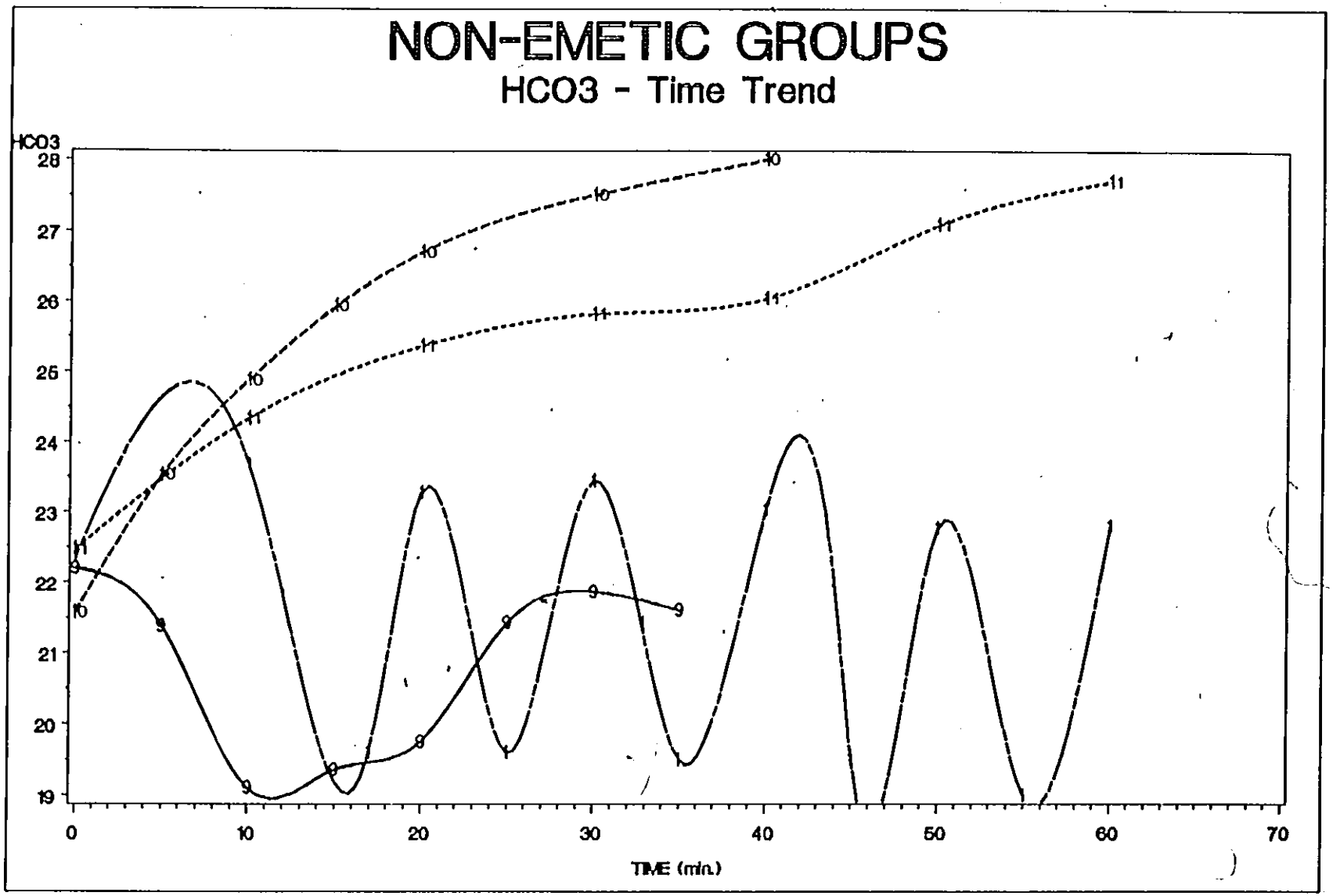

NON-EMETIC GROUPS
HCO3 - Time Trend
HCO3
28
27
26
25
24
23
22
21
20
19
0
10
20
30
40
50
60
70
TIME (min.)

Figure 6d: Changes in blood tot.CO_2 were significant during treatment with: 9) lactic acid; 10) sodium lactate; and 11) sodium bicarbonate (pooled data, n=4). Comparisons with control saline (1) showed all treatments were significantly different ($p<.05$). Comparison between treatments showed significant differences between lactic acid, sodium lactate, and sodium bicarbonate. No significant difference was found between sodium lactate and sodium bicarbonate treatments.

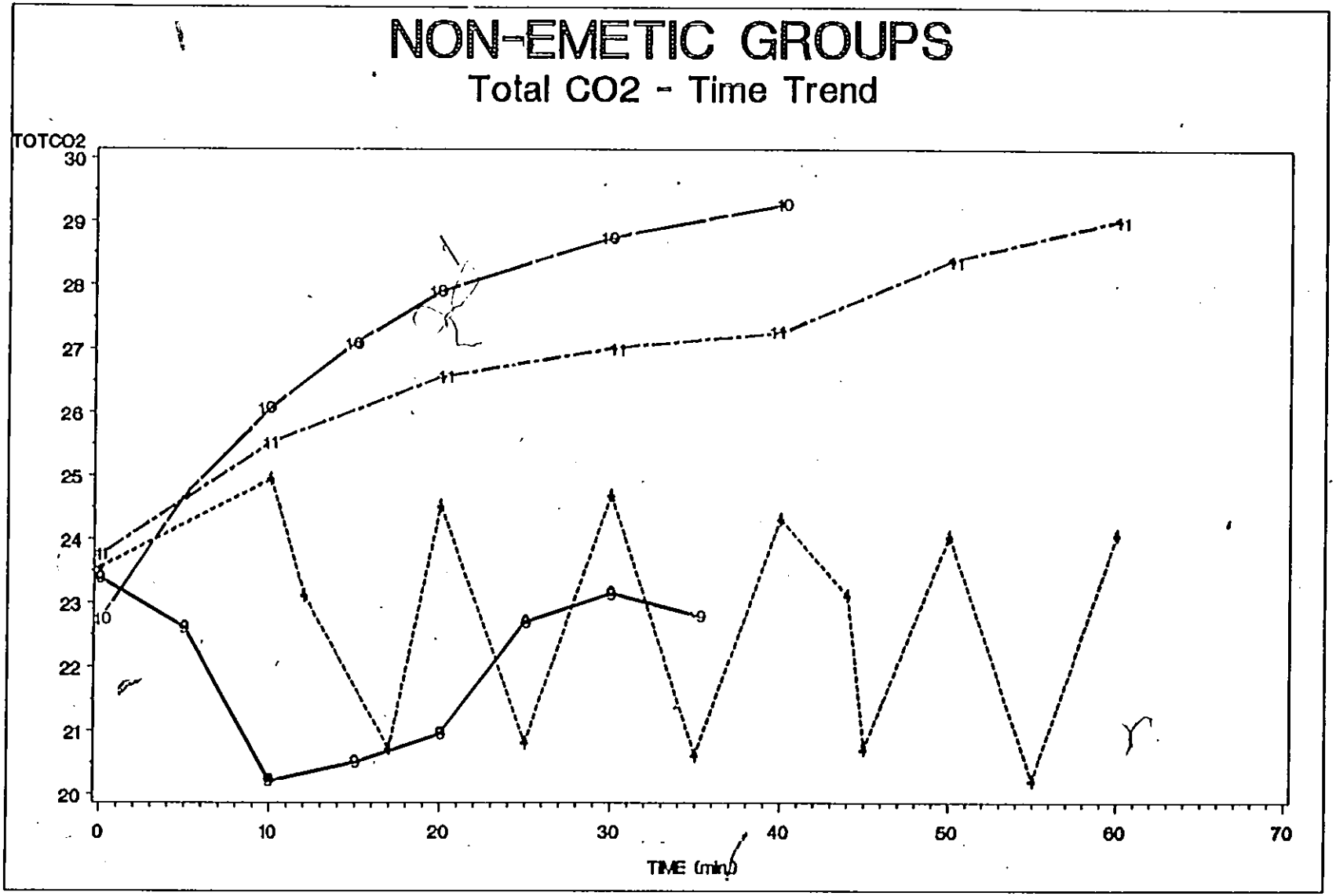
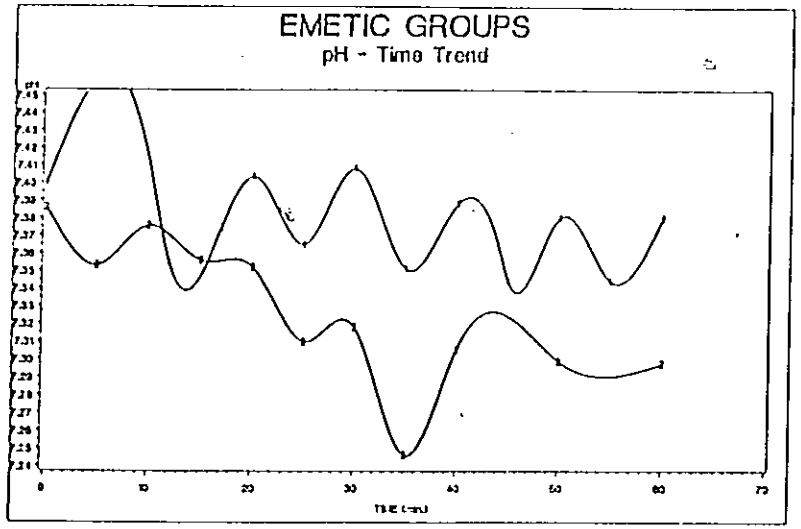
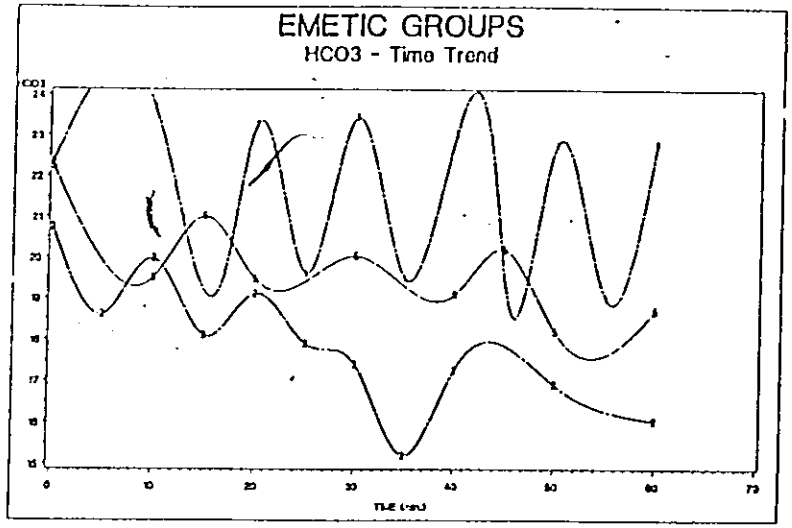
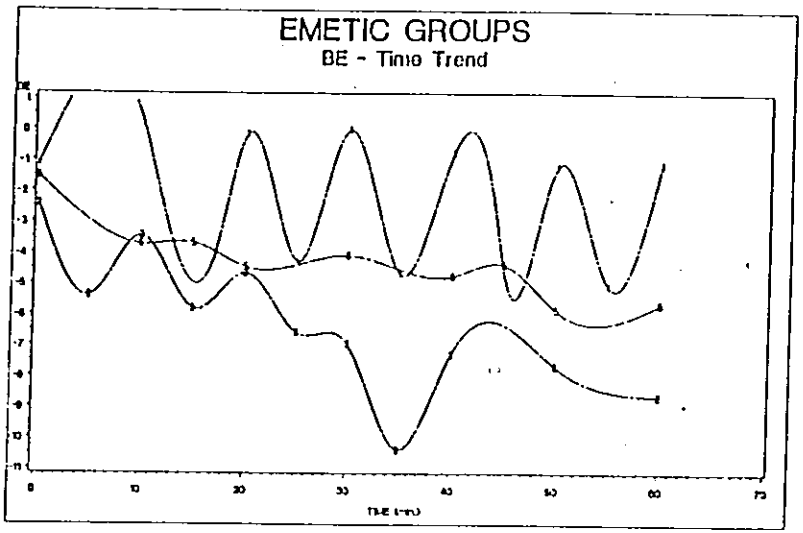

NON-EMETIC GROUPS
Total CO2 - Time Trend
TOTCO2
30
29
28
27
26
25
24
23
22
21
20
0
10
20
30
40
50
60
70
TIME (min)

Figure 7: Composite figures presenting pooled data for acid-base changes seen following treatment with various emetics. See captions to figures 7a-d for details.


EMETIC GROUPS
pH - Time Trend


EMETIC GROUPS
HCO3 - Time Trend


EMETIC GROUPS
BE - Time Trend

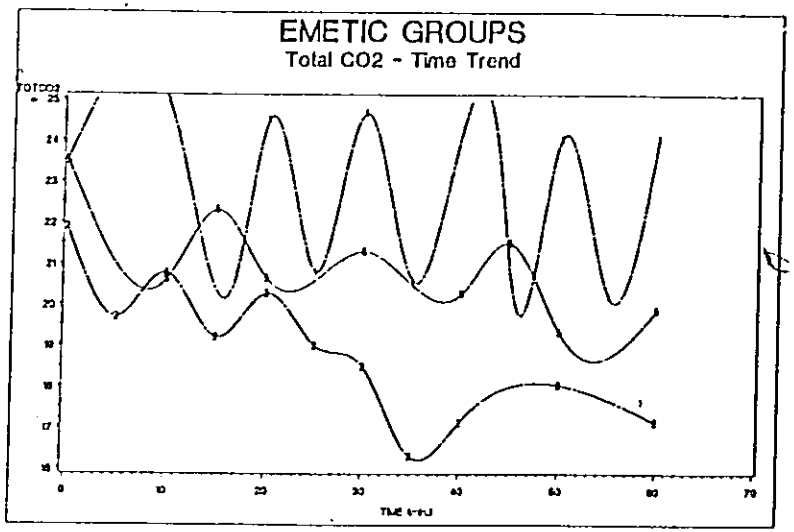

EMETIC GROUPS
Total CO2 - Time Trend

Figure 7a: Changes in blood pH were significant during treatment with (2) ammonium chloride iv (pooled data n=4). Comparison with control saline (1) showed NH_4Cl significantly different ($p<.05$)

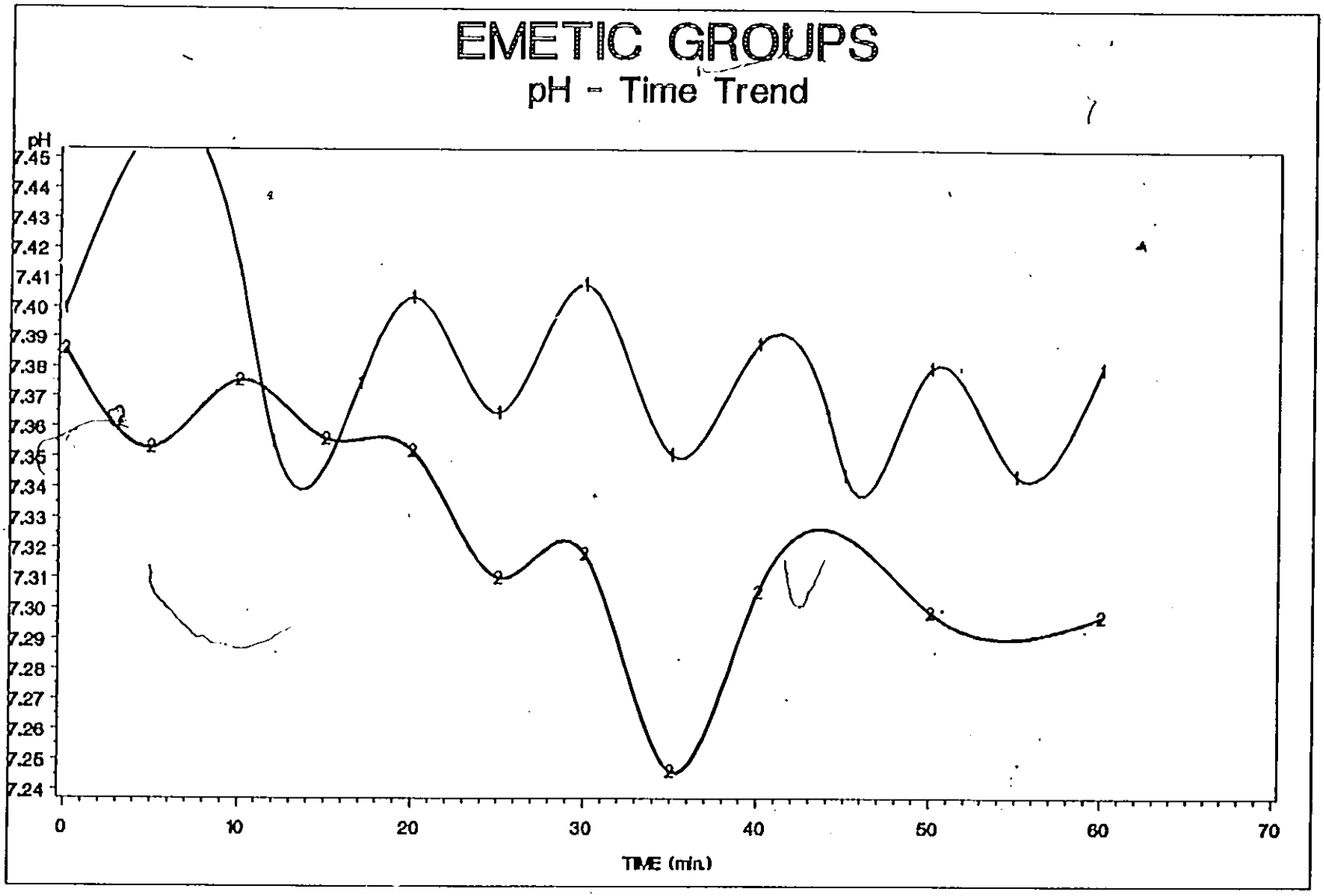

EMETIC GROUPS
pH - Time Trend
pH
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
0
10
20
30
40
50
60
70
TIME (min)

Figure 7b: Changes in blood BE were significant during treatment with ammonium chloride iv (2) and ammonium chloride gavage 40 ml (5; pooled data, n=4). Comparisons with control saline (1) showed both treatments were significantly different ($p<.05$). Comparison between treatments showed no significant differences.

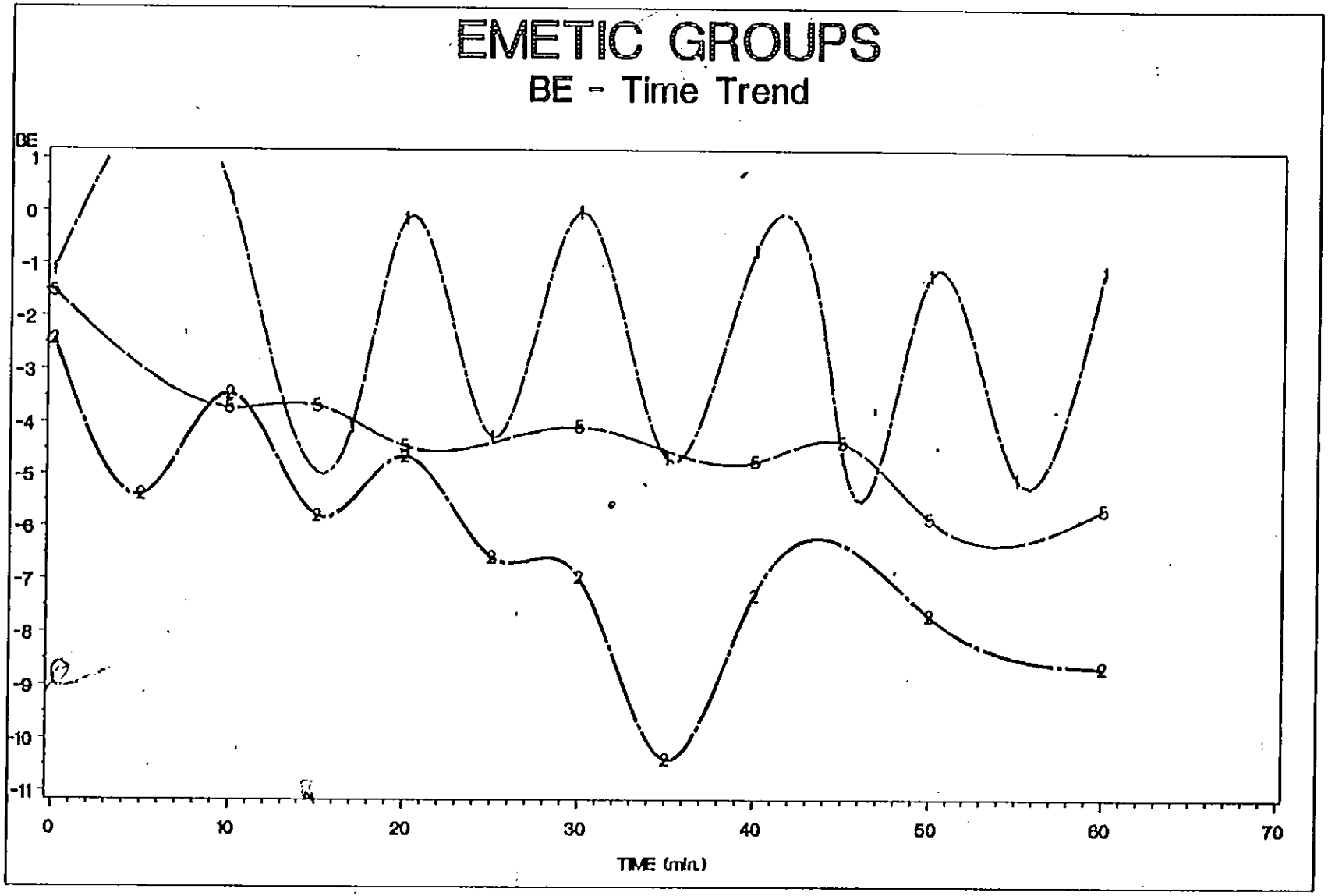

EMETIC GROUPS
BE - Time Trend
BE
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
0
10
20
30
40
50
60
70
TIME (min.)

Figure 7c: Changes in blood HCO_3^- were significant during treatment with ammonium chloride iv (2) and ammonium chloride gavage 40 ml (5; pooled data, n=4). Comparisons with control saline (1) showed both treatments were significantly different ($p<.05$). Comparison between treatments showed no significant differences.

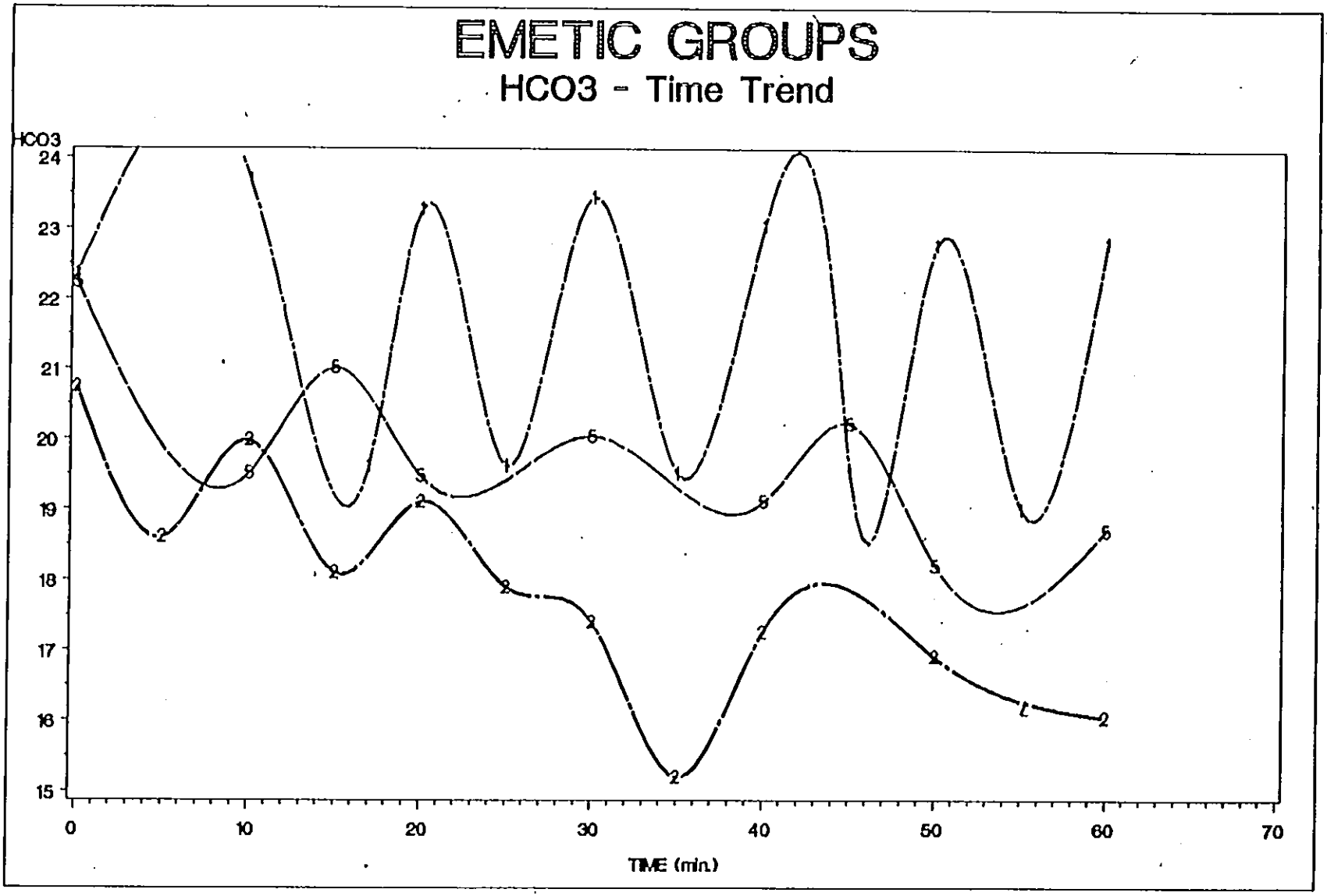

EMETIC GROUPS
HCO3 - Time Trend
HCO3
24
23
22
21
20
19
18
17
16
15
0
10
20
30
40
50
60
70
TIME (min.)

Figure 7d: Changes in blood tot.CO_2 were significant during treatment with ammonium chloride iv (2) and ammonium chloride gavage 40 ml (5; pooled data, n=4). Comparisons with control saline (1) showed both treatments were significantly different ($p<.05$). Comparison between treatments showed no significant differences.

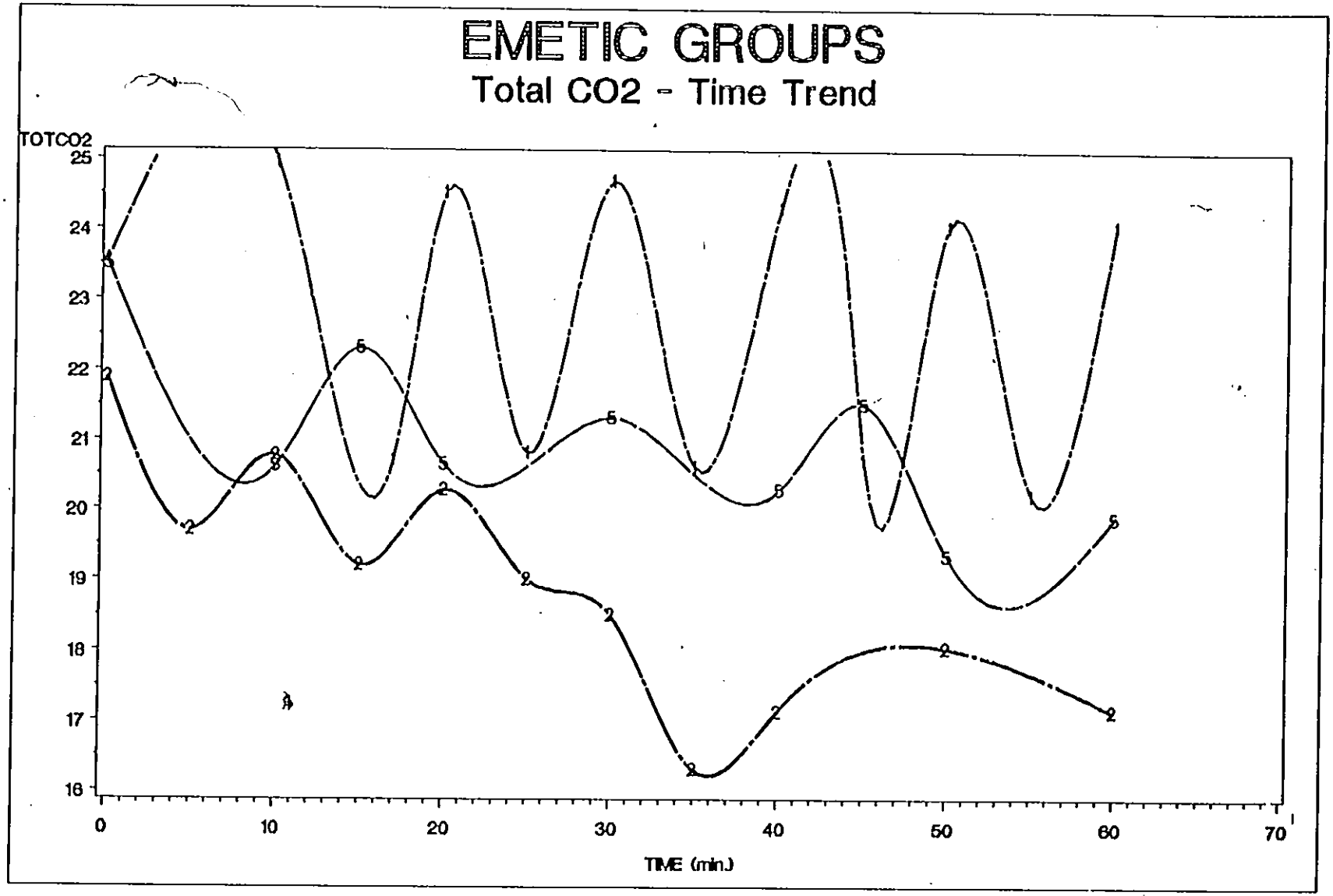
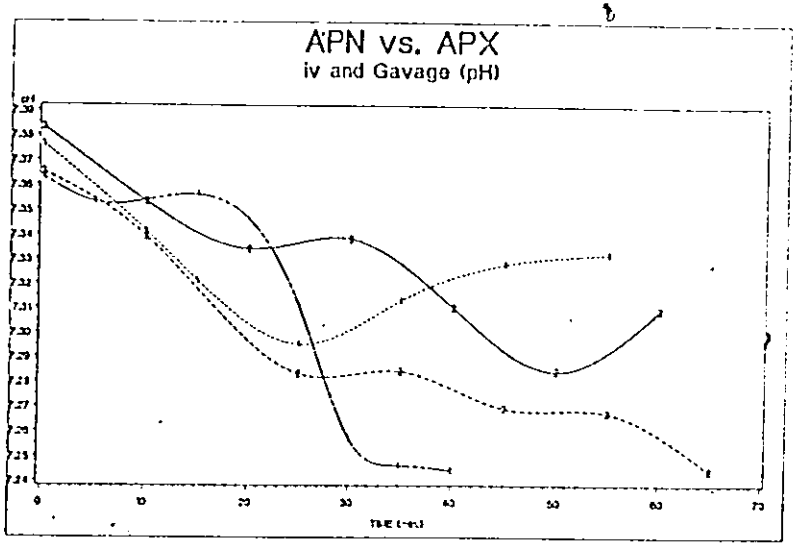
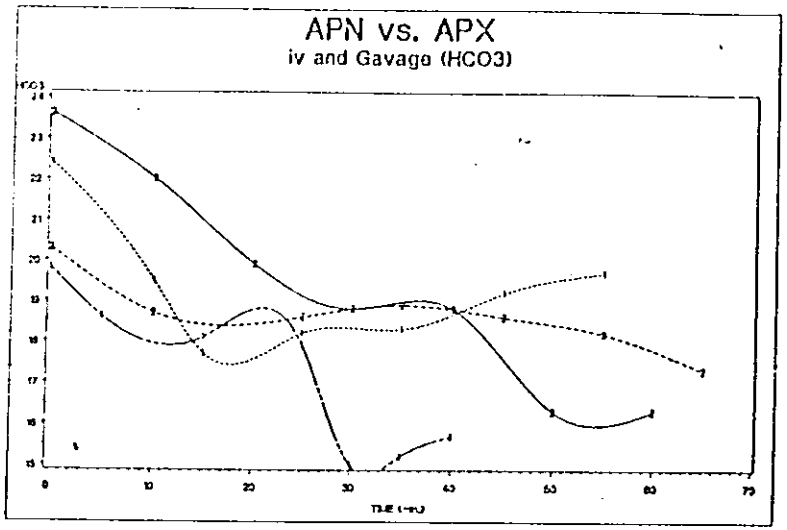
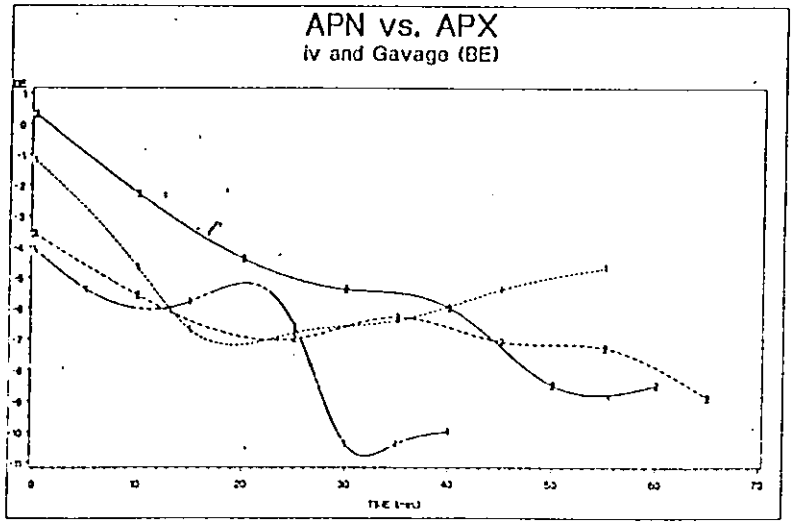

EMETIC GROUPS
Total CO2 - Time Trend
TOTCO2
25
24
23
22
21
20
19
18
17
16
0
10
20
30
40
50
60
70
TIME (min.)

Figure 8: Composite figure presenting acid-base responses of two animals to ammonium chloride delivered via different routes before and after APX. See captions to figures 8a-d for details of treatments.


APN vs. APX
iv and Gavage (pH)


APN vs. APX
iv and Gavage (HCO3)


APN vs. APX
iv and Gavage (BE)

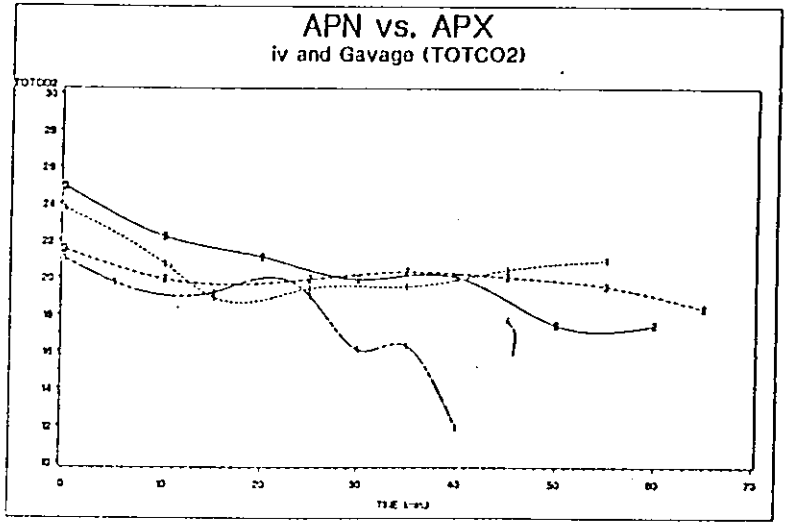

APN vs. APX
iv and Gavage (TOTCO2)

Figure 8a: Changes in blood pH during treatment with ammonium chloride in the same two animals before and after ablation of the AP (APX). The hatched lines (1,2) show intravenous treatment in two APN animals, and dotted lines (1,2) gavage 20 ml in two APX. Raw data are presented for the various time points, along with computer fitted lines.

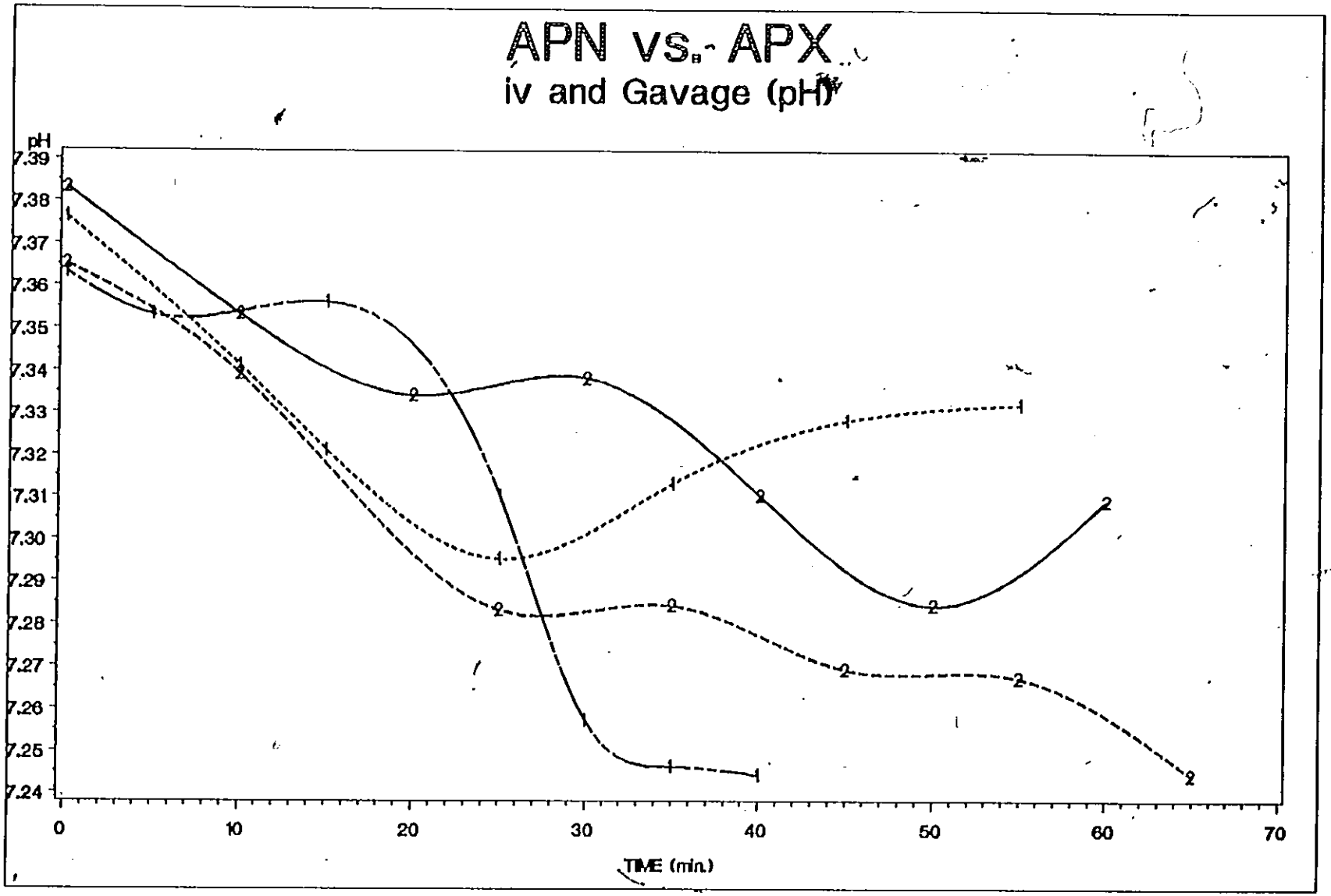

APN vs. APX
iv and Gavage (pH)
pH
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
0
10
20
30
40
50
60
70
TIME (min.)

Figure 8b: Changes in blood BE during treatment with ammonium chloride in the same two animals before and after AP ablation (i.e., APX). The hatched lines (1,2) show intravenous treatment in two APN animals, and dotted lines (1,2) gavage 20 ml in two APX. Raw data are presented for the various time points, along with computer fitted lines.

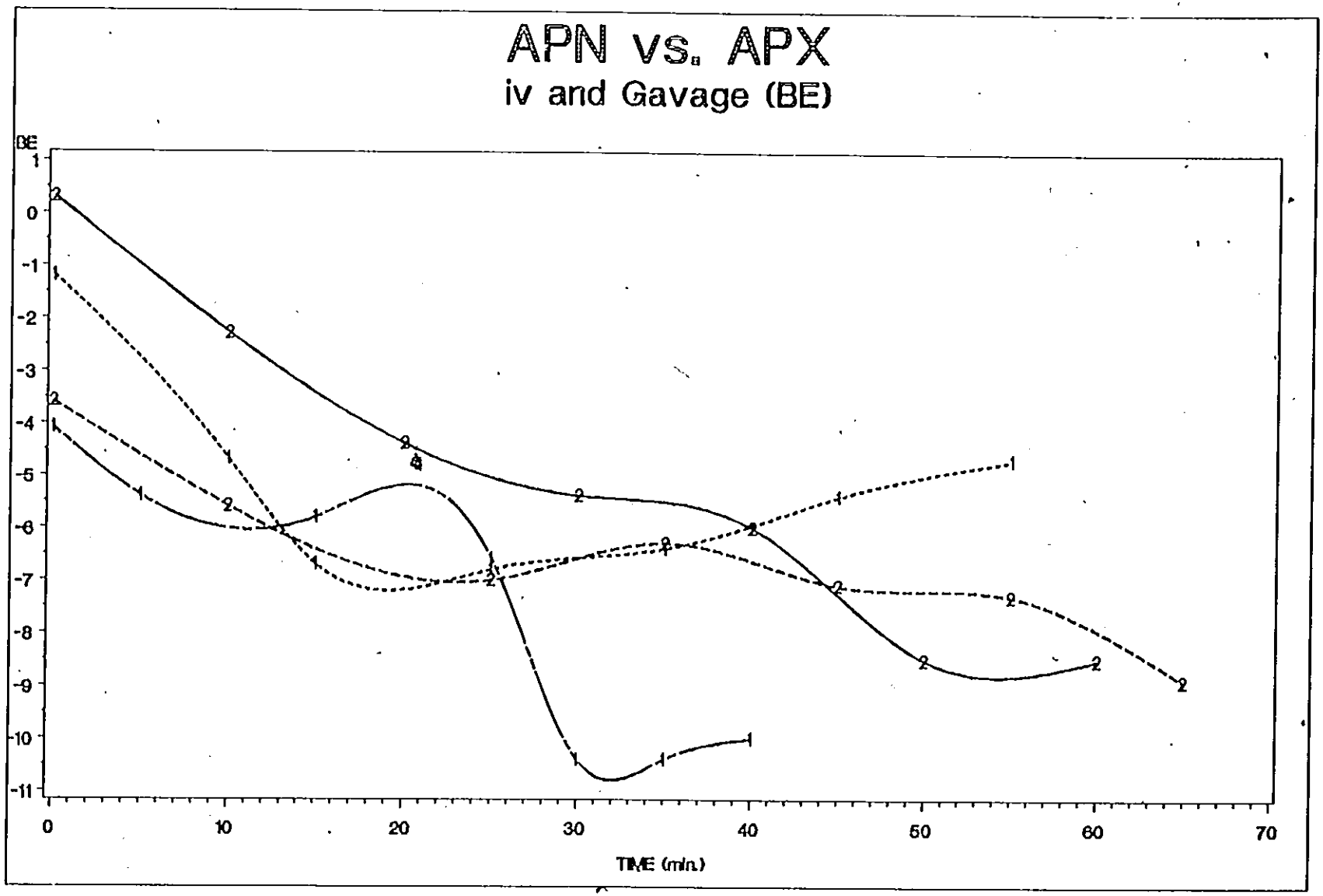

APN vs. APX
iv and Gavage (BE)
BE
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
0
10
20
30
40
50
60
70
TIME (min.)

Figure 8c: Changes in blood HCO_3^- during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment in two APN animals, and dotted lines (1,2) gavage 20 ml in two APX. Raw data are presented for the various time points, along with computer fitted lines.

FIG 8C

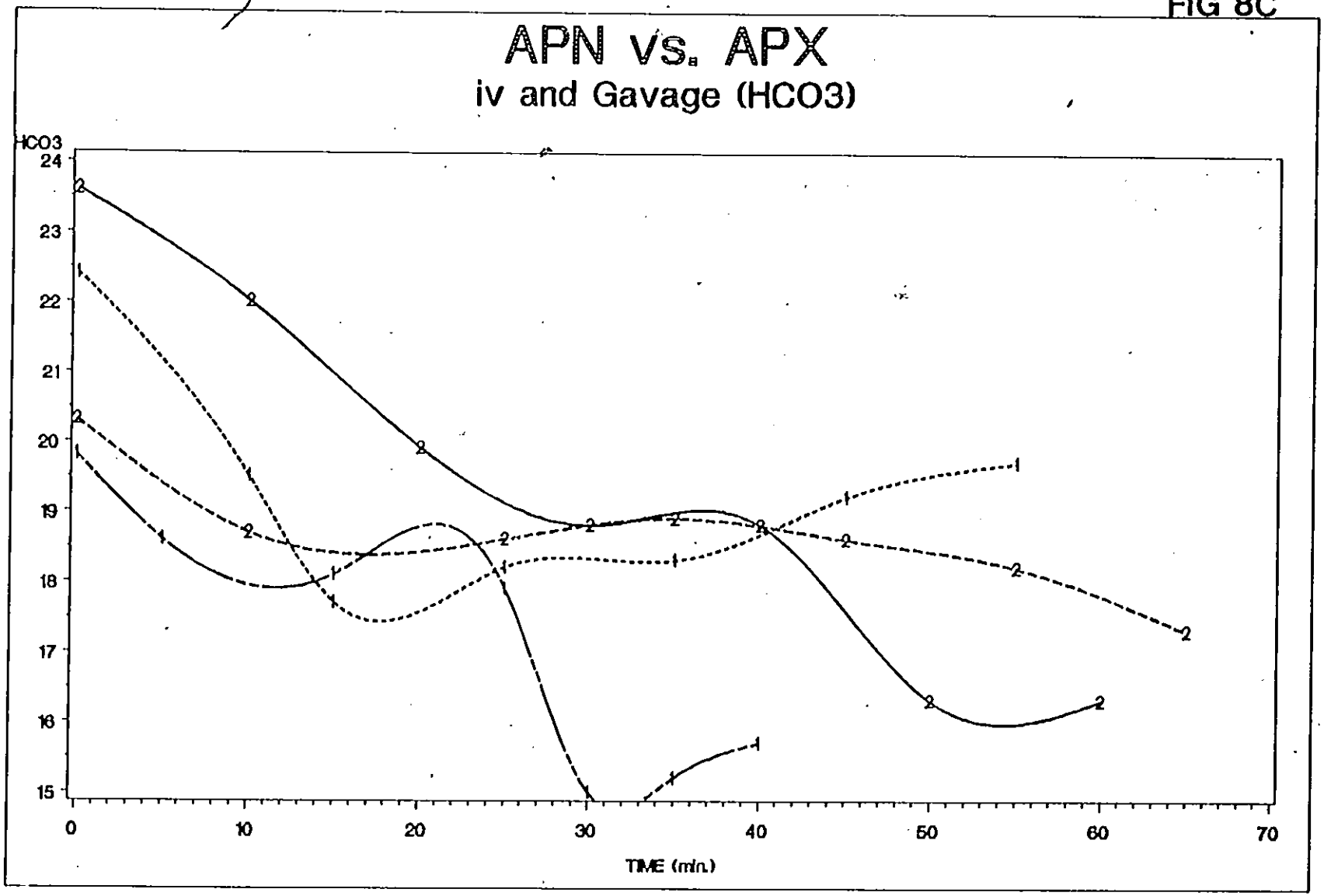

APN Vs. APX
iv and Gavage (HCO3)
HCO3
24
23
22
21
20
19
18
17
16
15
0
10
20
30
40
50
60
70
TIME (min)

Figure 8d: Changes in blood tot.CO_2 during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment in two APN animals, and dotted lines (1,2) gavage 20 ml in two APX. Raw data are presented for the various time points, along with computer fitted lines.

FIG 8D

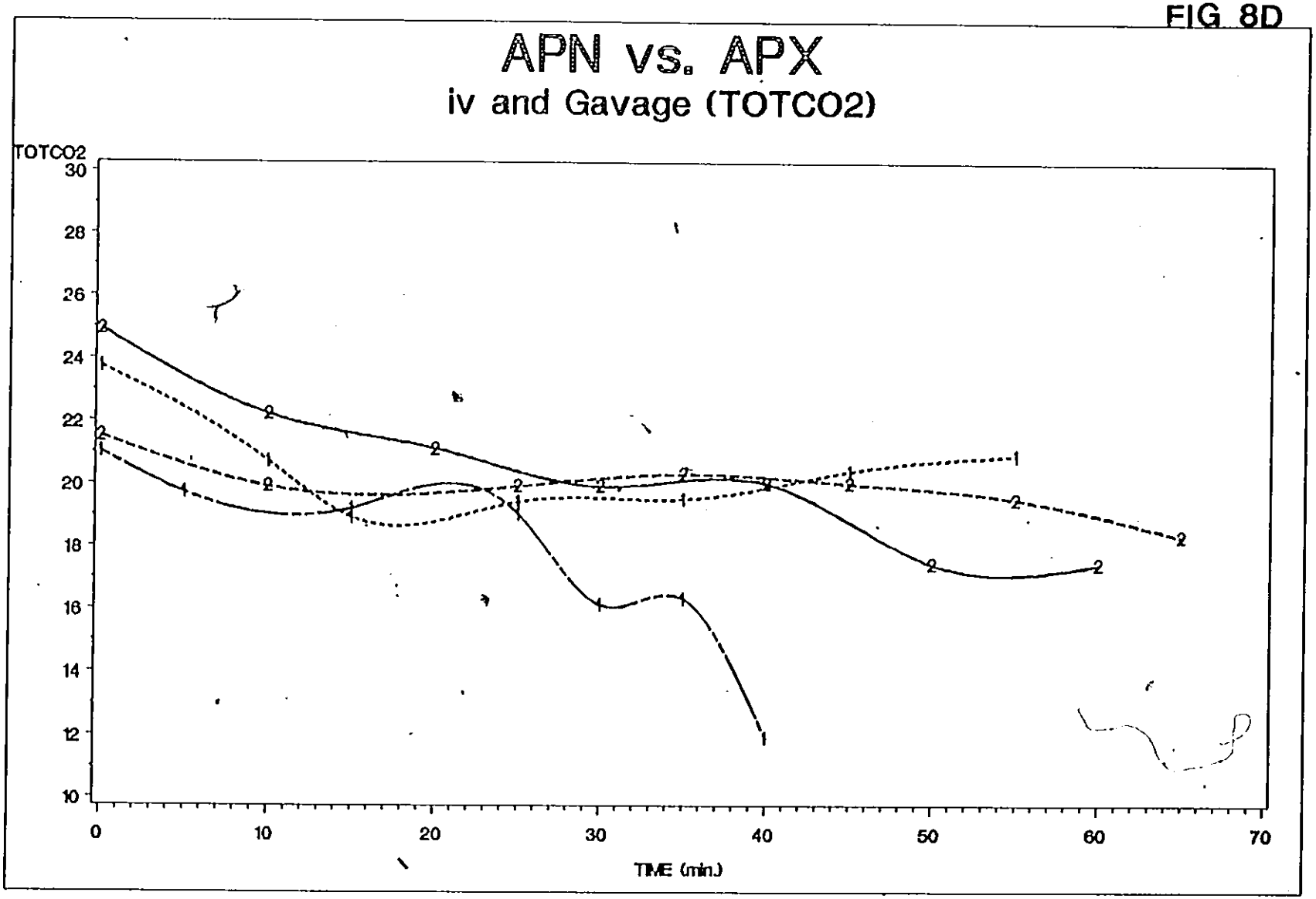
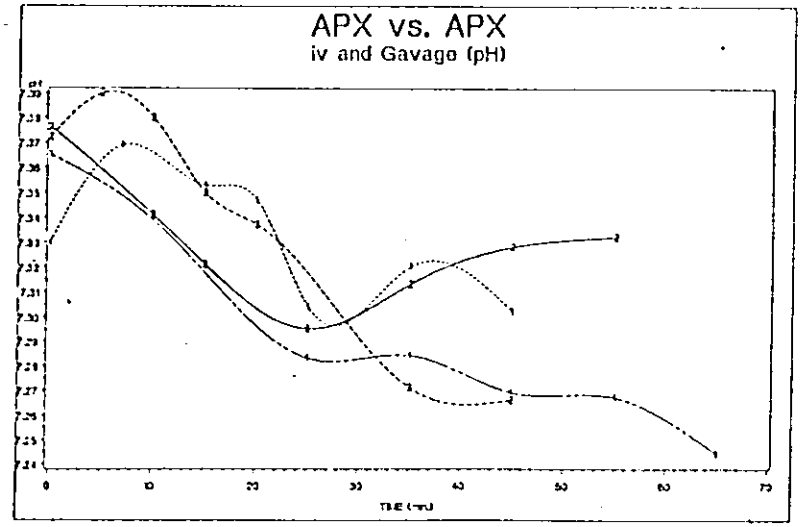
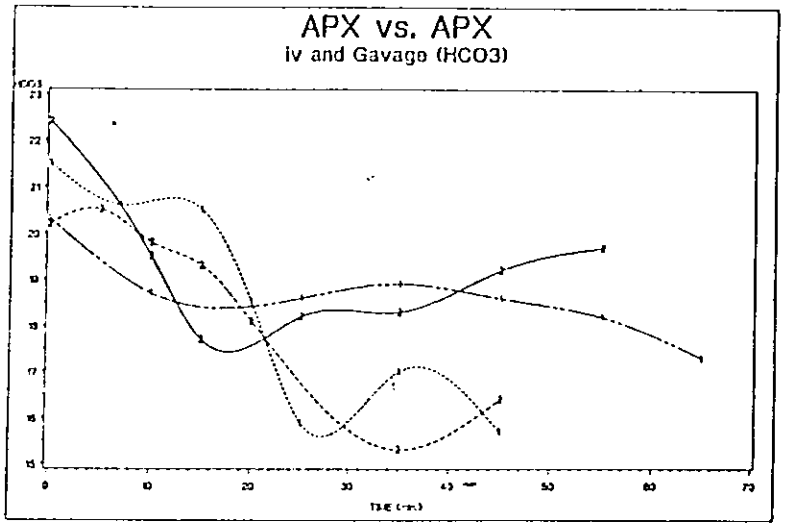
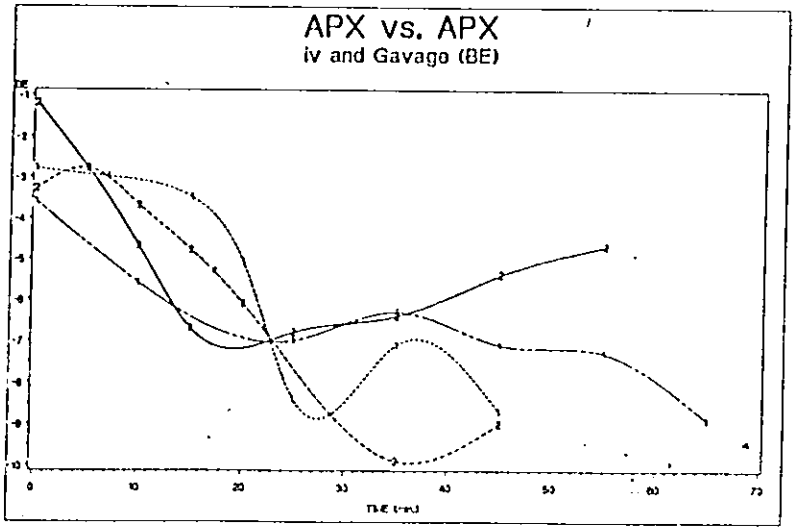

APN vs. APX
iv and Gavage (TOTCO2)
TOTCO2
30
28
26
24
22
20
18
16
14
12
10
0
10
20
30
40
50
60
70
TIME (min)

Figure 9: Composite figure presenting acid-base responses of two APX animals responding to the same treatment via intravenous and intragastric route. See figures 9a-d for details of treatment.


APX vs. APX
iv and Gavage (pH)


APX vs. APX
iv and Gavage (HCO3)


APX vs. APX
iv and Gavage (BE)

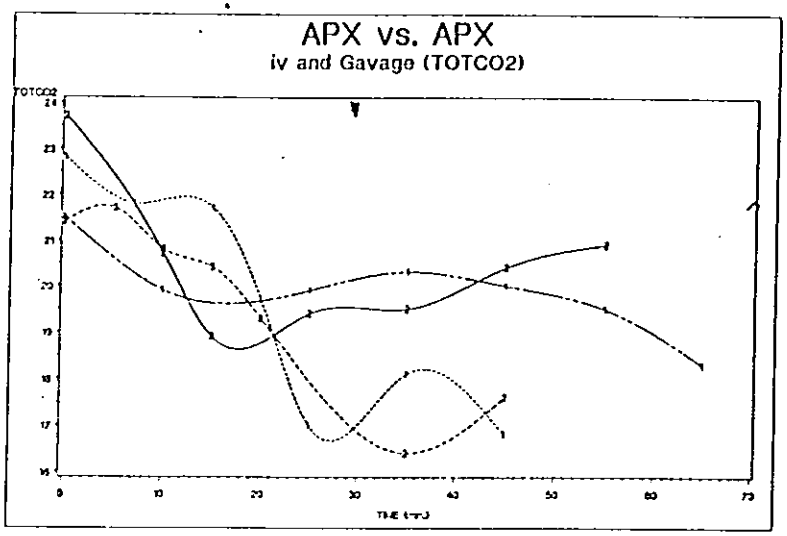

APX vs. APX
iv and Gavage (TOTCO2)

Figure 9a: Changes in blood pH during treatment with ammonium chloride in the same two animals after AP ablation. The hatched lines (1,2) show effect of gavage 20 ml, and dotted lines present effect of intravenous treatment. Raw data from the various time points are connected with computer fitted lines.

FIG 9A

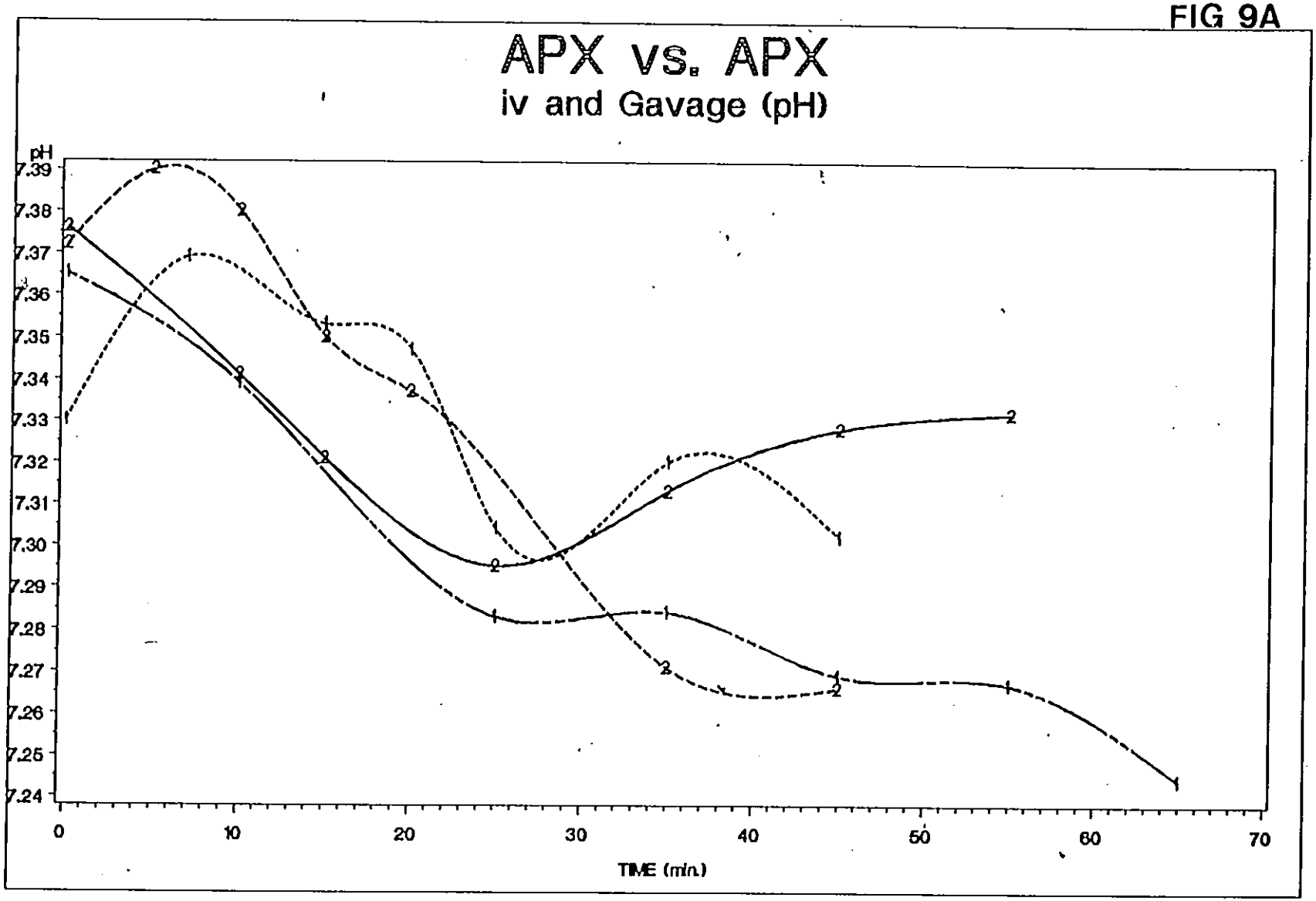

APX vs. APX
iv and Gavage (pH)
pH
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
0
10
20
30
40
50
60
70
TIME (min)

Figure 9b: Changes in blood BE during treatment with ammonium chloride in the same two animals after AP ablation. The hatched lines (1,2) show the effect of gavage 20 ml, and dotted lines present effect of intravenous treatment. Raw data from the various time points are connected with computer fitted lines.

FIG 9B

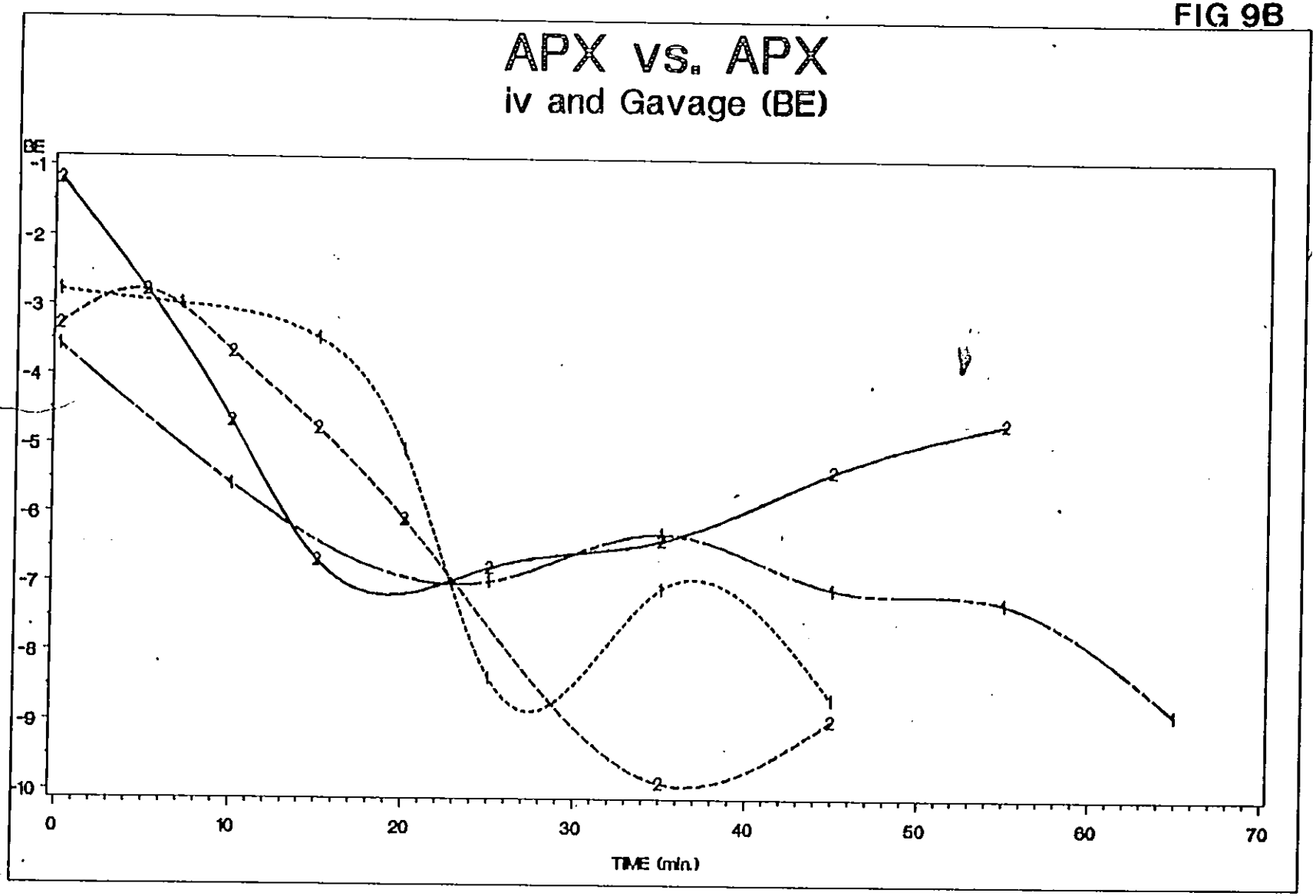

APX vs. APX
iv and Gavage (BE)
BE
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
0
10
20
30
40
50
60
70
TIME (min)

Figure 9c: Changes in blood HCO_3^- during treatment with ammonium chloride in the same two animals after AP ablation. The hatched lines (1,2) show effect of gavage 20 ml, and dotted lines present effects of intravenous treatment. Raw data from the various time points are connected with computer fitted lines.

FIG 9C

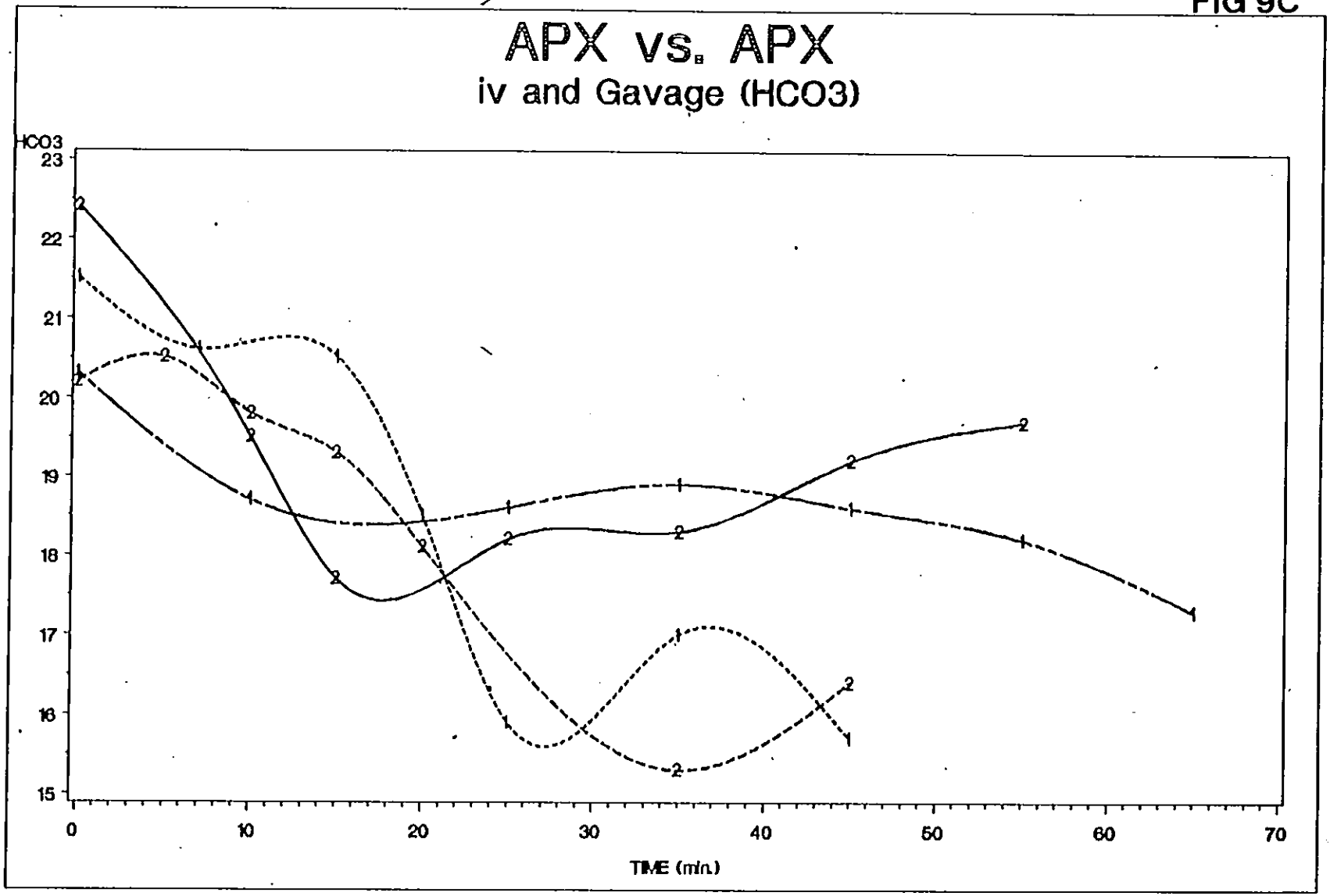

APX vs. APX
iv and Gavage (HCO3)
HCO3
23
22
21
20
19
18
17
16
15
0
10
20
30
40
50
60
70
TIME (min)

Figure 9d: Changes in blood tot.CO_2 during treatment with ammonium chloride in the same two animals after AP ablation. The hatched lines (1,2) show effects of gavage 20 ml, and dotted lines present effects of intravenous treatment. Raw data from the various time points are connected with computer fitted lines.

FIG 9D

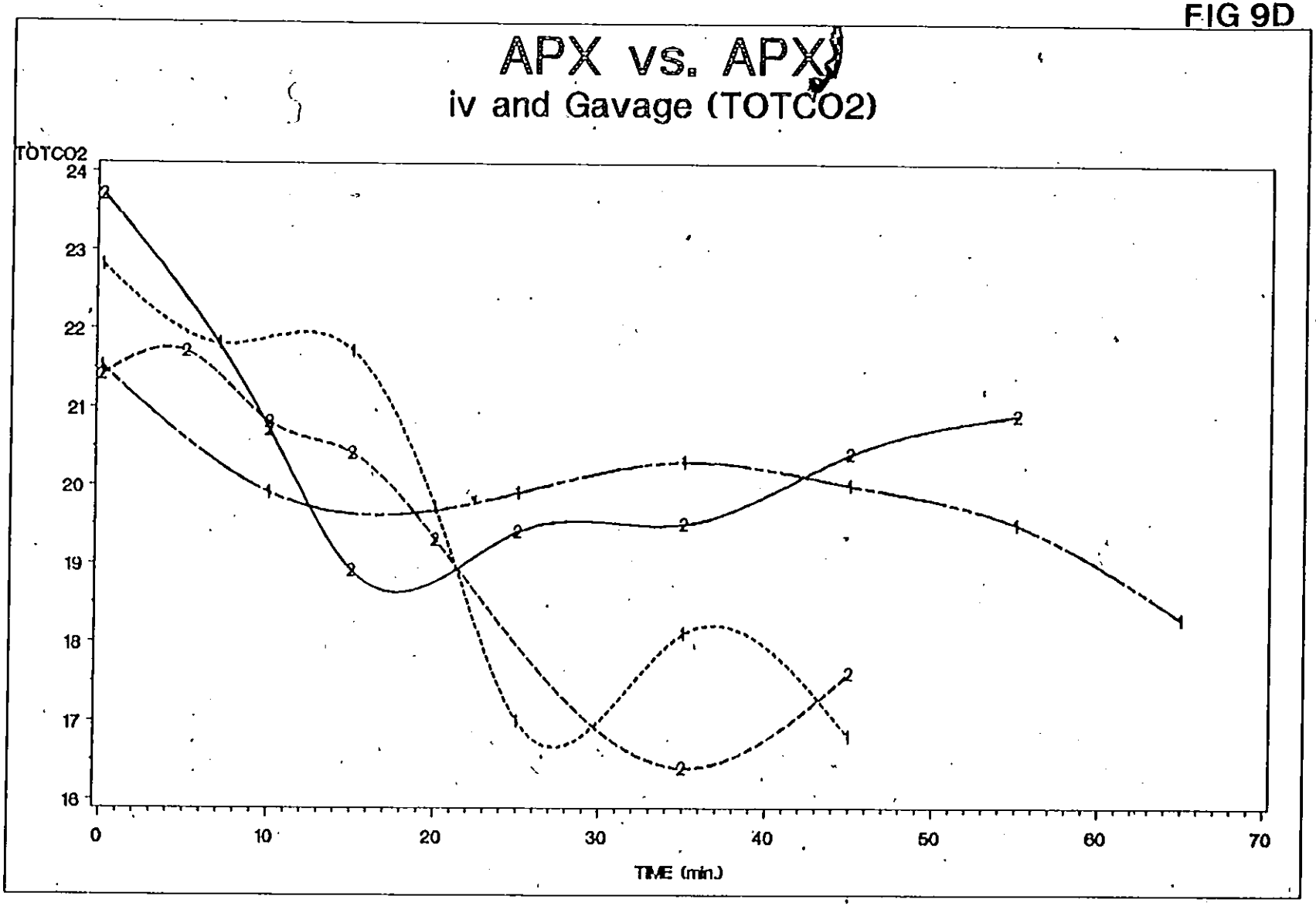
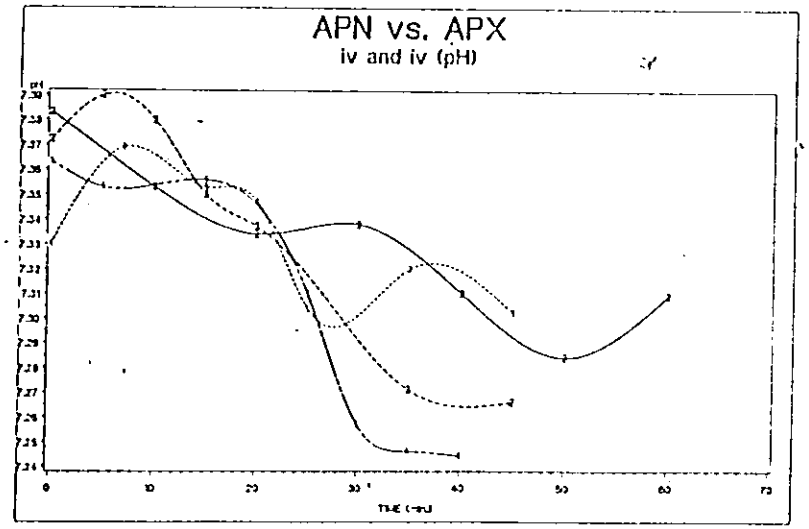
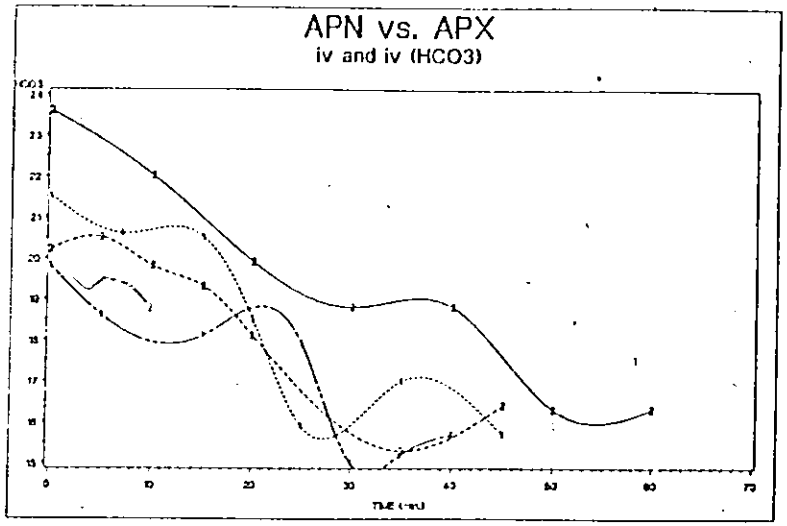
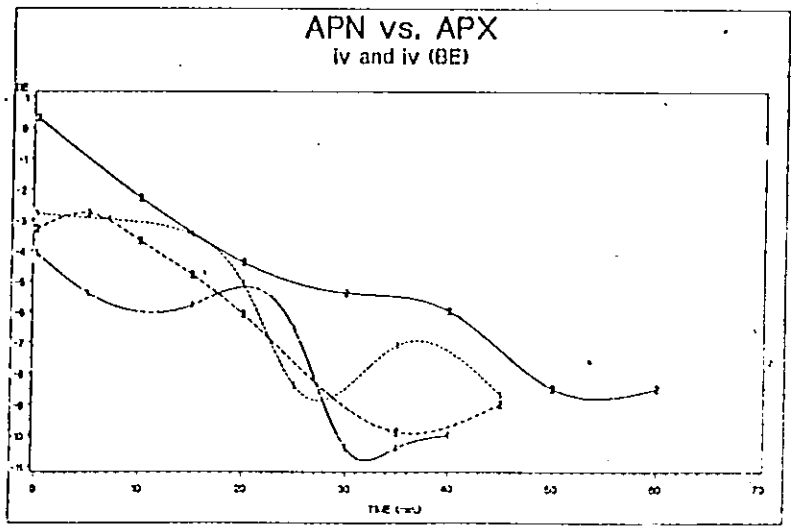

APX vs. APX)
iv and Gavage (TOTCO2)
TOTCO2
24
23
22
21
20
19
18
17
16
0
10
20
30
40
50
60
70
TIME (min.)

Figure 10: Composite figure presenting acid-base responses to intravenous infusion of ammonium chloride in two AP-intact animals and two with AP ablated. See captions to figures 10a-d for details of treatment.


APN vs. APX
iv and iv (pH)


APN vs. APX
iv and iv (HCO3)


APN vs. APX
iv and iv (BE)

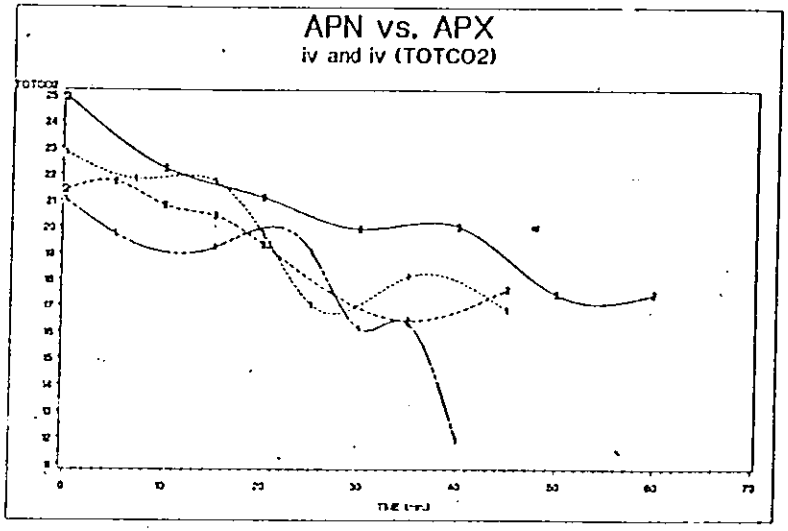

APN vs. APX
iv and iv (TOTCO2)

Figure 10a: Changes in blood pH during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment before AP ablation, and dotted lines (1,2) iv infusion in APX animals. Raw data are presented for the various time points, along with computer fitted lines.

FIG 10A

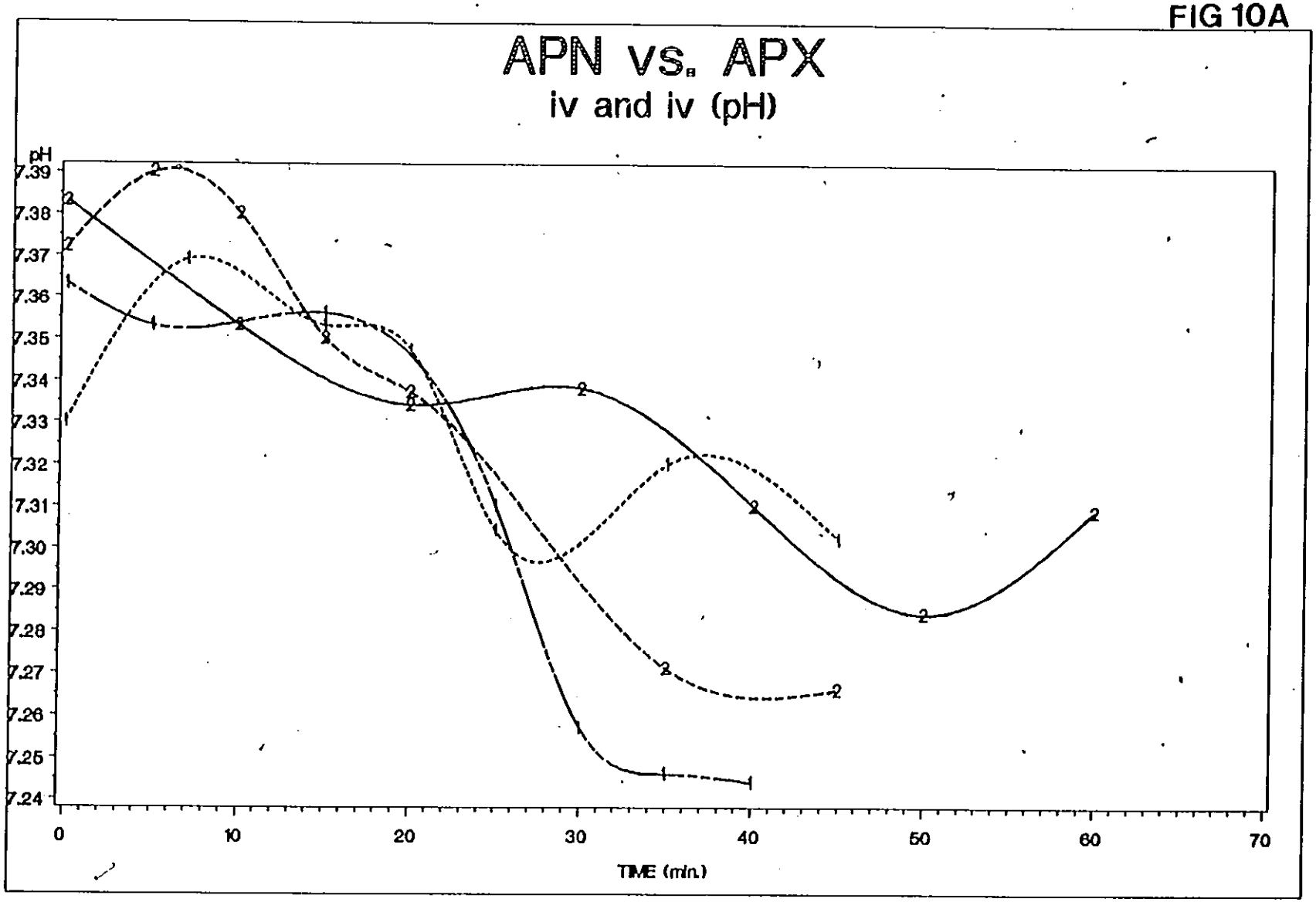

APN vs. APX
iv and iv (pH)
pH
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
0
10
20
30
40
50
60
70
TIME (min.)

Figure 10b: Changes in blood BE during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment before AP ablation, and dotted lines (1,2) iv infusion in APX animals. Raw data are presented for the various time points, along with computer fitted lines.

FIG 10B

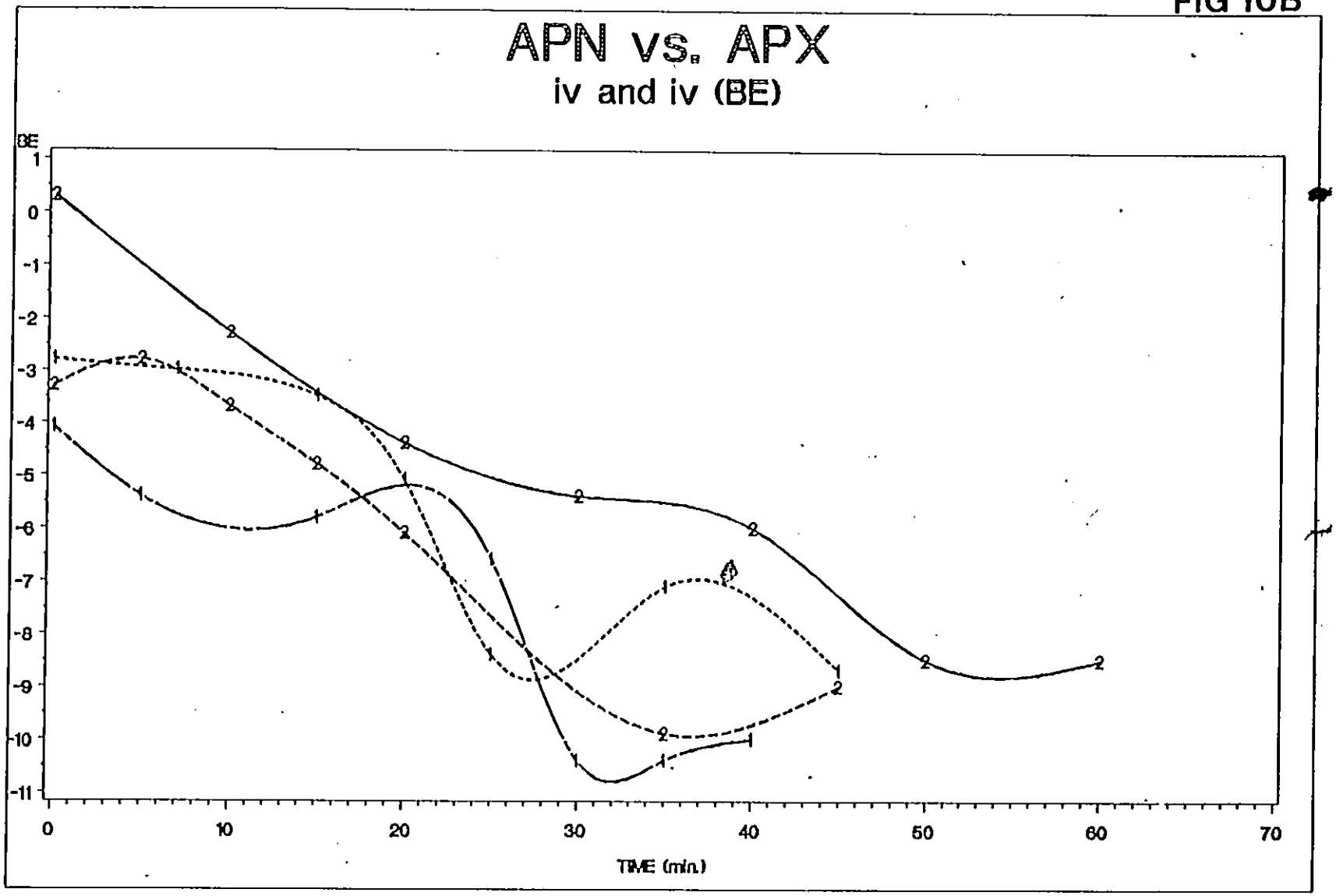

APN vs. APX
iv and iv (BE)
BE
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
0
10
20
30
40
50
60
70
TIME (min)

Figure 10c: Changes in blood HCO_3^- during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment before AP ablation, and dotted lines (1,2) iv infusion in APX animals. Raw data are presented for the various time points, along with computer fitted lines.

FIG 10C

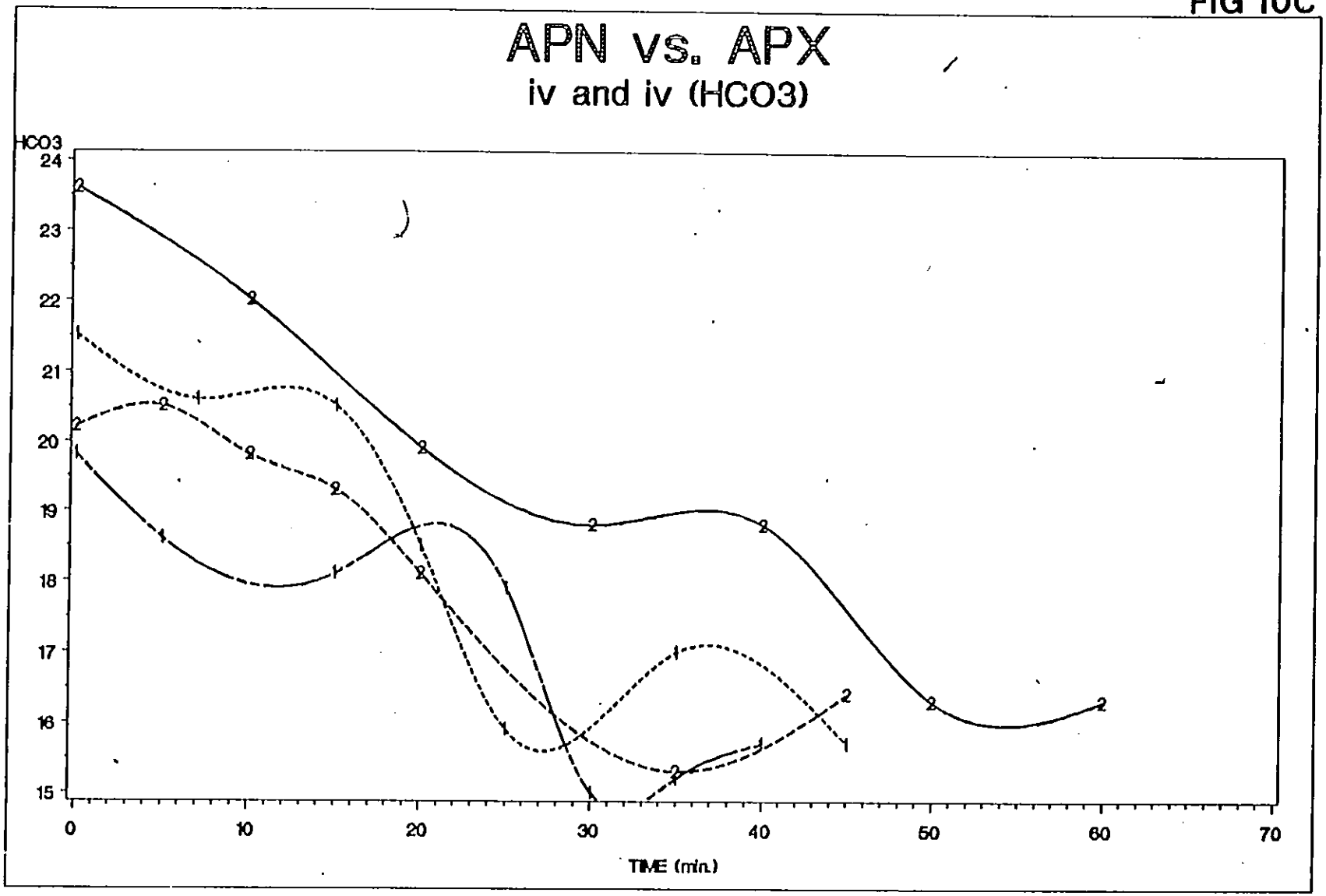

APN vs. APX
iv and iv (HCO3)
HCO3
24
23
22
21
20
19
18
17
16
15
0
10
20
30
40
50
60
70
TIME (min.)

Figure 10d: Changes in blood tot.CO_2 during treatment with ammonium chloride in the same two animals before and after AP ablation (APX). The hatched lines (1,2) show intravenous treatment before AP ablation, and dotted lines (1,2) iv infusion in APX animals. Raw data are presented for the various time points, along with computer fitted lines.

FIG 10D

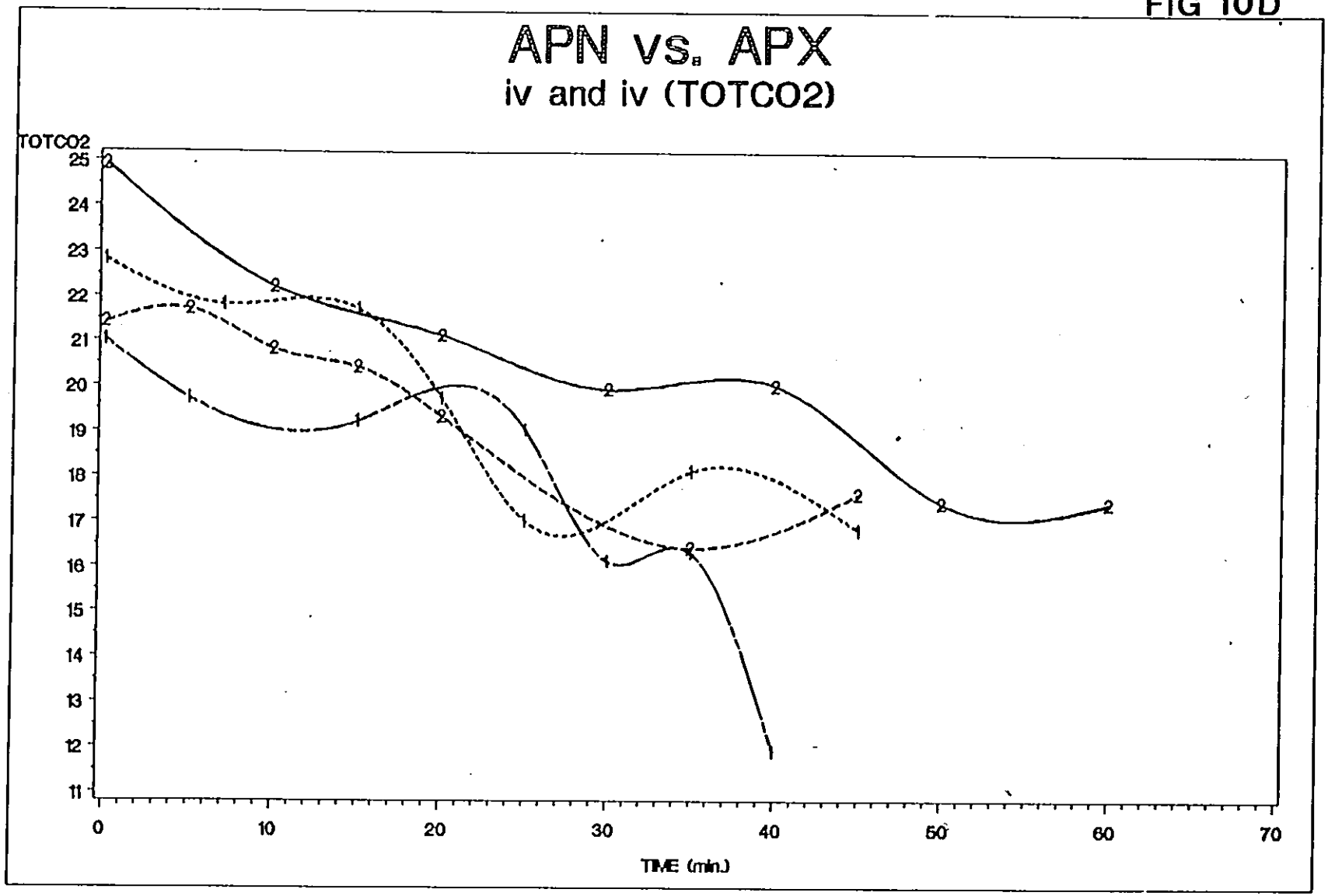
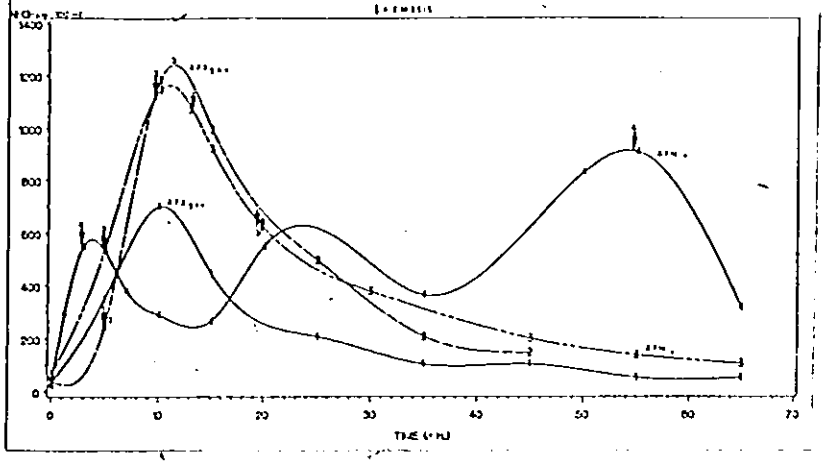

APN vs. APX
iv and iv (TOTCO2)
TOTCO2
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
0
10
20
30
40
50
60
70
TIME (min.)

Figure 11: Composite figure composed from figures 11a-c, to facilitate comparisons. Arrows indicate onset of emetic episodes. See figures 11a-c for details of treatments.

AMMONIA LEVELS

iv vs. Gavage

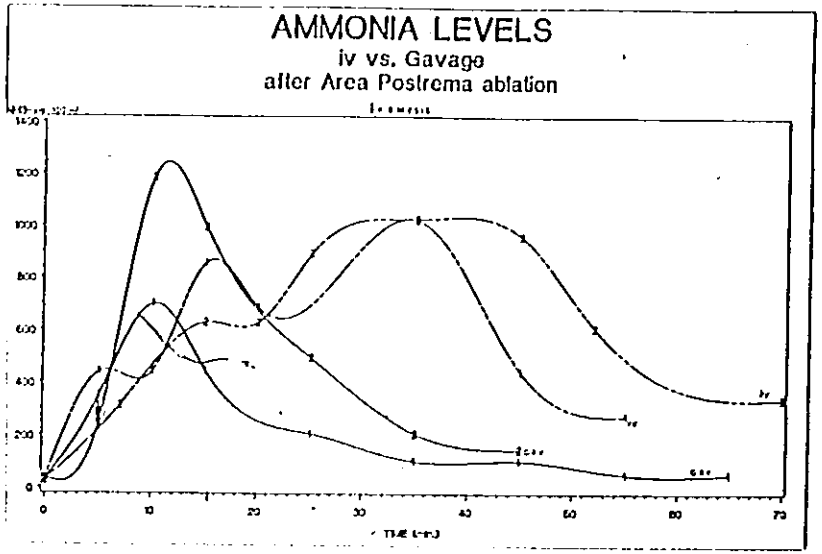
intact vs. Area Postrema ablation (APN - APX)



AMMONIA LEVELS

iv vs. Gavage

after Area Postrema ablation



AMMONIA LEVELS

iv vs. iv

intact vs. Area Postrema ablation (APN - APX)

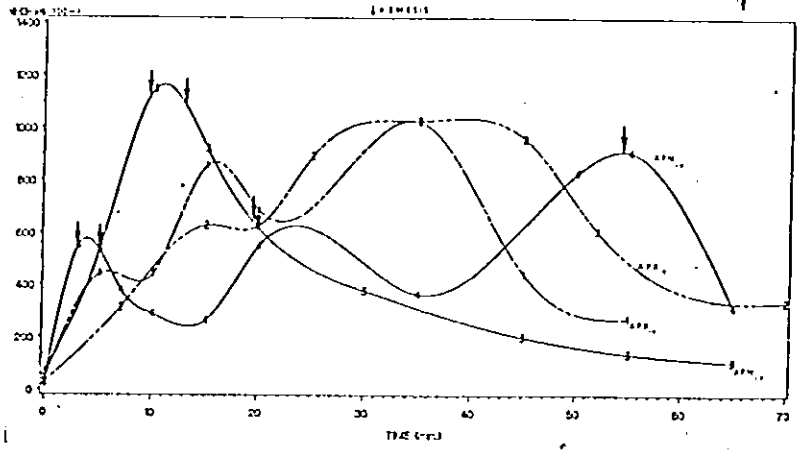


Figure 11a: Changes in plasma ammonia levels during treatment with ammonium chloride. Animals 1 and 2 were APX and received 20 ml NH_4Cl gavage. Animals 3 and 4 were APN and received a standard NH_4Cl intravenous treatment. Raw data are presented for the various time points, along with computer fitted lines.

FIG 11a

AMMONIA LEVELS

iv vs. Gavage

intact vs. Area Postrema ablation (APN - APX)

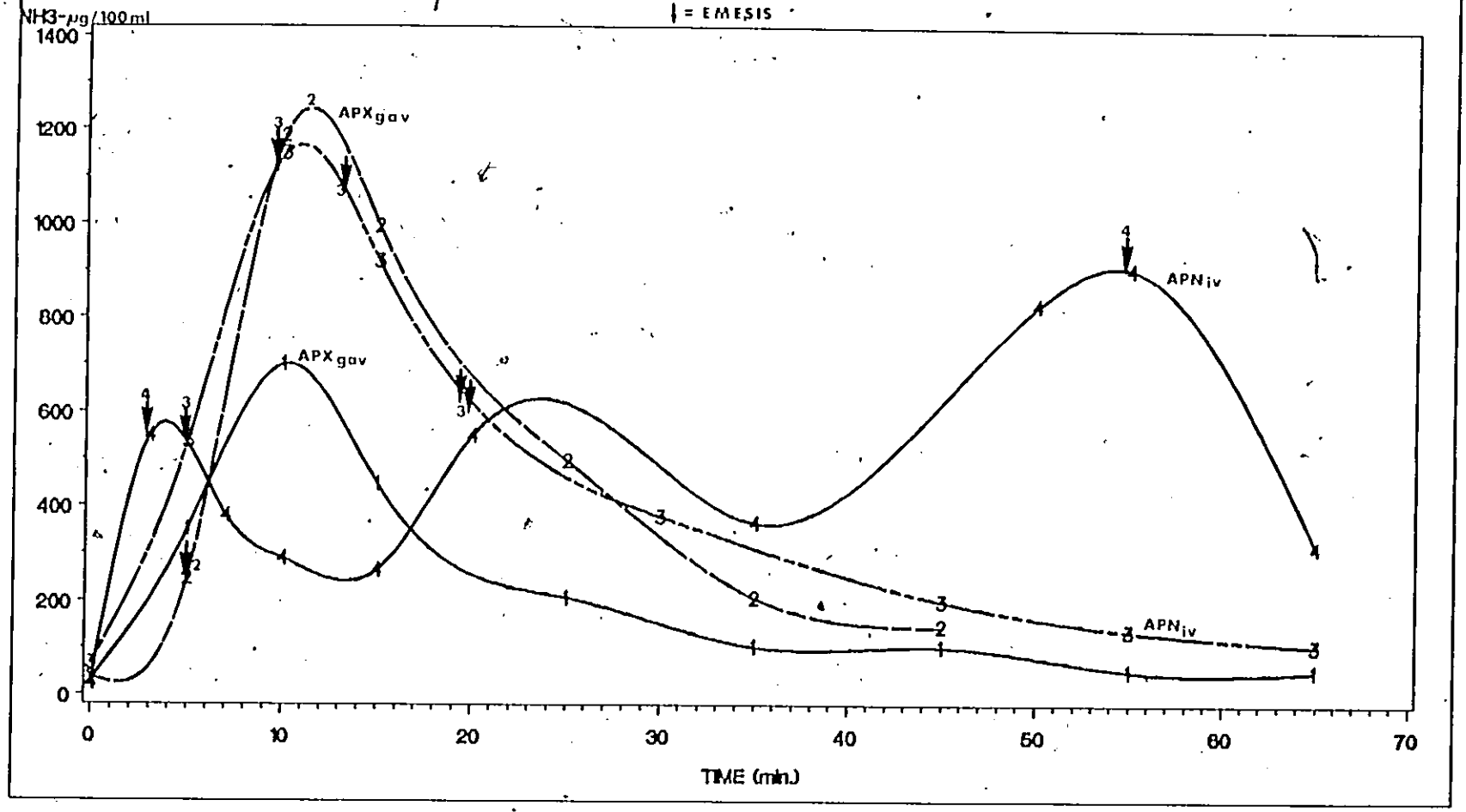


Figure 11b: Change in plasma ammonia levels during treatment with ammonium chloride. Two sets of data are presented for the two APX animals. The hatched lines reflect NH_3 values for animals given intravenous NH_4Cl, while the solid lines show NH_3 levels during gavage.

FIG. 11b

AMMONIA LEVELS

iv vs. Gavage
after Area Postrema ablation

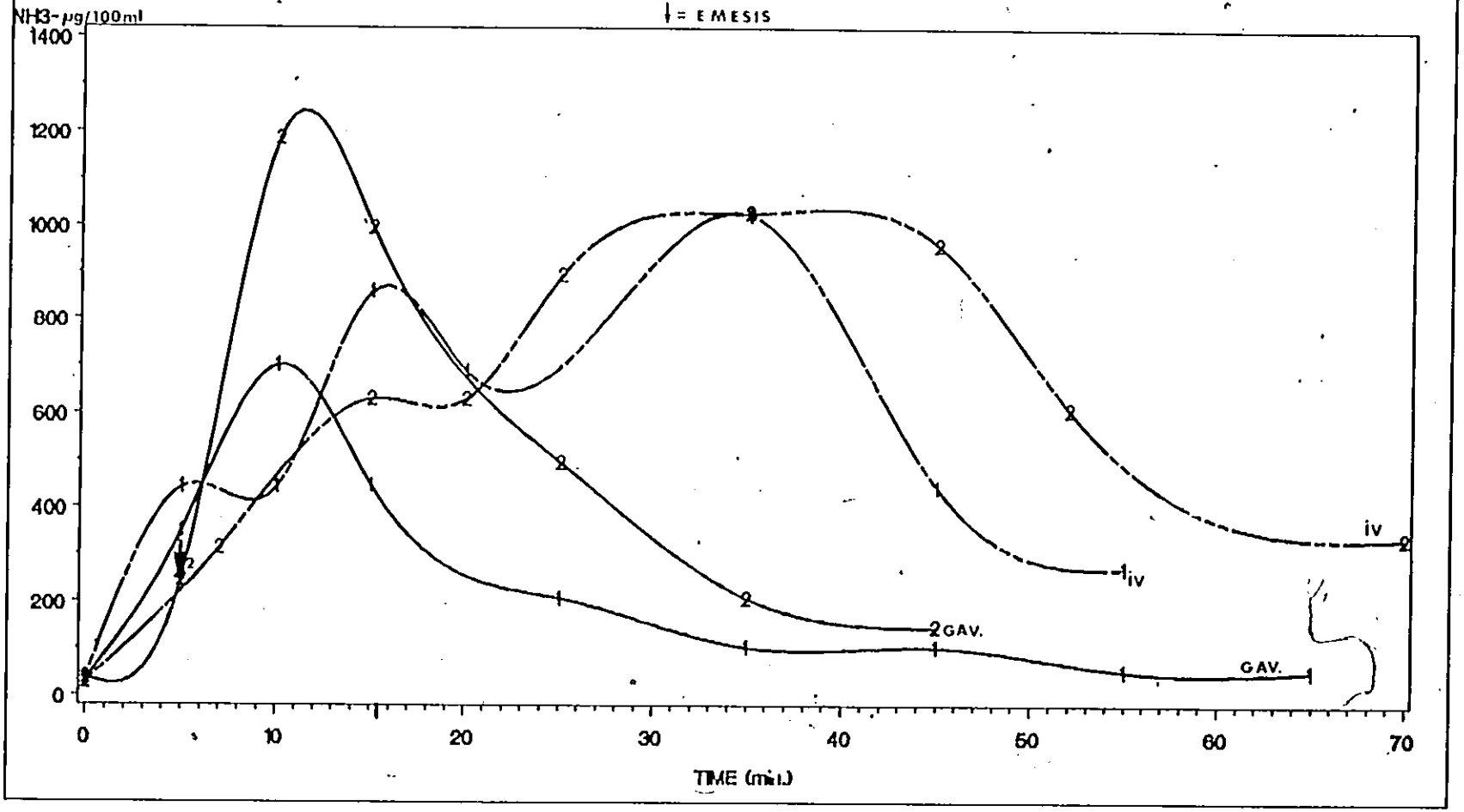


Figure 11c: Changes in plasma ammonia levels during intravenous infusion with ammonium chloride. Animals 1 and 2 were APK; 3 and 4, APN.

FIG 11c

AMMONIA LEVELS

iv vs. iv

intact vs. Area Postrema ablation (APN - APX)

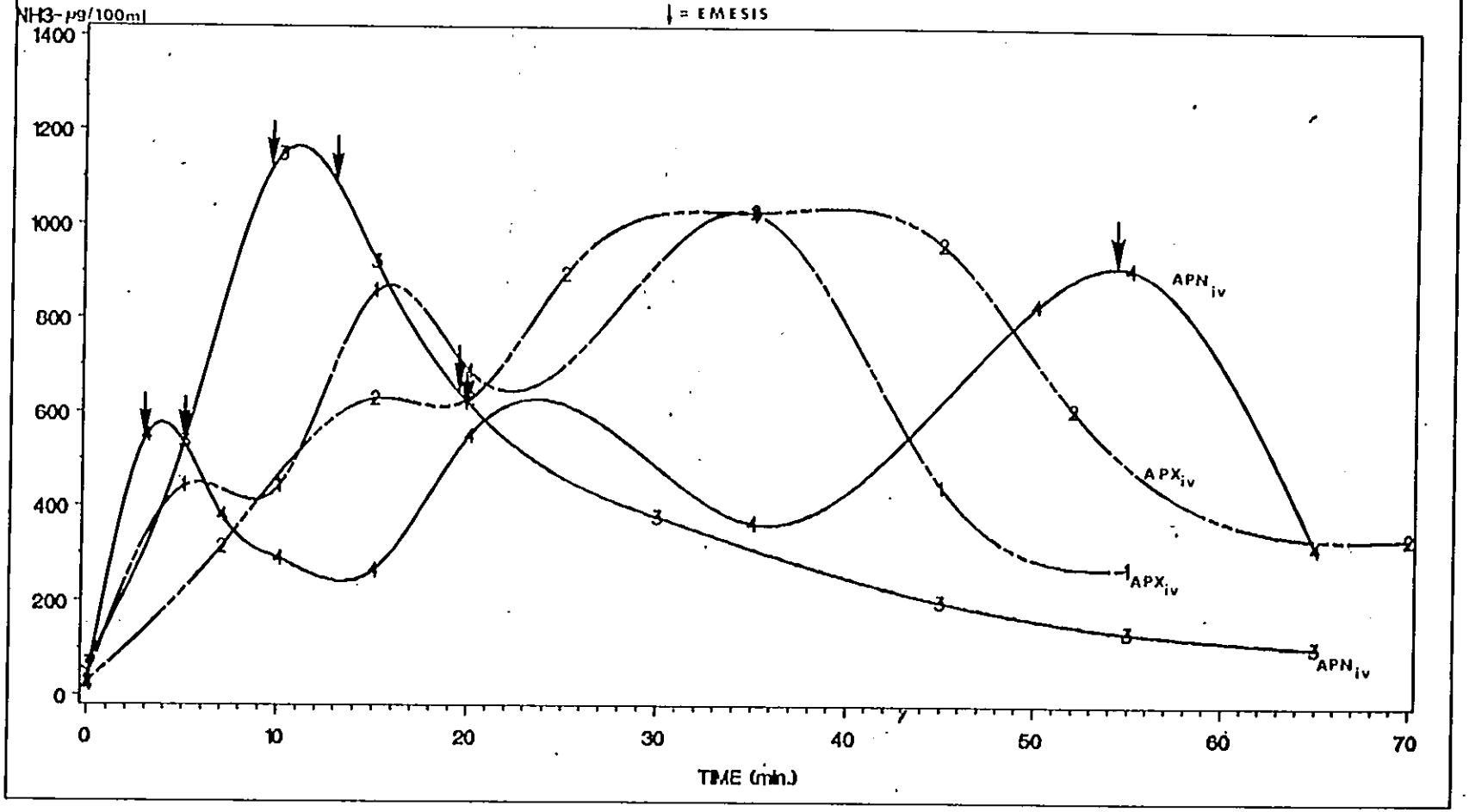


Figure 12: pH changes in cisplatin-treated animals during the infusion and observation periods. Raw data are presented for each animal (1-2, APX, 3-4, APN). The thick solid line is a computed mean of the four values and the vertical bar represents the SEM for each time point. The asterisks correspond to the time of the first vomiting episode.

FIG 12

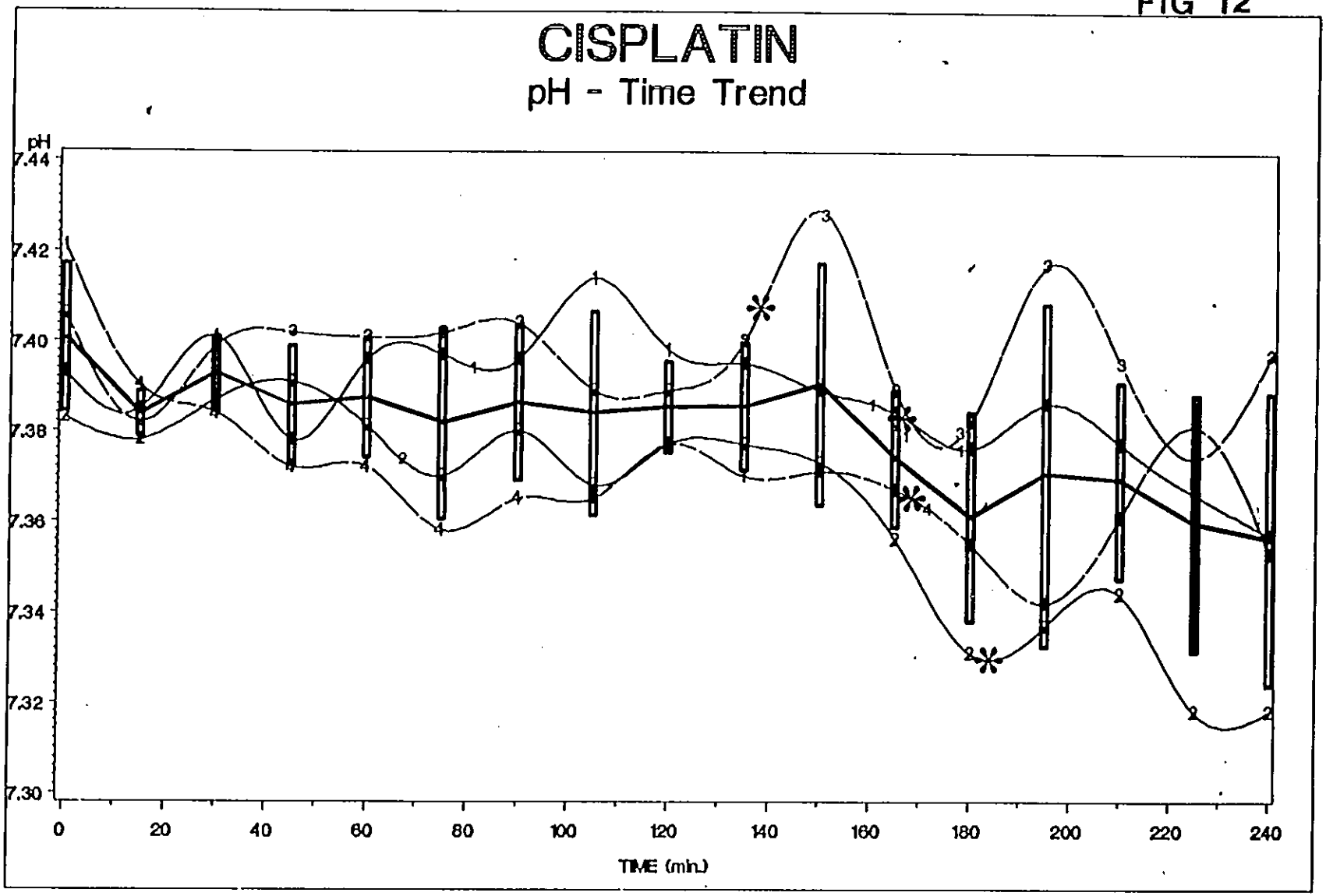
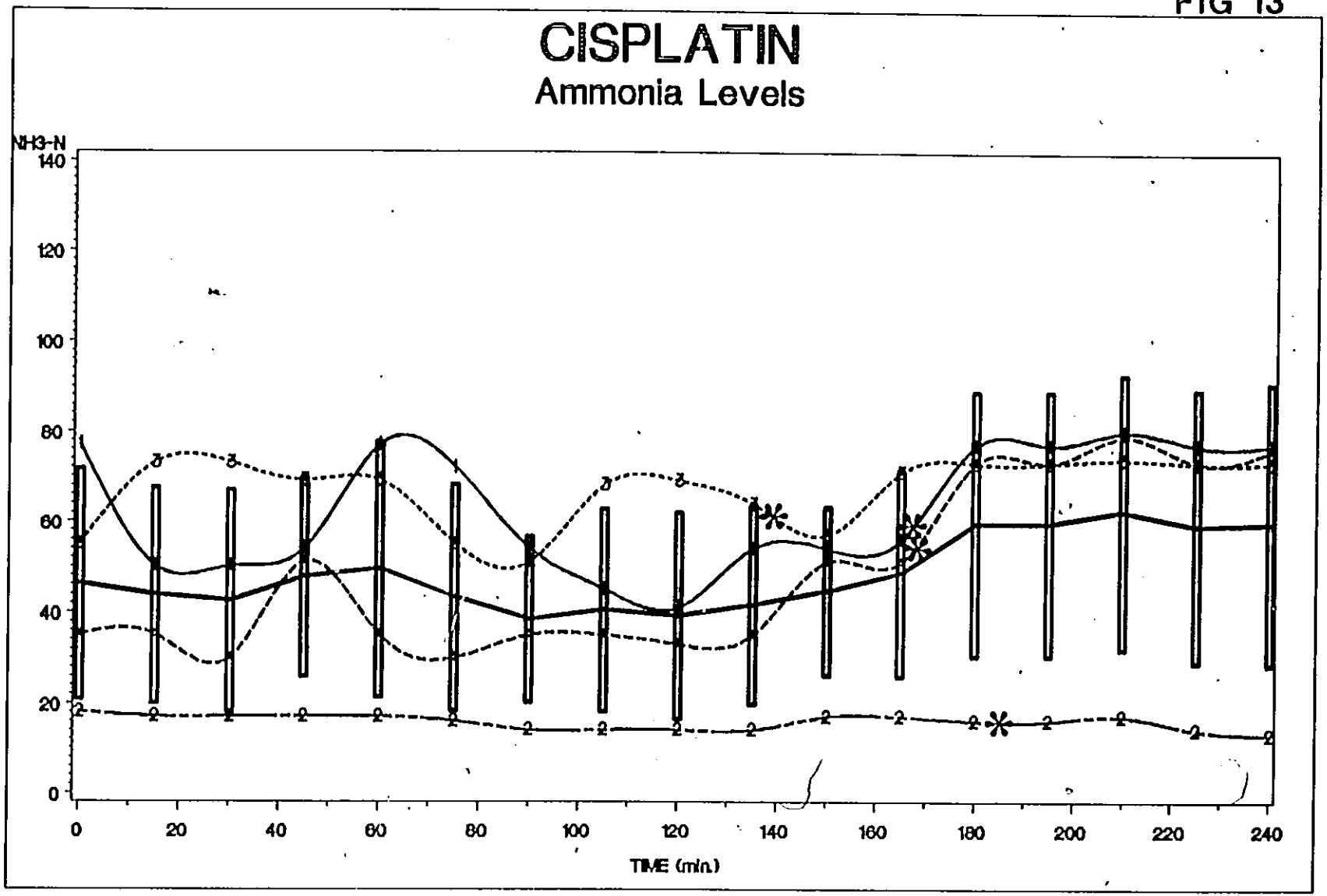

CISPLATIN
pH - Time Trend
pH
7.44
7.42
7.40
7.38
7.36
7.34
7.32
7.30
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (min)

Figure 13: Plasma ammonia levels during the infusion and observation periods. Raw data are presented for each animal at the various time points; (Subjects 1 & 2, APX, 3 & 4, APN). The thick solid line is a computed mean of the four values and the vertical bars represent the SEM for each time point.

FIG 13


CISPLATIN
Ammonia Levels
NH3-N
140
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (min)

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APPENDIX I

The following pages contain all of the raw data used to generate Figures 6-13. Also included are the computer generated statistical outputs including: the mean of the variable for each time point (n=4); the standard deviation, SD; the standard error, SE; the variance, and the sum.

The following abbreviations have been utilized:

Group	=	Treatment (as listed below)
Min	=	Sample time (minutes)
Time	=	Sample number
Subj	=	Subject, numerals refer to each of 6 dogs
Na-Old/NA-New K-Old /K-New	=	Refers to electryte data collected from two different flame photometers. Old = IL 443, New = Corning 480. The units are m mol/L.

GROUP #	TREATMENT	APN/APX	SUBJECT #
1	Saline 0.9%	APN	1,2,3,4
2	Ammonium chloride iv	APN	1,2,3,4
3	Ammonium chloride iv	APN	3,4 repeated
4	Ammonium chloride gavage, 20ml	APN	1,2,3,4
5	Ammonium chloride gavage, 40ml	APN	1,2,3,4
6	Ammonium chloride gavage, 20 ml	APX	1,2
7	Ammonium chloride iv	APX	1,2
8	Ammonium bicarbonate iv	APN	1,2,3,4
9	Lactic acid iv	APN	1,2,3,4
10	Sodium lactate iv	APN	1,2,3,4
11	Sodium bicarbonate iv	APN	1,2,3,4
12	Mannitol 904 mOsm/L iv	APN	1,2,3,4
13	Mannitol 674 mOsm/L iv	APN	1,2,3,4
14	Sodium lactate and sodium sulphate iv	APN	1=5, 2=6, 3,4
15	Cisplatin iv	APN or APX	3,4 1,3

APPENDIX I

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
01	0	01	1	7.405	84.7	69.3	-2.1	21.5	22.6
01	10	02	1	7.389	36.5	58.6	-2.2	21.7	22.9
01	20	03	1	7.386	36.9	58.0	-2.2	21.7	22.9
01	30	04	1	7.396	35.8	62.2	-2.2	21.6	22.8
01	40	05	1	7.364	39.0	52.2	-2.5	21.8	23.1
01	44	06	1	7.364	39.1	54.3	-2.5	21.9	23.1
01	50	07	1	7.365	39.2	56.4	-2.4	22.0	23.2
01	0	01	2	7.367	35.4	43.4	-3.9	19.9	21.1
01	12	02	2	7.355	39.7	37.9	-2.4	21.8	23.1
01	17	03	2	7.375	34.1	44.3	-4.1	19.6	20.7
01	25	04	2	7.365	34.9	44.4	-4.3	19.6	20.8
01	35	05	2	7.351	35.8	44.9	-4.7	19.5	20.6
01	45	06	2	7.344	36.5	44.2	-4.7	19.5	20.7
01	55	07	2	7.344	35.5	43.2	-5.1	19.0	20.2
01	0	01	3	7.430	39.7	50.5	2.8	25.9	27.2
01	10	02	3	7.441	40.7	54.0	4.0	27.2	28.6
01	20	03	3	7.430	39.7	48.9	2.8	25.9	27.2
01	30	04	3	7.442	40.2	58.5	3.8	26.9	28.2
01	40	05	3	7.423	40.3	59.5	2.4	25.9	27.2
01	50	06	3	7.422	40.4	54.9	2.4	25.9	27.2
01	60	07	3	7.397	41.5	54.0	1.2	25.1	26.4
01	0	01	4	7.396	36.6	46.0	-1.4	22.1	23.3
01	10	02	4	7.406	35.8	43.1	-1.1	22.1	23.3
01	20	03	4	7.395	36.9	38.4	-1.1	22.2	23.4
01	30	04	4	7.386	37.0	38.5	-1.7	21.8	23.0
01	40	05	4	7.377	37.1	38.6	-2.2	21.4	22.6
01	50	06	4	7.353	37.4	45.7	-3.7	20.4	21.7
01	60	07	4	7.363	36.8	52.2	-3.5	20.5	21.7
02	0	01	1	7.363	35.5	44.5	-4.1	19.8	21.0
02	5	02	1	7.353	34.1	48.3	-5.4	18.6	19.7
02	15	03	1	7.356	32.9	44.4	-5.8	18.1	19.2
02	25	04	1	7.310	36.0	36.7	-6.6	17.9	19.0
02	30	05	1	7.257	34.3	45.8	-10.4	15.0	16.1
02	35	06	1	7.246	35.5	45.8	-10.4	15.2	16.3
02	40	07	1	7.244	36.9	45.8	-10.0	15.7	11.9
02	0	01	2	7.383	40.3	43.7	0.3	23.6	24.9
02	10	02	2	7.353	40.3	43.3	-2.3	22.0	22.2
02	20	03	2	7.334	38.0	41.3	-4.4	19.9	21.1
02	30	04	2	7.338	35.5	44.0	-5.4	18.8	19.9
02	40	05	2	7.310	37.8	40.8	-6.0	18.8	20.0
02	50	06	2	7.284	35.0	42.5	-8.5	16.3	17.4
02	60	07	2	7.309	37.1	39.9	-8.5	16.3	17.4
02	0	01	3	7.401	35.1	49.3	-1.6	21.4	22.5
02	10	02	3	7.386	34.5	59.4	-2.9	20.3	21.5
02	20	03	3	7.350	35.1	54.2	-4.8	19.0	20.2
02	30	04	3	7.334	35.0	61.3	-5.9	18.3	19.4
02	40	05	3	7.331	34.3	57.9	-6.3	17.9	19.0
02	50	06	3	7.304	36.5	57.7	-6.9	17.8	19.0
02	60	07	3	7.285	35.4	56.0	-8.4	16.5	17.7
02	0	01	4	7.396	30.0	52.9	-4.4	18.1	19.1
02	10	02	4	7.388	29.6	61.0	-5.2	17.6	18.6

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
02	20	03	4	7.372	32.2	54.2	−4.8	18.4	19.5
02	30	04	4	7.343	32.7	53.4	−6.2	17.5	18.6
02	40	05	4	7.336	31.5	50.7	−7.0	16.6	17.6
02	50	06	4	7.308	33.6	50.9	−7.7	16.6	17.7
02	60	07	4	7.298	31.8	54.6	−9.1	15.3	16.3
03	0	01	3	7.375	34.6	66.6	−3.7	19.9	21.0
03	5	02	3	7.405	32.6	68.4	−2.7	20.1	21.2
03	10	03	3	7.339	34.5	72.6	−5.9	18.3	19.4
03	15	04	3	7.334	34.3	57.7	−6.1	17.9	19.1
03	30	05	3	7.338	34.7	70.6	−5.8	18.4	19.5
03	45	06	3	7.322	35.9	62.7	−6.2	18.3	19.5
03	55	07	3	7.320	38.5	52.5	−5.2	19.5	20.7
03	0	01	4	7.325	37.3	49.4	−5.2	19.1	20.4
03	3	02	4	7.347	31.2	89.3	−7.0	16.8	17.8
03	10	03	4	7.302	35.7	61.4	−7.5	17.4	18.5
03	15	04	4	7.302	37.1	57.2	−6.9	18.0	19.2
03	20	05	4	7.283	35.9	64.3	−8.5	16.7	17.9
03	35	06	4	7.270	36.9	66.5	−8.9	16.7	17.9
03	55	07	4	7.222	33.4	71.6	−12.7	13.5	14.6
04	0	01	1	7.333	34.8	54.8	−6.0	18.2	19.4
04	10	02	1	7.276	32.5	54.3	−10.0	14.9	16.0
04	20	03	1	7.264	34.9	57.6	−9.8	15.6	16.7
04	30	04	1	7.269	36.5	58.9	−9.0	16.5	17.6
04	40	05	1	7.267	36.5	61.7	−9.1	16.4	17.6
04	50	06	1	7.267	38.1	53.8	−8.4	17.1	18.4
04	60	07	1	7.263	36.2	58.4	−9.4	16.1	17.3
04	0	01	2	7.373	36.9	52.7	−2.4	21.2	22.4
04	10	02	2	7.408	29.1	87.5	−4.3	18.2	19.1
04	20	03	2	7.327	35.0	63.7	−6.2	18.1	19.3
04	30	04	2	7.321	37.4	48.4	−5.4	19.0	20.3
04	40	05	2	7.339	35.3	53.2	−5.3	18.8	19.9
04	50	06	2	7.349	38.1	47.3	−3.3	20.7	21.9
04	60	07	2	7.328	40.8	40.6	−3.3	21.1	22.4
04	0	01	3	7.359	37.3	43.3	−3.1	20.7	21.9
04	10	02	3	7.320	37.4	34.4	−5.0	19.0	20.2
04	20	03	3	7.284	36.0	49.4	−8.2	16.8	18.0
04	30	04	3	7.294	39.9	44.4	−5.9	19.1	20.4
04	40	05	3	7.335	35.5	62.4	−5.7	18.7	19.8
04	50	06	3	7.283	34.5	48.6	−8.8	16.1	17.2
04	60	07	3	7.304	34.5	46.5	−7.4	16.1	18.2
04	0	01	4	7.371	40.3	53.3	−1.0	23.0	24.4
04	10	02	4	7.395	36.3	60.9	−1.4	22.0	23.2
04	20	03	4	7.368	37.5	54.8	−2.5	21.3	22.6
04	30	04	4	7.382	35.6	60.7	−2.6	20.9	22.1
04	40	05	4	7.381	36.0	66.8	−2.5	21.1	22.3
04	50	06	4	7.372	36.1	63.9	−3.0	20.7	21.9
04	60	07	4	7.376	35.6	68.2	−3.1	20.6	21.7
05	0	01	1	7.345	41.4	39.5	−1.9	22.3	23.6
05	10	02	1	7.360	32.4	71.4	−5.5	18.1	19.1
05	20	03	1	7.334	36.0	64.1	−5.4	18.9	20.1
05	30	04	1	7.323	40.0	42.9	−4.0	20.4	21.8

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
05	40	05	1	7.343	34.7	65.6	−5.4	18.6	19.8
05	50	06	1	7.322	33.0	78.0	−7.4	16.9	18.0
05	60	07	1	7.299	36.3	50.8	−7.1	17.6	18.8
05	0	01	2	7.318	42.2	42.0	−3.4	21.4	22.7
05	15	02	2	7.331	40.3	55.6	−3.7	21.0	22.3
05	30	03	2	7.322	40.0	50.3	−4.3	20.4	21.7
05	45	04	2	7.313	40.4	40.6	−4.4	20.2	21.5
05	60	05	2	7.298	38.9	55.6	−6.3	18.8	20.0
05	75	06	2	7.295	36.5	51.8	−7.3	17.5	18.7
05	95	07	2	7.274	36.6	53.4	−8.5	16.7	17.9
05	0	01	3	7.343	34.2	59.3	0.1	22.6	23.8
05	10	02	3	7.384	34.4	40.2	−2.5	20.3	21.5
05	20	03	3	7.361	34.4	55.8	−4.3	19.3	20.4
05	30	04	3	7.364	35.0	66.6	−4.0	19.7	20.9
05	40	05	3	7.366	35.1	60.9	−3.8	19.8	21.0
05	50	06	3	7.367	34.9	65.2	−3.9	19.8	21.0
05	60	07	3	7.382	35.2	62.5	−2.8	20.7	21.9
05	0	01	4	7.387	38.1	52.2	−1.0	22.6	23.8
05	10	02	4	7.385	34.0	67.9	−3.2	20.1	21.2
05	20	03	4	7.353	36.8	51.3	−3.7	20.2	21.4
05	30	04	4	7.361	35.1	58.7	−4.1	19.6	20.8
05	40	05	4	7.350	34.6	71.9	−5.1	18.9	20.0
05	50	06	4	7.332	34.3	62.4	−6.3	17.9	19.0
05	60	07	4	7.330	34.1	72.9	−6.5	17.7	18.8
06	0	01	1	7.365	36.2	64.1	−3.6	20.3	21.5
06	10	02	1	7.339	35.3	87.2	−5.6	18.7	19.9
06	25	03	1	7.283	39.9	65.4	−7.0	18.6	19.9
06	35	04	1	7.284	40.5	47.0	−6.3	18.9	20.3
06	45	05	1	7.269	41.1	50.8	−7.1	18.6	20.0
06	55	06	1	7.267	40.3	51.1	−7.3	18.2	19.5
06	65	07	1	7.244	40.6	58.2	−8.9	17.3	18.3
06	0	01	2	7.376	38.9	43.2	−1.2	22.4	23.7
06	10	02	2	7.341	36.6	56.0	−4.7	19.5	20.7
06	15	03	2	7.321	34.8	65.1	−6.7	17.7	18.9
06	25	04	2	7.295	38.0	49.9	−6.8	18.2	19.4
06	35	05	2	7.313	36.7	57.9	−6.4	18.3	19.5
06	45	06	2	7.328	37.1	60.0	−5.4	19.2	20.4
06	55	07	2	7.332	37.8	49.9	−4.7	19.7	20.9
07	0	01	1	7.372	35.3	56.4	−3.3	20.2	21.4
07	5	02	1	7.390	34.4	71.1	−2.8	20.5	21.7
07	10	03	1	7.380	33.9	70.3	−3.7	19.8	20.8
07	15	04	1	7.350	35.4	69.6	−4.8	19.3	20.4
07	20	05	1	7.337	34.4	76.1	−6.1	18.1	19.3
07	35	06	1	7.271	38.3	67.1	−9.9	15.3	16.4
07	45	07	1	7.266	36.7	57.7	−9.0	16.4	17.6
07	0	01	2	7.330	41.4	39.1	−2.8	21.5	22.8
07	7	02	2	7.369	36.3	50.2	−3.0	20.6	21.8
07	15	03	2	7.353	37.4	48.0	−3.5	20.5	21.7
07	20	04	2	7.347	34.4	46.7	−5.1	18.5	19.7
07	25	05	2	7.304	32.5	51.1	−8.4	15.9	17.0
07	35	06	2	7.320	33.5	51.0	−7.1	17.0	18.1

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
07	45	07	2	7.302	32.3	57.7	−8.7	15.7	16.8
08	0	01	1	7.411	33.1	73.4	−2.0	20.8	21.9
08	10	02	1	7.398	34.6	64.4	−2.1	21.1	22.2
08	20	03	1	7.394	35.9	59.3	−1.7	21.6	22.8
08	30	04	1	7.397	35.8	50.2	−1.3	21.8	23.0
08	40	05	1	7.368	36.5	42.2	−2.7	20.7	21.9
08	50	06	1	7.395	32.7	83.4	−3.3	19.7	20.8
08	60	07	1	7.374	36.0	49.3	−2.7	20.7	21.9
08	0	01	2	7.370	45.2	41.0	1.5	25.8	27.2
08	10	02	2	7.408	41.2	41.8	2.3	25.7	17.0
08	20	03	2	7.427	35.9	58.1	0.6	23.4	24.6
08	30	04	2	7.417	35.4	60.3	−0.4	22.5	23.7
08	40	05	2	7.429	35.8	57.2	0.7	23.4	24.6
08	50	06	2	7.403	38.7	48.0	0.6	23.9	25.1
08	60	07	2	7.403	38.7	48.0	0.6	23.9	25.1
08	0	01	3	7.410	34.2	63.7	−1.5	21.4	22.5
08	10	02	3	7.446	33.3	60.1	0.4	22.6	23.7
08	20	03	3	7.421	35.2	74.5	−0.4	22.6	23.7
08	30	04	3	7.387	35.8	62.8	−2.2	21.2	22.4
08	40	05	3	7.379	37.4	49.1	−1.7	21.8	23.0
08	50	06	3	7.382	37.2	50.1	−1.7	21.8	23.0
08	60	07	3	7.388	37.3	52.3	−1.3	22.1	23.3
08	0	01	4	7.395	36.9	50.8	−1.0	22.3	23.5
08	10	02	4	7.406	36.7	45.7	−0.3	22.7	23.9
08	20	03	4	7.371	38.5	47.1	−1.7	22.0	23.2
08	30	04	4	7.383	39.1	42.0	−0.5	23.0	24.2
08	40	05	4	7.361	41.4	41.6	−0.9	23.1	24.4
08	50	06	4	7.367	40.2	39.7	−0.9	22.8	24.1
08	60	07	4	7.355	40.4	38.9	−1.6	22.3	23.6
09	0	01	1	7.400	34.6	61.1	−2.3	21.1	22.3
09	5	02	1	7.354	37.7	40.1	−3.3	20.7	21.9
09	10	03	1	7.303	33.0	55.6	−8.6	16.1	17.2
09	15	04	1	7.359	28.5	65.5	−7.7	15.8	16.8
09	20	05	1	7.342	35.8	59.4	−5.2	19.1	20.3
09	25	06	1	7.377	36.7	46.0	−2.5	21.2	22.4
09	35	07	1	7.368	38.1	41.1	−2.3	21.6	22.8
09	0	01	2	7.401	38.2	49.5	0.1	23.4	24.6
09	5	02	2	7.369	39.5	44.8	−1.3	22.5	23.8
09	10	03	2	7.364	38.4	38.7	−1.9	21.6	22.6
09	15	04	2	7.360	38.4	46.8	−2.5	21.4	22.7
09	20	05	2	7.338	38.9	37.8	−3.3	20.6	21.9
09	25	06	2	7.338	38.9	37.8	−3.3	20.6	21.9
09	30	07	2	7.338	38.9	37.8	−3.3	20.6	21.9
09	0	01	3	7.396	36.9	47.8	−0.8	22.4	23.6
09	5	02	3	7.360	38.3	45.5	−2.5	21.4	22.6
09	10	03	3	7.316	33.1	64.4	−7.6	16.7	17.8
09	15	04	3	7.321	38.2	46.7	−5.0	19.5	20.7
09	20	05	3	7.329	34.7	64.2	−6.3	18.0	19.2
09	25	06	3	7.333	41.7	38.6	−2.5	21.8	23.2
09	30	07	3	7.334	41.9	40.6	−2.4	22.0	23.3
09	0	01	4	7.410	34.9	49.1	−0.9	21.9	23.0

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
09	5	02	4	7.387	35.2	48.8	-2.3	20.9	22.1
09	10	03	4	7.389	37.0	47.1	-1.3	22.0	23.2
09	15	04	4	7.394	34.3	47.0	-2.2	20.7	21.8
09	20	05	4	7.394	35.3	43.4	-1.7	21.3	22.4
09	25	06	4	7.406	35.7	41.5	-0.6	22.1	23.3
09	30	07	4	7.409	36.9	42.4	0.1	23.0	24.2
10	0	01	1	7.404	34.5	66.3	-1.7	21.3	22.4
10	5	02	1	7.438	33.5	77.7	0.0	22.4	23.5
10	10	03	1	7.440	36.1	58.5	1.5	24.2	25.4
10	15	04	1	7.476	36.4	65.1	4.3	26.5	27.7
10	20	05	1	7.479	37.5	59.9	5.1	27.5	28.7
10	30	06	1	7.487	37.2	68.0	5.6	27.8	29.0
10	40	07	1	7.483	37.9	60.3	5.7	28.1	29.3
10	0	01	2	7.356	39.0	49.5	-2.5	21.6	22.8
10	5	02	2	7.390	40.3	44.1	0.5	24.0	25.3
10	10	03	2	7.409	38.4	54.0	0.7	24.0	25.3
10	15	04	2	7.416	39.5	48.0	1.8	25.1	26.3
10	20	05	2	7.425	39.6	46.6	2.5	25.6	26.9
10	30	06	2	7.433	42.2	48.1	4.5	27.8	29.2
10	40	07	2	7.433	42.2	48.1	4.5	27.8	29.2
10	0	01	3	7.429	35.1	74.4	0.2	23.0	24.1
10	5	02	3	7.474	34.3	81.2	2.9	24.9	26.1
10	10	03	3	7.485	36.1	78.8	4.8	26.9	28.1
10	15	04	3	7.485	35.8	76.7	4.6	26.6	27.8
10	20	05	3	7.480	36.2	74.0	4.4	26.8	27.8
10	30	06	3	7.500	37.8	80.9	6.9	29.1	30.3
10	40	07	3	7.500	37.8	80.9	6.9	29.1	30.3
10	0	01	4	7.384	34.7	56.9	-2.9	20.4	21.6
10	5	05	4	7.436	34.3	63.5	0.3	22.8	23.9
10	10	03	4	7.426	33.5	77.6	2.5	24.4	25.5
10	15	04	4	7.482	34.4	70.3	3.6	25.5	26.6
10	20	05	4	7.504	34.8	70.9	5.4	27.1	28.2
10	30	06	4	7.468	35.4	65.0	3.1	25.3	26.5
10	40	07	4	7.491	35.8	70.0	5.1	27.0	28.2
11	0	01	1	7.396	34.3	60.6	-2.3	20.7	21.9
11	10	02	1	7.453	34.3	59.6	1.5	23.7	24.9
11	20	03	1	7.450	37.2	46..	3.1	25.5	26.7
11	30	04	1	7.454	38.1	37.2	4.2	26.4	27.6
11	40	05	1	7.459	39.3	38.4	5.1	27.5	28.8
11	50	06	1	7.460	40.0	37.7	5.6	28.1	29.4
11	60	07	1	7.460	40.0	37.7	5.6	28.1	29.4
11	0	01	2	7.372	41.7	38.5	0.1	23.9	25.2
11	10	02	2	7.461	37.8	42.0	4.4	26.7	27.9
11	20	03	2	7.467	39.9	33.6	6.3	28.5	29.8
11	30	04	2	7.474	38.7	41.0	5.8	28.1	29.3
11	40	05	2	7.458	39.1	43.8	4.8	27.3	28.6
11	50	06	2	7.460	40.9	36.4	6.2	28.7	30.1
11	60	07	2	7.460	40.9	36.4	6.2	28.7	30.1
11	0	01	3	7.434	35.5	83.7	0.8	23.5	24.7
11	10	02	3	7.442	37.7	62.4	2.5	25.4	26.6
11	20	03	3	7.460	35.5	73.6	2.6	24.9	26.1

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
11	30	04	3	7.440	38.1	52.9	2.8	25.6	26.8
11	40	05	3	7.445	37.8	51.8	3.0	25.7	26.9
11	50	06	3	7.440	39.5	44.4	3.7	26.5	27.8
11	60	07	3	7.438	41.7	39.8	4.8	27.8	29.2
11	0	01	4	7.325	42.4	40.4	-2.7	21.8	23.2
11	10	02	4	7.404	34.8	56.0	-1.5	21.5	22.7
11	20	03	4	7.419	35.2	54.3	-0.3	22.5	23.6
11	30	04	4	7.415	36.6	57.9	0.1	23.1	24.3
11	40	05	4	7.436	35.5	61.9	0.9	23.6	24.7
11	50	06	4	7.454	36.0	62.4	2.5	25.0	26.2
11	60	07	4	7.472	36.3	57.2	4.0	26.2	27.4
12	0	01	1	7.432	36.0	69.9	0.7	23.7	24.9
12	10	02	1	7.423	39.2	71.5	1.8	25.3	26.6
12	20	03	1	7.418	39.2	61.1	1.9	25.4	26.7
12	30	04	1	7.429	39.0	63.4	2.2	25.5	26.8
12	40	05	1	7.384	41.4	52.7	0.3	24.4	25.7
12	50	06	1	7.403	40.9	45.9	1.5	25.2	26.5
12	60	07	1	7.383	42.7	44.0	1.0	25.1	26.4
12	0	01	2	7.403	38.4	54.2	0.3	23.7	24.9
12	10	02	2	7.414	40.6	47.7	2.3	25.7	27.0
12	15	03	2	7.422	37.9	55.7	1.3	24.4	25.6
12	25	04	2	7.403	37.7	69.5	-0.3	23.2	24.4
12	40	05	2	7.394	36.4	56.3	-1.3	22.0	23.2
12	50	06	2	7.417	36.9	60.4	0.4	23.5	24.7
12	60	07	2	7.417	36.9	60.4	0.4	23.5	24.7
12	0	01	3	7.386	34.7	59.7	-2.7	20.6	21.7
12	10	02	3	7.407	35.1	64.2	-1.2	21.8	23.0
12	20	03	3	7.395	31.8	63.4	-3.6	19.2	20.3
12	30	04	3	7.398	37.2	61.0	-0.8	22.7	23.9
12	40	05	3	7.387	35.0	62.2	-2.6	20.8	21.9
12	50	06	3	7.392	35.4	65.7	-2.0	21.3	22.5
12	60	07	3	7.392	33.7	72.3	-2.9	20.3	21.4
12	0	01	4	7.394	32.6	75.5	-3.3	19.7	20.8
12	10	02	4	7.414	32.1	78.9	-2.3	20.3	21.4
12	20	03	4	7.372	33.2	80.1	-4.4	19.1	20.2
12	30	04	4	7.416	33.9	76.4	-1.3	21.5	22.6
12	40	05	4	7.375	33.0	83.8	-4.3	19.1	20.1
12	50	06	4	7.397	34.4	72.8	-2.3	20.9	22.0
12	60	07	4	7.384	33.3	83.7	-3.7	19.6	20.7
13	0	01	1	7.385	40.3	43.5	-0.1	23.8	25.1
13	10	02	1	7.397	40.3	52.2	0.8	24.7	26.0
13	20	03	1	7.374	39.3	65.3	-1.6	22.6	23.9
13	30	04	1	7.370	41.0	58.2	-0.9	23.4	24.7
13	40	05	1	7.369	43.7	43.7	0.6	24.9	26.3
13	50	06	1	7.346	47.7	37.1	1.0	25.7	27.2
13	60	07	1	7.342	46.4	35.5	0.2	24.8	26.3
13	0	01	2	7.363	43.4	46.2	0.0	24.4	25.8
13	10	02	2	7.332	42.0	50.5	-2.9	21.9	23.2
13	20	03	2	7.341	41.5	44.6	-2.4	22.1	23.4
13	30	04	2	7.322	42.3	47.1	-3.3	21.6	22.9
13	40	05	2	7.323	42.0	47.6	-3.4	21.5	22.8
13	50	06	2	7.325	41.4	48.3	-3.5	21.3	22.6

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
13	60	07	2	7.326	40.9	49.0	-3.6	21.2	22.5
13	0	01	3	7.390	37.8	65.2	-1.1	22.6	23.8
13	10	02	3	7.376	37.2	69.2	-2.3	21.6	22.8
13	20	03	3	7.389	37.8	57.4	-1.0	22.5	23.8
13	30	04	3	7.351	38.6	50.9	-3.0	21.2	22.3
13	40	05	3	7.352	40.4	49.5	-2.1	22.1	23.4
13	50	06	3	7.361	38.9	58.7	-2.4	21.7	23.0
13	60	07	3	7.347	38.1	59.1	-3.7	20.6	21.8
13	0	01	4	7.397	37.1	60.0	-0.9	22.5	23.7
13	10	02	4	7.414	35.8	64.9	-0.4	22.6	23.8
13	20	03	4	7.380	35.6	62.9	-2.8	20.8	21.9
13	30	04	4	7.391	36.4	61.5	-1.7	21.8	23.0
13	40	05	4	7.388	35.8	60.8	-2.1	21.3	22.5
13	50	06	4	7.382	36.7	53.7	-2.0	21.5	22.7
13	60	07	4	7.389	37.0	51.1	-1.4	22.0	23.2
14	0	01	3	7.428	35.5	62.3	0.3	23.1	24.2
14	5	02	3	7.450	36.0	72.7	2.0	24.6	25.8
14	10	03	3	7.455	37.7	65.3	3.4	26.1	27.3
14	15	04	3	7.470	37.7	59.5	4.5	27.0	28.2
14	20	05	3	7.473	38.8	51.4	5.5	28.0	29.2
14	25	06	3	7.496	38.0	60.3	6.7	28.9	30.1
14	35	07	3	7.474	41.7	49.2	7.2	30.1	31.4
14	45	08	3	7.459	42.7	44.5	6.7	29.8	31.2
14	55	09	3	7.458	43.3	40.4	7.1	30.2	31.6
14	65	10	3	7.465	39.9	31.7	6.1	28.2	29.5
14	80	11	3	7.485	38.0	70.1	5.8	28.1	29.4
14	90	12	3	7.457	39.7	59.6	4.6	27.6	28.9
14	100	13	3	7.451	38.7	67.6	3.6	26.5	27.8
14	110	14	3	7.476	36.8	59.1	4.5	26.7	27.9
14	120	15	3	7.458	39.4	52.7	4.7	27.5	28.7
14	140	16	3	7.446	38.6	65.5	3.2	26.2	27.4
14	150	17	3	7.434	40.4	59.1	3.4	26.7	28.0
14	0	01	4	7.378	34.8	65.0	-3.3	20.2	21.3
14	5	02	4	7.411	35.3	64.5	-0.9	22.1	23.3
14	10	03	4	7.442	35.2	61.6	1.2	23.7	24.8
14	15	04	4	7.451	35.8	64.9	2.1	24.6	25.8
14	20	05	4	7.477	36.6	57.4	4.5	26.7	27.9
14	25	06	4	7.471	37.3	65.1	4.4	26.8	28.0
14	35	07	4	7.461	37.8	61.4	4.0	26.6	27.8
14	45	08	4	7.460	37.6	65.2	3.7	26.3	27.6
14	55	09	4	7.455	38.2	64.7	3.7	26.5	27.7
14	65	10	4	7.447	37.8	68.5	2.9	25.7	26.9
14	75	11	4	7.434	38.4	68.4	2.3	25.4	26.6
14	85	12	4	7.422	40.4	69.4	2.4	25.9	27.2
14	95	13	4	7.417	39.8	61.2	1.8	25.2	26.5
14	105	14	4	7.427	38.0	64.6	1.6	24.7	25.9
14	115	15	4	7.432	35.9	70.5	0.8	23.6	24.7
14	130	16	4	7.432	35.9	59.8	0.9	23.6	24.8
14	141	17	4	7.371	39.0	73.0	-1.9	22.2	23.5
14	0	01	1	7.383	33.3	66.1	-3.7	19.5	20.6
14	10	02	1	7.436	35.9	58.6	1.1	23.8	25.0

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
14	20	03	1	7.477	35.0	52.1	3.6	25.6	26.7
14	30	04	1	7.480	35.5	50.6	4.1	26.1	27.2
14	40	05	1	7.464	37.4	49.3	4.1	26.5	27.7
14	50	06	1	7.466	37.1	52.2	4.0	26.4	27.6
14	60	07	1	7.477	34.5	56.1	3.2	25.1	26.3
14	70	08	1	7.466	35.9	55.4	3.2	25.5	26.7
14	80	09	1	7.455	37.3	54.6	3.3	25.8	27.1
14	90	10	1	7.451	37.4	56.5	3.0	25.7	26.9
14	100	11	1	7.447	38.8	53.0	3.5	26.4	27.6
14	110	12	1	7.474	35.6	62.8	3.6	25.8	26.9
14	127	13	1	7.496	31.9	67.6	3.0	24.4	25.2
14	130	14	1	7.515	30.4	57.3	3.5	24.2	25.3
14	137	15	1	7.472	32.7	62.1	1.8	23.5	24.6
14	145	16	1	7.432	36.6	68.0	1.2	24.1	25.3
14	155	17	1	7.414	38.1	51.1	0.9	24.0	25.3
14	0	01	2	7.417	34.7	51.8	−0.7	22.0	23.1
14	10	02	2	7.426	36.8	52.3	1.0	23.9	25.1
14	20	03	2	7.437	39.1	43.0	3.2	26.0	27.3
14	30	04	2	7.456	40.5	46.4	5.3	28.1	29.4
14	40	05	2	7.479	40.5	32.5	7.6	29.6	31.0
14	50	06	2	7.466	42.4	30.3	7.8	30.1	31.5
14	60	07	2	7.473	40.3	33.2	7.0	29.1	30.4
14	70	08	2	7.481	40.0	37.8	7.2	29.4	30.7
14	80	09	2	7.478	40.3	31.0	7.5	29.4	30.8
14	90	10	2	7.473	39.5	39.5	6.2	28.5	29.8
14	100	11	2	7.455	38.7	43.5	4.2	26.7	28.0
14	115	12	2	7.456	39.4	56.7	4.4	27.3	28.6
14	125	13	2	7.474	37.8	44.3	5.1	27.3	28.6
14	135	14	2	7.477	37.3	43.9	5.1	27.1	28.4
14	145	15	2	7.480	35.3	66.3	3.9	25.9	27.1
14	155	16	2	7.458	37.7	73.1	3.6	26.3	27.5
14	165	17	2	7.458	37.7	73.1	3.6	26.3	27.5
15	0	01	1	7.421	36.3	54.9	0.4	23.3	24.5
15	15	02	1	7.390	38.3	44.2	−0.5	22.9	24.1
15	30	03	1	7.384	39.2	41.9	−0.4	23.1	24.1
15	45	04	1	7.372	40.9	36.2	−0.2	23.4	24.7
15	60	05	1	7.372	40.8	43.8	−0.6	23.3	24.7
15	75	06	1	7.358	41.7	40.5	−1.0	23.1	24.4
15	90	07	1	7.365	40.7	42.8	−1.1	22.9	24.2
15	105	08	1	7.365	40.9	40.5	−0.9	23.0	24.4
15	120	09	1	7.377	41.9	34.3	0.7	24.2	25.6
15	135	10	1	7.370	41.4	41.7	−0.4	23.6	24.9
15	150	11	1	7.371	41.2	35.8	−0.1	23.5	24.9
15	165	12	1	7.367	41.6	33.8	−0.1	23.5	24.8
15	180	13	1	7.355	39.9	39.9	−1.9	21.8	23.2
15	195	14	1	7.342	38.2	46.1	−3.7	20.4	21.7
15	210	15	1	7.361	37.8	45.9	−2.7	21.1	22.3
15	225	16	1	7.381	37.3	45.8	−1.6	21.8	23.0
15	240	17	1	7.353	40.9	36.7	−1.5	22.4	23.7
15	0	01	2	7.393	36.0	50.8	−1.6	21.7	22.8
15	15	02	2	7.385	40.5	32.7	0.7	23.9	25.2
15	30	03	2	7.401	39.3	38.3	0.9	24.0	25.3

Group	Min.	Time	Subj.	pH	PCO2	PO2	BE	HCO3	TOTCO2
15	45	04	2	7.378	38.9	47.8	-1.1	22.6	23.9
15	60	05	2	7.396	36.1	46.2	-1.3	21.8	23.0
15	75	06	2	7.397	38.1	44.4	-0.2	23.0	24.3
15	90	07	2	7.396	36.6	47.9	-1.0	22.2	23.4
15	105	08	2	7.414	36.9	42.2	0.5	23.3	24.5
15	120	09	2	7.398	38.3	32.7	0.6	23.3	24.5
15	135	10	2	7.395	38.7	33.6	0.5	23.4	24.6
15	150	11	2	7.389	39.4	35.0	0.4	23.5	24.8
15	165	12	2	7.384	40.0	36.3	0.3	23.6	24.9
15	180	13	2	7.376	42.1	34.6	0.8	24.3	25.7
15	195	14	2	7.386	41.2	31.1	1.2	24.3	25.6
15	210	15	2	7.377	39.1	39.4	-0.8	22.6	23.9
15	225	16	2	7.366	40.0	37.6	-1.1	22.5	23.8
15	240	17	2	7.357	44.2	24.6	1.0	24.4	25.8
15	0	01	3	7.406	37.7	49.4	0.2	23.4	24.6
15	15	02	3	7.382	40.4	45.0	-0.1	23.7	25.0
15	30	03	3	7.399	38.3	57.2	-0.2	23.3	24.6
15	45	04	3	7.402	36.7	57.3	-0.7	22.6	23.8
15	60	05	3	7.401	37.9	43.2	0.0	23.2	24.4
15	75	06	3	7.402	36.5	54.8	-0.9	22.4	23.5
15	90	07	3	7.404	34.5	60.8	-1.8	21.3	22.4
15	105	08	3	7.389	37.9	49.4	-0.9	22.6	23.8
15	120	09	3	7.389	38.5	45.0	-0.5	22.9	24.2
15	135	10	3	7.400	38.4	55.3	0.0	23.4	24.7
15	150	11	3	7.429	34.2	45.2	0.0	22.3	23.4
15	165	12	3	7.389	34.0	76.0	-3.0	20.3	21.4
15	180	13	3	7.382	38.7	58.4	-1.2	22.7	23.9
15	195	14	3	7.417	32.4	45.0	-1.8	20.6	21.7
15	210	15	3	7.395	35.0	56.7	-2.0	21.2	22.3
15	225	16	3	7.374	37.7	63.4	-2.2	21.7	22.9
15	240	17	3	7.397	35.6	81.5	-1.8	21.6	22.7
15	0	01	4	7.383	34.6	52.9	-2.9	20.3	21.5
15	15	02	4	7.378	34.5	44.2	-3.1	20.1	21.2
15	30	03	4	7.387	35.2	43.6	-2.2	20.8	22.0
15	45	04	4	7.391	35.3	47.3	-1.9	21.1	22.3
15	60	05	4	7.381	35.7	53.8	-2.5	20.9	22.0
15	75	06	4	7.370	36.8	50.0	-2.7	20.9	22.1
15	90	07	4	7.380	36.4	42.3	-2.0	21.2	22.4
15	105	08	4	7.368	36.1	45.0	-3.0	20.5	21.7
15	120	09	4	7.377	36.5	45.8	-2.2	21.2	22.4
15	135	10	4	7.377	34.9	77.1	-3.4	20.2	21.4
15	150	11	4	7.373	35.8	78.3	-3.3	20.5	21.7
15	165	12	4	7.356	35.7	59.3	-4.2	19.7	20.9
15	180	13	4	7.331	36.6	81.5	-5.5	19.0	20.2
15	195	14	4	7.337	35.6	88.6	-5.5	18.7	19.9
15	210	15	4	7.344	34.5	85.7	-5.6	18.5	19.7
15	225	16	4	7.318	40.1	53.7	-4.6	20.3	21.5
15	240	17	4	7.318	40.1	53.7	-4.6	20.3	21.5

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
01	0	01	1	141.4	5.1		
01	10	02	1	141.8	5.1		
01	20	03	1	142.7	5.2		
01	30	04	1	143.1	5.2		
01	40	05	1	142.8	5.2		
01	44	06	1	142.4	5.0		
01	50	07	1	142.4	5.0		
01	0	01	2	141.8	4.9		
01	12	02	2	142.0	4.8		
01	17	03	2	142.3	4.8		
01	25	04	2	142.6	4.8		
01	35	05	2	143.7	4.8		
01	45	06	2	145.9	4.9		
01	55	07	2	147.0	4.9		
01	0	01	3	144.0	4.4	148.5	4.6
01	10	02	3	145.0	4.2	149.0	4.4
01	20	03	3	145.0	4.3	149.0	4.5
01	30	04	3	145.0	4.3	149.0	4.4
01	40	05	3	145.0	4.1	149.0	4.3
01	50	06	3	146.0	4.6	149.5	4.4
01	60	07	3	135.0	3.5	149.5	3.9
01	0	01	4	143.0	4.2		
01	10	02	4	143.0	4.2		
01	20	03	4	141.0	4.1		
01	30	04	4	142.0	4.3		
01	40	05	4	139.0	4.1		
01	50	06	4	144.0	4.1		
01	60	07	4	141.0	3.7		
02	0	01	1	142.0	4.5		
02	5	02	1	141.6	4.5		
02	15	03	1	141.1	4.5		
02	25	04	1	140.5	4.7		
02	30	05	1	139.5	4.9		
02	35	06	1	140.0	4.5		
02	40	07	1	142.0	4.3		
02	0	01	2	138.8	4.5		
02	10	02	2	140.0	4.5		
02	20	03	2	140.0	4.6		
02	30	04	2	143.1	5.3		
02	40	05	2	141.3	4.7		
02	50	06	2	142.6	4.8		
02	60	07	2	143.0	4.9		
02	0	01	3	144.0	4.2	148.0	4.3
02	10	02	3	145.0	4.4	147.5	4.5
02	20	03	3	143.0	4.0	147.0	4.1
02	30	04	3	144.0	4.5	147.0	4.6
02	40	05	3	143.0	4.5	147.5	4.6
02	50	06	3	142.0	4.3	147.0	4.4
02	60	07	3	143.0	4.6	146.0	4.7
02	0	01	4	142.0	4.1	145.0	4.3
02	10	02	4	142.0	4.2	145.0	4.3
02	20	03	4	144.0	4.4	145.5	4.4
02	30	04	4	144.0	4.4	145.0	4.5

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
02	40	05	4	142.0	5.1	144.5	5.2
02	50	06	4	140.0	4.7	145.0	4.9
02	60	07	4	141.0	4.6	145.5	4.8
03	0	01	3			147.0	4.6
03	5	02	3			147.0	5.0
03	10	03	3			147.5	4.6
03	15	04	3			147.0	4.4
03	30	05	3			147.0	4.5
03	45	06	3			147.0	4.5
03	55	07	3			147.5	4.5
03	0	01	4			147.0	4.4
03	3	02	4			146.0	4.9
03	10	03	4			144.5	4.6
03	15	04	4			145.5	4.7
03	20	05	4			145.0	4.7
03	35	06	4			144.0	5.1
03	55	07	4			143.0	5.6
04	0	01	1	138.0	3.9	150.0	3.9
04	10	02	1	138.0	4.2	149.0	4.2
04	20	03	1	138.0	4.0	149.5	4.0
04	30	04	1	138.0	4.0	150.0	4.3
04	40	05	1	137.0	4.1	149.0	4.5
04	50	06	1	138.0	4.1	148.5	4.4
04	60	07	1	138.0	4.0	148.5	4.4
04	0	01	2			148.0	4.8
04	10	02	2			147.0	5.8
04	20	03	2			142.5	4.9
04	30	04	2			151.5	4.7
04	40	05	2			148.0	4.5
04	50	06	2			153.5	4.7
04	60	07	2			150.0	4.6
04	0	01	3	140.0	4.1	150.5	4.4
04	10	02	3			155.0	5.0
04	20	03	3	140.0	3.9	148.5	4.0
04	30	04	3			149.5	3.9
04	40	05	3	138.0	4.5	148.0	4.8
04	50	06	3	140.0	4.0	148.0	4.2
04	60	07	3	140.0	4.1	149.0	4.4
04	0	01	4	145.5	4.3	151.0	4.7
04	10	02	4	140.5	4.3	146.5	4.7
04	20	03	4	142.0	4.3	148.0	4.8
04	30	04	4	132.0	4.0	135.5	4.4
04	40	05	4	148.5	4.5	153.0	4.9
04	50	06	4	145.5	4.4	149.5	4.8
04	60	07	4	150.5	4.3	153.0	4.6
05	0	01	1			149.0	4.7
05	10	02	1			148.0	4.9
05	20	03	1			148.0	4.6

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
05	30	04	1			149.5	4.7
05	40	05	1			157.5	5.0
05	50	06	1			148.5	4.8
05	60	07	1			148.0	4.7
05	0	01	2	137.0	4.4	152.0	5.0
05	15	02	2	137.0	4.5	150.0	5.0
05	30	03	2	137.0	4.4	148.5	5.0
05	45	04	2	136.0	4.6	150.5	4.6
05	60	05	2	137.0	4.5	151.0	5.2
05	75	06	2	137.0	4.6	149.0	5.1
05	95	07	2	136.0	4.6	148.0	5.0
05	0	01	3			147.5	4.6
05	10	02	3			147.0	5.3
05	20	03	3			149.0	5.0
05	30	04	3			147.5	4.7
05	40	05	3			150.0	4.9
05	50	06	3			152.5	5.0
05	60	07	3			150.0	5.0
05	0	01	4			150.0	4.7
05	10	02	4			149.0	5.1
05	20	03	4			152.5	4.9
05	30	04	4			149.0	4.9
05	40	05	4			150.0	5.1
05	50	06	4			152.5	5.1
05	60	07	4			150.0	5.1
06	0	01	1			145.0	4.4
06	10	02	1			144.5	4.8
06	25	03	1			144.0	5.0
06	35	04	1			144.5	4.7
06	45	05	1			144.5	4.3
06	55	06	1			145.5	4.1
06	65	07	1			145.5	4.2
06	0	01	2			142.5	4.7
06	10	02	2			143.0	5.2
06	15	03	2			142.5	5.3
06	25	04	2			142.0	5.3
06	35	05	2			142.0	5.0
06	45	06	2			142.5	4.5
06	55	07	2			143.0	4.7
07	0	01	1			149.0	4.6
07	5	02	1			148.5	4.6
07	10	03	1			148.5	4.6
07	15	04	1			148.0	4.9
07	20	05	1			148.0	4.7
07	35	06	1			147.0	4.6
07	45	07	1			147.5	4.5
07	0	01	2			148.0	4.8
07	7	02	2			148.0	4.9

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
07	15	03	2			147.5	5.0
07	20	04	2			147.0	5.3
07	25	05	2			147.0	5.2
07	35	06	2			146.0	5.3
07	45	07	2			145.0	5.6
08	0	01	1			149.0	4.5
08	10	02	1			149.0	4.3
08	20	03	1			148.0	4.8
08	30	04	1			152.0	4.5
08	40	05	1			148.0	4.6
08	50	06	1			150.5	4.6
08	60	07	1			153.0	4.7
08	0	01	2			151.0	4.6
08	10	02	2			150.0	5.0
08	20	03	2			148.5	4.9
08	30	04	2			148.5	5.0
08	40	05	2			148.0	4.7
08	50	06	2			149.0	4.6
08	60	07	2			150.0	4.8
08	0	01	3			151.5	4.9
08	10	02	3			147.5	4.8
08	20	03	3			147.0	4.4
08	30	04	3			152.0	4.6
08	40	05	3			147.0	4.2
08	50	06	3			146.0	4.3
08	60	07	3			146.5	4.5
08	0	01	4			149.5	4.4
08	10	02	4			149.5	4.6
08	20	03	4			149.5	4.5
08	30	04	4			149.5	4.7
08	40	05	4			149.5	4.7
08	50	06	4			150.0	4.9
08	60	07	4			150.0	4.8
09	0	01	1	141.0	4.2	150.0	4.5
09	5	02	1	141.0	3.9	149.5	4.1
09	10	03	1	140.0	4.0	148.5	4.2
09	15	04	1	140.0	4.0	149.0	4.3
09	20	05	1	140.0	3.9	148.0	4.2
09	25	06	1	141.0	4.0	148.0	4.3
09	35	07	1	141.0	3.9	150.0	4.2
09	0	01	2			146.0	4.7
09	5	02	2			158.5	4.6
09	10	03	2			162.0	4.8
09	15	04	2			148.0	4.2
09	20	05	2			148.0	4.3
09	25	06	2				
09	30	07	2				
09	0	01	3				

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
09	5	02	3				
09	10	03	3				
09	15	04	3				
09	20	05	3				
09	25	06	3				
09	30	07	3				
09	0	01	4				
09	5	02	4				
09	10	03	4				
09	15	04	4				
09	20	05	4				
09	25	06	4				
09	30	07	4				
10	0	01	1				
10	5	02	1				
10	10	03	1				
10	15	04	1				
10	20	05	1				
10	30	06	1				
10	40	07	1				
10	0	01	2	140.0	4.9	147.0	5.2
10	5	02	2	142.0	4.5	149.0	4.8
10	10	03	2	143.0	4.4	150.5	4.6
10	15	04	2	146.0	4.4	152.5	4.6
10	20	05	2	144.0	4.2	151.0	4.4
10	30	06	2	145.0	4.0	150.5	4.1
10	40	07	2				
10	0	01	3	144.0	4.7	150.5	5.1
10	5	02	3	152.0	4.2	155.0	4.5
10	10	03	3	150.5	4.2	151.5	4.5
10	15	04	3	135.0	3.6	136.0	3.8
10	20	05	3	153.5	4.1	155.0	4.4
10	30	06	3				
10	40	07	3				
10	0	01	4			146.5	4.4
10	5	05	4			148.0	4.3
10	10	03	4			149.0	4.3
10	15	04	4			149.5	4.2
10	20	05	4			150.5	4.1
10	30	06	4			149.5	4.1
10	40	07	4			149.5	4.1
11	0	01	1			148.5	4.6
11	10	02	1			150.0	4.1
11	20	03	1			152.0	4.2
11	30	04	1			129.0	3.5
11	40	05	1			151.5	4.0
11	50	06	1			154.0	4.0
11	60	07	1			154.0	4.0

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
11	0	01	2			147.5	4.7
11	10	02	2			149.0	4.7
11	20	03	2			151.5	4.3
11	30	04	2			151.0	4.2
11	40	05	2			151.5	4.0
11	50	06	2			152.0	4.0
11	60	07	2			148.5	4.3
11	0	01	3			147.0	4.6
11	10	02	3			148.0	4.6
11	20	03	3			149.0	4.5
11	30	04	3			149.0	4.3
11	40	05	3			150.0	4.3
11	50	06	3			149.5	4.4
11	60	07	3			150.5	4.3
11	0	01	4			146.5	4.6
11	10	02	4			146.5	4.6
11	20	03	4			146.5	4.9
11	30	04	4			147.0	4.7
11	40	05	4			148.0	4.5
11	50	06	4			149.0	4.4
11	60	07	4			148.5	4.3
12	0	01	1			150.0	4.7
12	10	02	1			178.0	5.1
12	20	03	1			146.5	4.4
12	30	04	1			146.0	4.4
12	40	05	1			155.0	4.5
12	50	06	1			146.0	4.5
12	60	07	1			146.0	4.5
12	0	01	2			145.5	5.0
12	10	02	2			142.5	4.8
12	15	03	2			135.5	4.6
12	25	04	2			140.0	4.8
12	40	05	2			142.0	4.7
12	50	06	2			143.0	4.7
12	60	07	2			143.0	4.7
12	0	01	3			148.0	4.3
12	10	02	3			145.5	4.4
12	20	03	3			143.5	4.3
12	30	04	3			143.5	4.4
12	40	05	3			142.5	4.4
12	50	06	3			141.5	4.3
12	60	07	3			140.0	4.3
12	0	01	4			151.0	4.5
12	10	02	4			150.0	4.5
12	20	03	4			149.0	4.5
12	30	04	4			148.0	4.4
12	40	05	4			147.0	4.3
12	50	06	4			146.0	4.5

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
12	60	07	4			146.0	4.5
13	0	01	1	143.0	4.2	151.5	4.5
13	10	02	1	144.0	4.2	150.0	4.4
13	20	03	1	141.0	4.3	148.5	4.5
13	30	04	1	142.0	4.3	149.0	4.5
13	40	05	1	140.0	4.3	148.0	4.5
13	50	06	1	140.0	4.2	147.5	4.5
13	60	07	1	142.0	4.4	149.0	4.7
13	0	01	2	140.0	4.4	149.0	4.7
13	10	02	2	138.0	4.5	146.5	4.8
13	20	03	2	138.0	4.6	145.5	4.9
13	30	04	2	137.0	4.4	144.0	4.7
13	40	05	2	138.0	4.5	144.5	4.8
13	50	06	2	138.0	4.5	144.5	4.8
13	60	07	2	138.0	4.5	145.5	4.7
13	0	01	3	138.0	4.2	146.5	4.4
13	10	02	3	137.0	4.2	145.0	4.4
13	20	03	3	137.0	4.1	145.0	4.4
13	30	04	3	135.0	3.9	144.0	4.4
13	40	05	3	134.0	4.1	143.0	4.4
13	50	06	3	134.0	4.1	142.0	4.3
13	60	07	3	134.0	4.1	142.0	4.3
13	0	01	4	143.0	4.2	147.5	4.0
13	10	02	4	138.0	4.1	146.0	4.0
13	20	03	4	138.0	4.1	145.5	4.0
13	30	04	4	139.0	4.2	145.0	4.0
13	40	05	4	139.0	4.2	145.0	4.1
13	50	06	4	136.0	4.1	144.0	4.0
13	60	07	4	138.0	4.1	143.0	4.0
14	0	01	3			145.5	4.5
14	5	02	3			149.0	3.9
14	10	03	3			150.0	4.1
14	15	04	3			150.5	4.0
14	20	05	3			152.5	4.0
14	25	06	3			152.5	4.0
14	35	07	3			155.0	3.9
14	45	08	3			157.7	4.0
14	55	09	3			160.5	4.1
14	65	10	3			159.5	3.9
14	80	11	3			158.5	3.7
14	90	12	3			161.0	3.7
14	100	13	3			159.0	3.7
14	110	14	3			157.5	3.8
14	120	15	3			157.0	3.7
14	140	16	3			155.5	3.5
14	150	17	3			156.0	3.5
14	0	01	4			147.0	4.3
14	5	02	4			149.0	4.1

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
14	10	03	4			149.5	4.1
14	15	04	4			151.0	4.0
14	20	05	4			153.5	3.9
14	25	06	4			155.0	3.7
14	35	07	4			157.5	3.8
14	45	08	4			159.0	3.7
14	55	09	4			160.0	3.7
14	65	10	4			161.0	3.4
14	75	11	4			162.5	3.5
14	85	12	4			160.0	3.4
14	95	13	4			159.0	3.4
14	105	14	4			159.0	3.4
14	115	15	4			157.0	3.5
14	130	16	4			156.0	4.0
14	141	17	4			154.5	3.5
14	0	01	1			147.0	3.9
14	10	02	1			149.5	3.8
14	20	03	1			153.0	3.9
14	30	04	1			156.5	4.0
14	40	05	1			159.0	3.7
14	50	06	1			160.5	3.8
14	60	07	1			161.0	3.8
14	70	08	1			157.0	3.6
14	80	09	1			157.7	3.7
14	90	10	1			156.0	3.7
14	100	11	1			155.0	3.6
14	110	12	1			154.5	3.7
14	127	13	1			155.0	3.8
14	130	14	1			154.5	3.6
14	137	15	1			154.0	3.5
14	145	16	1			153.0	3.4
14	155	17	1			153.0	3.4
14	0	01	2			143.5	4.0
14	10	02	2			149.0	3.7
14	20	03	2			151.0	3.9
14	30	04	2			152.0	3.9
14	40	05	2			154.5	3.9
14	50	06	2			156.0	3.9
14	60	07	2			158.0	3.7
14	70	08	2			160.5	3.6
14	80	09	2			162.5	3.6
14	90	10	2			164.0	3.5
14	100	11	2			161.5	3.5
14	115	12	2			160.0	3.5
14	125	13	2			159.5	3.6
14	135	14	2			158.0	3.6
14	145	15	2			157.5	3.5
14	155	16	2			156.0	3.1

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
14	165	17	2			156.0	3.1
15	0	01	1			149.5	4.1
15	15	02	1			147.5	4.2
15	30	03	1			146.5	4.0
15	45	04	1			147.0	4.0
15	60	05	1			146.0	4.2
15	75	06	1			147.0	4.1
15	90	07	1			148.0	4.4
15	105	08	1			148.0	4.5
15	120	09	1			148.0	4.5
15	135	10	1			147.0	4.2
15	150	11	1			147.5	4.1
15	165	12	1			148.0	4.5
15	180	13	1			148.0	4.7
15	195	14	1			148.0	4.0
15	210	15	1			146.0	4.3
15	225	16	1			148.5	4.4
15	240	17	1			148.0	4.3
15	0	01	2			147.0	4.5
15	15	02	2			147.0	4.3
15	30	03	2			147.0	4.3
15	45	04	2			145.5	4.1
15	60	05	2			146.0	4.2
15	75	06	2			147.5	4.5
15	90	07	2			149.0	4.6
15	105	08	2			149.0	4.4
15	120	09	2			150.0	4.6
15	135	10	2			150.0	4.5
15	150	11	2			150.0	4.3
15	165	12	2			151.0	4.3
15	180	13	2			150.5	4.4
15	195	14	2			151.0	4.4
15	210	15	2			151.0	4.2
15	225	16	2			151.0	4.4
15	240	17	2			151.0	4.5
15	0	01	3			147.5	4.9
15	15	02	3			146.5	4.7
15	30	03	3			146.0	4.7
15	45	04	3			144.5	4.5
15	60	05	3			145.5	4.3
15	75	06	3			145.5	4.6
15	90	07	3			146.0	4.5
15	105	08	3			147.0	4.4
15	120	09	3			147.0	4.6
15	135	10	3			147.5	5.0
15	150	11	3			147.0	4.3
15	165	12	3			147.5	4.2
15	180	13	3			147.0	4.5

Group	Min.	Time	Subj.	Na-OLD	K-OLD	Na-NEW	K-NEW
15	195	14	3			147.0	4.5
15	210	15	3			147.5	4.0
15	225	16	3			147.0	4.0
15	240	17	3			147.5	3.8
15	0	01	4			148.5	4.6
15	15	02	4			147.5	4.3
15	30	03	4			147.0	4.4
15	45	04	4			146.0	4.2
15	60	05	4			146.0	4.4
15	75	06	4			147.0	4.0
15	90	07	4			147.5	4.5
15	105	08	4			147.0	4.2
15	120	09	4			147.5	4.4
15	135	10	4			147.0	4.3
15	150	11	4			147.5	4.3
15	165	12	4			147.5	4.7
15	180	13	4			148.0	4.2
15	195	14	4			147.5	4.8
15	210	15	4			148.0	4.3
15	225	16	4			148.5	4.4
15	240	17	4			148.5	4.0

Group	Time	Subj.	Min.	NH3
03	1	3	0	65.0
03	2	3	5	534.0
03	3	3	10	1147.0
03	4	3	15	918.0
03	5	3	30	376.0
03	6	3	45	199.0
03	7	3	55	136.0
03	8	3	65	105.0
03	9	3	75	102.0
03	1	4	0	22.0
03	2	4	3	548.0
03	3	4	7	378.0
03	4	4	10	288.0
03	5	4	15	263.0
03	6	4	20	548.0
03	7	4	35	363.0
03	8	4	50	829.0
03	9	4	55	908.0
03	10	4	65	316.0
03	11	4	75	138.0
03	12	4	85	87.0
03	13	4	95	58.0
06	1	1	0	30.0
06	2	1	5	348.0
06	3	1	10	700.0
06	4	1	15	444.0
06	5	1	25	206.0
06	6	1	35	102.0
06	7	1	45	102.0
06	7	1	55	51.0
06	8	1	65	51.0
06	9	1	75	60.0
06	1	2	0	36.0
06	2	2	5	245.0
06	3	2	10	1184.0
06	4	2	15	994.0
06	5	2	25	494.0
06	6	2	35	206.0
06	7	2	45	145.0
06	8	2	75	43.0
06	9	2	85	36.0
07	1	1	0	31.0
07	2	1	5	441.0
07	3	1	10	441.0
07	4	1	15	856.0
07	5	1	20	686.0
07	6	1	35	1022.0
07	7	1	45	441.0
07	8	1	55	271.0
07	9	1		182.0
07	1	2	0	27.0
07	2	2	7	312.0

Group	Time	Subj.	Min.	NH3
07	3	2	15	628.0
07	4	2	20	628.0
07	5	2	25	892.0
07	6	2	35	1026.0
07	7	2	45	957.0
07	8	2	52	607.0
07	9	2	70	335.0
07	10	2	95	40.0
14	1	3	0	52.0
14	2	3	5	32.0
14	3	3	10	61.0
14	4	3	15	9999.9
14	5	3	20	9999.9
14	6	3	25	9999.9
14	7	3	35	9999.9
14	8	3	45	32.0
14	9	3	55	49.0
14	10	3	65	9999.9
14	11	3	80	9999.9
14	12	3	90	49.0
14	13	3	100	49.0
14	14	3	110	76.0
14	15	3	120	32.0
14	16	3	140	9999.9
14	17	3	150	32.0
14	1	4	0	18.0
14	2	4	5	18.0
14	3	4	10	17.0
14	4	4	15	17.0
14	5	4	20	37.0
14	6	4	25	37.0
14	7	4	35	37.0
14	8	4	45	82.0
14	9	4	55	9999.9
14	10	4	65	9999.9
14	11	4	75	9999.9
14	12	4	85	9999.9
14	13	4	95	9999.9
14	14	4	105	9999.9
14	15	4	115	9999.9
14	16	4	130	9999.9
14	17	4	141	9999.9
14	1	5	0	18.0
14	2	5	10	20.0
14	3	5	20	18.0
14	4	5	30	18.0
14	5	5	40	18.0
14	6	5	50	18.0

Group	Time	Subj.	Min.	NH3
14	7	5	60	18.0
14	8	5	70	18.0
14	9	5	80	18.0
14	10	5	90	10.0
14	11	5	100	19.0
14	12	5	110	20.0
14	13	5	127	24.0
14	14	5	130	18.0
14	15	5	137	31.0
14	16	5	145	26.0
14	17	5	155	18.0
14	1	6	0	29.0
14	2	6	10	40.0
14	3	6	20	32.0
14	4	6	30	36.0
14	5	6	40	23.0
14	6	6	50	23.0
14	7	6	60	23.0
14	8	6	70	22.0
14	9	6	80	19.0
14	10	6	90	19.0
14	11	6	100	19.0
14	12	6	115	23.0
14	13	6	125	26.0
14	14	6	135	26.0
14	15	6	145	18.0
14	16	6	155	40.0
14	17	6	165	40.0
15	1	1	0	77.0
15	2	1	15	50.0
15	3	1	30	50.0
15	4	1	45	54.0
15	5	1	60	77.0
15	6	1	75	72.0
15	7	1	90	54.0
15	8	1	105	45.0
15	9	1	120	41.0
15	10	1	135	54.0
15	11	1	150	54.0
15	12	1	165	56.0
15	13	1	180	77.0
15	14	1	195	77.0
15	15	1	210	80.0
15	16	1	225	77.0
15	17	1	240	77.0
15	1	2	0	18.0
15	2	2	15	17.0
15	3	2	30	17.0

Group	Time	Subj.	Min.	NH3
15	4	2	45	17.0
15	5	2	60	17.0
15	6	2	75	16.0
15	7	2	90	14.0
15	8	2	105	14.0
15	9	2	120	14.0
15	10	2	135	14.0
15	11	2	150	17.0
15	12	2	165	17.0
15	13	2	180	16.0
15	14	2	195	16.0
15	15	2	210	17.0
15	16	2	225	14.0
15	17	2	240	13.0
15	1	3	0	55.0
15	2	3	15	73.0
15	3	3	30	73.0
15	4	3	45	69.0
15	5	3	60	69.0
15	6	3	75	55.0
15	7	3	90	51.0
15	8	3	105	68.0
15	9	3	120	69.0
15	10	3	135	63.9
15	11	3	150	57.0
15	12	3	165	71.0
15	13	3	180	73.0
15	14	3	195	73.0
15	15	3	210	73.9
15	16	3	225	73.0
15	17	3	240	73.0
15	1	4	0	35.0
15	2	4	15	35.0
15	3	4	30	30.0
15	4	4	45	51.0
15	5	4	60	35.0
15	6	4	75	30.0
15	7	4	90	35.0
15	8	4	105	35.0
15	9	4	120	33.0
15	10	4	135	35.0
15	11	4	150	51.0
15	12	4	165	51.0
15	13	4	180	73.0
15	14	4	195	73.0
15	15	4	210	79.0
15	16	4	225	73.0
15	17	4	240	76.0

SAS

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=1 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39950000	0.02600641	0.01300320	0.00067633	29.59800000
PCO2	4	49.10000000	23.80238083	11.90119042	566.55333333	196.40000000
PO2	4	52.30000000	11.70669324	5.85334662	137.04666667	209.20000000
BE	4	-1.15000000	2.83607710	1.41803855	8.04333333	-4.60000000
HCO3	4	22.35000000	2.54230866	1.27115433	6.46333333	89.40000000
TOTCO2	4	23.55000000	2.60064095	1.30032047	6.76333333	94.20000000
NAOLD	4	142.55000000	1.18180653	0.59090326	1.39666667	570.20000000
KOLD	4	4.65000000	0.42031734	0.21015867	0.17666667	18.60000000
NANEW	1	148.50000000	.	.	.	148.50000000
KNEW	1	4.60000000	.	.	.	4.60000000
GROUP=1 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39775000	0.03578990	0.01789495	0.00128092	29.59100000
PCO2	4	38.17500000	2.39078090	1.19539045	5.71583333	152.70000000
PO2	4	48.40000000	9.55231211	4.77615606	91.24666667	193.60000000
BE	4	-0.42500000	3.00485718	1.50242859	9.02916667	-1.70000000
HCO3	4	23.20000000	2.67207784	1.33603892	7.14000000	92.80000000
TOTCO2	4	24.47500000	2.75484422	1.37742211	7.58916667	97.90000000
NAOLD	4	142.95000000	1.46401275	0.73200638	2.14333333	571.80000000
KOLD	4	4.57500000	0.45000000	0.22500000	0.20250000	18.30000000
NANEW	1	149.00000000	.	.	.	149.00000000
KNEW	1	4.40000000	.	.	.	4.40000000
GROUP=1 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39650000	0.02378375	0.01189187	0.00056567	29.58600000
PCO2	4	36.90000000	2.28619043	1.14309521	5.22666667	147.60000000
PO2	4	47.40000000	8.27083228	4.13541614	68.40666667	189.60000000
BE	4	-1.15000000	2.91032644	1.45516322	8.47000000	-4.60000000
HCO3	4	22.35000000	2.62106848	1.31053424	6.87000000	89.40000000
TOTCO2	4	23.55000000	2.70123429	1.35061714	7.29666667	94.20000000
NAOLD	4	142.75000000	1.66633330	0.83316665	2.77666667	571.00000000
KOLD	4	4.60000000	0.49665548	0.24832774	0.24666667	18.40000000
NANEW	1	149.00000000	.	.	.	149.00000000
KNEW	1	4.50000000	.	.	.	4.50000000
GROUP=1 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39725000	0.03251025	0.01625513	0.00105692	29.58900000
PCO2	4	36.97500000	2.31570724	1.15785362	5.36250000	147.90000000
PO2	4	50.90000000	11.27622868	5.63811434	127.15333333	203.60000000
BE	4	-1.10000000	3.45543051	1.72771525	11.94000000	-4.40000000
HCO3	4	22.47500000	3.11274263	1.55637131	9.68916667	89.90000000
TOTCO2	4	23.70000000	3.16016877	1.58008439	9.98666667	94.80000000
NAOLD	4	143.17500000	1.29711218	0.64855609	1.68250000	572.70000000
KOLD	4	4.65000000	0.43588989	0.21794495	0.19000000	18.60000000
NANEW	1	149.00000000	.	.	.	149.00000000
KNEW	1	4.40000000	.	.	.	4.40000000

SAS

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=1 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37875000	0.03135150	0.01567575	0.00098292	29.51500000
PCO2	4	38.05000000	1.99415813	0.99707907	3.97666667	152.20000000
PO2	4	48.80000000	9.04249228	4.52124614	81.76666667	195.20000000
BE	4	-1.75000000	2.98272806	1.49136403	8.89666667	-7.00000000
HCO3	4	22.15000000	2.69382009	1.34691004	7.25666667	88.60000000
TOTCO2	4	23.37500000	2.76932603	1.38466302	7.66916667	93.50000000
NAOLD	4	142.62500000	2.57989018	1.28994509	6.65583333	570.50000000
KOLD	4	4.55000000	0.54467115	0.27233558	0.29666667	18.20000000
NANEW	1	149.00000000	.	.	.	149.00000000
KNEW	1	4.30000000	.	.	.	4.30000000
GROUP=1 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37075000	0.03513189	0.01756595	0.00123425	29.48300000
PCO2	4	38.35000000	1.74068952	0.87034476	3.03000000	153.40000000
PO2	4	49.77500000	5.61033273	2.80516636	31.47583333	199.10000000
BE	4	-2.12500000	3.14788289	1.57394144	9.90916667	-8.50000000
HCO3	4	21.92500000	2.82886903	1.41443452	8.00250000	87.70000000
TOTCO2	4	23.17500000	2.85817541	1.42908770	8.16916667	92.70000000
NAOLD	4	144.57500000	1.71731379	0.85865690	2.94916667	578.30000000
KOLD	4	4.65000000	0.40414519	0.20207259	0.16333333	18.60000000
NANEW	1	149.50000000	.	.	.	149.50000000
KNEW	1	4.40000000	.	.	.	4.40000000
GROUP=1 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36725000	0.02197536	0.01098768	0.00048292	29.46900000
PCO2	4	38.25000000	2.65392791	1.32696395	7.04333333	153.00000000
PO2	4	51.45000000	5.76281181	2.88140591	33.21000000	205.80000000
BE	4	-2.45000000	2.67394839	1.33697420	7.15000000	-9.80000000
HCO3	4	21.65000000	2.60576284	1.30288142	6.79000000	86.60000000
TOTCO2	4	22.87500000	2.65000000	1.32500000	7.02250000	91.50000000
NAOLD	4	141.35000000	4.94873721	2.47436861	24.49000000	565.40000000
KOLD	4	4.27500000	0.78475049	0.39237525	0.61583333	17.10000000
NANEW	1	149.50000000	.	.	.	149.50000000
KNEW	1	3.90000000	.	.	.	3.90000000
GROUP=2 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38575000	0.01695828	0.00847914	0.00028758	29.54300000
PCO2	4	35.22500000	4.20901810	2.10450905	17.71583333	140.90000000
PO2	4	47.60000000	4.31277173	2.15638587	18.60000000	190.40000000
BE	4	-2.45000000	2.22186108	1.11093054	4.93666667	-9.80000000
HCO3	4	20.72500000	2.34289707	1.17144853	5.48916667	82.90000000
TOTCO2	4	21.87500000	2.45000000	1.22500000	6.00250000	87.50000000
NAOLD	4	141.70000000	2.15096877	1.07548439	4.62666667	566.80000000
KOLD	4	4.32500000	0.20615528	0.10307764	0.04250000	17.30000000
NANEW	2	146.50000000	2.12132034	1.50000000	4.50000000	293.00000000
KNEW	2	4.30000000	0.00000000	0.00000000	0.00000000	8.60000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=2 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37000000	0.01964688	0.00982344	0.00038600	29.48000000
PCO2	4	34.62500000	4.38738723	2.19369361	19.24916667	138.50000000
PO2	4	53.00000000	8.58564694	4.29282347	73.71333333	212.00000000
BE	4	-3.95000000	1.58008439	0.79004219	2.49666667	-15.80000000
HCO3	4	19.62500000	1.93627650	0.96813825	3.74916667	78.50000000
TOTCO2	4	20.50000000	1.64721988	0.82360994	2.71333333	82.00000000
NAOLD	4	142.15000000	2.08726296	1.04363148	4.35666667	568.60000000
KOLD	4	4.40000000	0.14142136	0.07071068	0.02000000	17.60000000
NANEW	2	146.25000000	1.76776695	1.25000000	3.12500000	292.50000000
KNEW	2	4.40000000	0.14142136	0.10000000	0.02000000	8.80000000
GROUP=2 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35300000	0.01570563	0.00785281	0.00024667	29.41200000
PCO2	4	34.55000000	2.61087469	1.30543735	6.81666667	138.20000000
PO2	4	48.52500000	6.67401678	3.33700839	44.54250000	194.10000000
BE	4	-4.95000000	0.59721576	0.29860788	0.35666667	-19.80000000
HCO3	4	18.85000000	0.79372539	0.39686270	0.63000000	75.40000000
TOTCO2	4	20.00000000	0.84459063	0.42229532	0.71333333	80.00000000
NAOLD	4	142.02500000	1.80808370	0.90404185	3.26916667	568.10000000
KOLD	4	4.37500000	0.26299556	0.13149778	0.06916667	17.50000000
NANEW	2	146.25000000	1.06066017	0.75000000	1.12500000	292.50000000
KNEW	2	4.25000000	0.21213203	0.15000000	0.04500000	8.50000000
GROUP=2 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.33125000	0.01463728	0.00731864	0.00021425	29.32500000
PCO2	4	34.80000000	1.45830952	0.72915476	2.12666667	139.20000000
PO2	4	48.85000000	10.75251908	5.37625954	115.61666667	195.40000000
BE	4	-6.02500000	0.50579970	0.25289985	0.25583333	-24.10000000
HCO3	4	18.12500000	0.55602758	0.27801379	0.30916667	72.50000000
TOTCO2	4	19.22500000	0.55602758	0.27801379	0.30916667	76.90000000
NAOLD	4	142.90000000	1.65529454	0.82764727	2.74000000	571.60000000
KOLD	4	4.72500000	0.40311289	0.20155644	0.16250000	18.90000000
NANEW	2	146.00000000	1.41421356	1.00000000	2.00000000	292.00000000
KNEW	2	4.55000000	0.07071068	0.05000000	0.00500000	9.10000000
GROUP=2 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.30850000	0.03613401	0.01806700	0.00130567	29.23400000
PCO2	4	34.47500000	2.57989018	1.28994509	6.65583333	137.90000000
PO2	4	48.80000000	7.28971879	3.64485939	53.14000000	195.20000000
BE	4	-7.42500000	2.02710796	1.01355398	4.10916667	-29.70000000
HCO3	4	17.07500000	1.65201897	0.82600948	2.72916667	68.30000000
TOTCO2	4	18.17500000	1.69779268	0.84889634	2.88250000	72.70000000
NAOLD	4	141.45000000	1.47535307	0.73767653	2.17666667	565.80000000
KOLD	4	4.80000000	0.25819889	0.12909944	0.06666667	19.20000000
NANEW	2	146.00000000	2.12132034	1.50000000	4.50000000	292.00000000
KNEW	2	4.90000000	0.42426407	0.30000000	0.18000000	9.80000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=2 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.28550000	0.02834902	0.01417451	0.00080367	29.14200000
PCO2	4	35.15000000	1.20692447	0.60346223	1.45666667	140.60000000
PO2	4	49.22500000	6.62287702	3.31143851	43.86250000	196.90000000
BE	4	-8.37500000	1.49972220	0.74986110	2.24916667	-33.50000000
HCO3	4	16.47500000	1.06887792	0.53443896	1.14250000	65.90000000
TOTCO2	4	17.60000000	1.11055542	0.55527771	1.23333333	70.40000000
NAOLD	4	141.15000000	1.35030861	0.67515430	1.82333333	564.60000000
KOLD	4	4.57500000	0.22173558	0.11086779	0.04916667	18.30000000
NANEW	2	146.00000000	1.41421356	1.00000000	2.00000000	292.00000000
KNEW	2	4.65000000	0.35355339	0.25000000	0.12500000	9.30000000
GROUP=2 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.28400000	0.02841361	0.01420681	0.00080733	29.13600000
PCO2	4	35.30000000	2.45356883	1.22678441	6.02000000	141.20000000
PO2	4	49.07500000	7.60235709	3.80117855	57.79583333	196.30000000
BE	4	-9.00000000	0.73484692	0.36742346	0.54000000	-36.00000000
HCO3	4	15.95000000	0.55075705	0.27537853	0.30333333	63.80000000
TOTCO2	4	15.82500000	2.68498914	1.34249457	7.20916667	63.30000000
NAOLD	4	142.25000000	0.95742711	0.47871355	0.91666667	569.00000000
KOLD	4	4.60000000	0.24494897	0.12247449	0.06000000	18.40000000
NANEW	2	145.75000000	0.35355339	0.25000000	0.12500000	291.50000000
KNEW	2	4.75000000	0.07071068	0.05000000	0.00500000	9.50000000
GROUP=3 TIME=1						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.35000000	0.03535534	0.02500000	0.00125000	14.70000000
PCO2	2	35.95000000	1.90918831	1.35000000	3.64500000	71.90000000
PO2	2	58.00000000	12.16223664	8.60000000	147.92000000	116.00000000
BE	2	-4.45000000	1.06066017	0.75000000	1.12500000	-8.90000000
HCO3	2	19.50000000	0.56568542	0.40000000	0.32000000	39.00000000
TOTCO2	2	20.70000000	0.42426407	0.30000000	0.18000000	41.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	147.00000000	0.00000000	0.00000000	0.00000000	294.00000000
KNEW	2	4.50000000	0.14142136	0.10000000	0.02000000	9.00000000
GROUP=3 TIME=2						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.37600000	0.04101219	0.02900000	0.00168200	14.75200000
PCO2	2	31.90000000	0.98994949	0.70000000	0.98000000	63.80000000
PO2	2	78.85000000	14.77853173	10.45000000	218.40500000	157.70000000
BE	2	-4.85000000	3.04055916	2.15000000	9.24500000	-9.70000000
HCO3	2	18.45000000	2.33345238	1.65000000	5.44500000	36.90000000
TOTCO2	2	19.50000000	2.40416306	1.70000000	5.78000000	39.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.50000000	0.70710678	0.50000000	0.50000000	293.00000000
KNEW	2	4.95000000	0.07071068	0.05000000	0.00500000	9.90000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=3 TIME=3						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.32050000	0.02616295	0.01850000	0.00068450	14.64100000
PCO2	2	35.10000000	0.84852814	0.60000000	0.72000000	70.20000000
PO2	2	67.00000000	7.91959595	5.60000000	62.72000000	134.00000000
BE	2	-6.70000000	1.13137085	0.80000000	1.28000000	-13.40000000
HCO3	2	17.85000000	0.63639610	0.45000000	0.40500000	35.70000000
TOTCO2	2	18.95000000	0.63639610	0.45000000	0.40500000	37.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.00000000	2.12132034	1.50000000	4.50000000	292.00000000
KNEW	2	4.60000000	0.00000000	0.00000000	0.00000000	9.20000000
GROUP=3 TIME=4						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.31800000	0.02262742	0.01600000	0.00051200	14.63600000
PCO2	2	35.70000000	1.97989899	1.40000000	3.92000000	71.40000000
PO2	2	57.45000000	0.35355339	0.25000000	0.12500000	114.90000000
BE	2	-6.50000000	0.56568542	0.40000000	0.32000000	-13.00000000
HCO3	2	17.95000000	0.07071068	0.05000000	0.00500000	35.90000000
TOTCO2	2	19.15000000	0.07071068	0.05000000	0.00500000	38.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.25000000	1.06066017	0.75000000	1.12500000	292.50000000
KNEW	2	4.55000000	0.21213203	0.15000000	0.04500000	9.10000000
GROUP=3 TIME=5						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.31050000	0.03889087	0.02750000	0.00151250	14.62100000
PCO2	2	35.30000000	0.84852814	0.60000000	0.72000000	70.60000000
PO2	2	67.45000000	4.45477272	3.15000000	19.84500000	134.90000000
BE	2	-7.15000000	1.90918831	1.35000000	3.64500000	-14.30000000
HCO3	2	17.55000000	1.20208153	0.85000000	1.44500000	35.10000000
TOTCO2	2	18.70000000	1.13137085	0.80000000	1.28000000	37.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.00000000	1.41421356	1.00000000	2.00000000	292.00000000
KNEW	2	4.60000000	0.14142136	0.10000000	0.02000000	9.20000000
GROUP=3 TIME=6						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.29600000	0.03676955	0.02600000	0.00135200	14.59200000
PCO2	2	36.40000000	0.70710678	0.50000000	0.50000000	72.80000000
PO2	2	64.60000000	2.68700577	1.90000000	7.22000000	129.20000000
BE	2	-7.55000000	1.90918831	1.35000000	3.64500000	-15.10000000
HCO3	2	17.50000000	1.13137085	0.80000000	1.28000000	35.00000000
TOTCO2	2	18.70000000	1.13137085	0.80000000	1.28000000	37.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	145.50000000	2.12132034	1.50000000	4.50000000	291.00000000
KNEW	2	4.80000000	0.42426407	0.30000000	0.18000000	9.60000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=3 TIME=7						
ID	2	3.50000000	0.70710678	0.50000000	0.50000000	7.00000000
PH	2	7.27100000	0.06929646	0.04900000	0.00480200	14.54200000
PCO2	2	35.95000000	3.60624458	2.55000000	13.00500000	71.90000000
PO2	2	62.05000000	13.50573952	9.55000000	182.40500000	124.10000000
BE	2	-8.95000000	5.30330086	3.75000000	28.12500000	-17.90000000
HCO3	2	16.50000000	4.24264069	3.00000000	18.00000000	33.00000000
TOTCO2	2	17.65000000	4.31335137	3.05000000	18.60500000	35.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	145.25000000	3.18198052	2.25000000	10.12500000	290.50000000
KNEW	2	5.05000000	0.77781746	0.55000000	0.60500000	10.10000000
GROUP=4 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35900000	0.01840290	0.00920145	0.00033867	29.43600000
PCO2	4	37.32500000	2.26623770	1.13311885	5.13583333	149.30000000
PO2	4	51.02500000	5.22517942	2.61258971	27.30250000	204.10000000
BE	4	-3.12500000	2.10614181	1.05307091	4.43583333	-12.50000000
HCO3	4	20.77500000	1.98053023	0.99026512	3.92250000	83.10000000
TOTCO2	4	22.02500000	2.05649378	1.02824689	4.22916667	88.10000000
NAOLD	3	141.16666667	3.88372673	2.24227067	15.08333333	423.50000000
KOLD	3	4.10000000	0.20000000	0.11547005	0.04000000	12.30000000
NANEW	4	149.87500000	1.31497782	0.65748891	1.72916667	599.50000000
KNEW	4	4.45000000	0.40414519	0.20207259	0.16333333	17.80000000
GROUP=4 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.34975000	0.06262255	0.03131127	0.00392158	29.39900000
PCO2	4	33.82500000	3.78538858	1.89269429	14.32916667	135.30000000
PO2	4	59.27500000	21.93024928	10.96512464	480.93583333	237.10000000
BE	4	-5.17500000	3.57432977	1.78716489	12.77583333	-20.70000000
HCO3	4	18.52500000	2.91819008	1.45909504	8.51583333	74.10000000
TOTCO2	4	19.62500000	2.97363414	1.48681707	8.84250000	78.50000000
NAOLD	2	139.25000000	1.76776695	1.25000000	3.12500000	278.50000000
KOLD	2	4.25000000	0.07071068	0.05000000	0.00500000	8.50000000
NANEW	4	149.37500000	3.90245649	1.95122825	15.22916667	597.50000000
KNEW	4	4.92500000	0.67019898	0.33509949	0.44916667	19.70000000
GROUP=4 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.31075000	0.04634203	0.02317101	0.00214758	29.24300000
PCO2	4	35.85000000	1.20692447	0.60346223	1.45666667	143.40000000
PO2	4	56.37500000	5.95224047	2.97612024	35.42916667	225.50000000
BE	4	-6.67500000	3.14894162	1.57447081	9.91583333	-26.70000000
HCO3	4	17.95000000	2.45560583	1.22780292	6.03000000	71.80000000
TOTCO2	4	19.15000000	2.53311403	1.26655701	6.41666667	76.60000000
NAOLD	3	140.00000000	2.00000000	1.15470054	4.00000000	420.00000000
KOLD	3	4.06666667	0.20816660	0.12019504	0.04333333	12.20000000
NANEW	4	147.12500000	3.14576435	1.57288217	9.89583333	588.50000000
KNEW	4	4.42500000	0.49244289	0.24622145	0.24250000	17.70000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=4 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.31650000	0.04855581	0.02427790	0.00235767	29.26600000
PCO2	4	37.35000000	1.85202592	0.92601296	3.43000000	149.40000000
PO2	4	53.10000000	7.94103268	3.97051634	63.06000000	212.40000000
BE	4	-5.72500000	2.62218103	1.31109051	6.87583333	-22.90000000
HCO3	4	18.87500000	1.80808370	0.90404185	3.26916667	75.50000000
TOTCO2	4	20.10000000	1.86010752	0.93005376	3.46000000	80.40000000
NAOLD	2	135.00000000	4.24264069	3.00000000	18.00000000	270.00000000
KOLD	2	4.00000000	0.00000000	0.00000000	0.00000000	8.00000000
NANEW	4	146.62500000	7.46519703	3.73259851	55.72916667	586.50000000
KNEW	4	4.32500000	0.33040379	0.16520190	0.10916667	17.30000000
GROUP=4 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.33050000	0.04716991	0.02358495	0.00222500	29.32200000
PCO2	4	35.82500000	0.53774219	0.26887110	0.28916667	143.30000000
PO2	4	61.02500000	5.68411529	2.84205765	32.30916667	244.10000000
BE	4	-5.65000000	2.70493376	1.35246688	7.31666667	-22.60000000
HCO3	4	18.75000000	1.91920122	0.95960061	3.68333333	75.00000000
TOTCO2	4	19.90000000	1.92006944	0.96003472	3.68666667	79.60000000
NAOLD	3	141.16666667	6.37050495	3.67801275	40.58333333	423.50000000
KOLD	3	4.36666667	0.23094011	0.13333333	0.05333333	13.10000000
NANEW	4	149.50000000	2.38047614	1.19023807	5.66666667	598.00000000
KNEW	4	4.67500000	0.20615528	0.10307764	0.04250000	18.70000000
GROUP=4 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.31775000	0.05067133	0.02533566	0.00256758	29.27100000
PCO2	4	36.70000000	1.74355958	0.87177979	3.04000000	146.80000000
PO2	4	53.40000000	7.54232502	3.77116251	56.88666667	213.60000000
BE	4	-5.87500000	3.153[illegible]301	1.57658650	9.94250000	-23.50000000
HCO3	4	18.65000000	2.40208243	1.20104121	5.77000000	74.60000000
TOTCO2	4	19.85000000	2.41729877	1.20864938	5.84333333	79.40000000
NAOLD	3	141.16666667	3.88372673	2.24227067	15.08333333	423.50000000
KOLD	3	4.16666667	0.20816660	0.12018504	0.04333333	12.50000000
NANEW	4	149.87500000	2.49582986	1.24791493	6.22916667	599.50000000
KNEW	4	4.52500000	0.27537853	0.13768926	0.07583333	18.10000000
GROUP=4 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.31775000	0.04720434	0.02360217	0.00222825	29.27100000
PCO2	4	36.77500000	2.77413650	1.38706825	7.69583333	147.10000000
PO2	4	53.42500000	12.32189785	6.16094893	151.82916667	213.70000000
BE	4	-5.80000000	3.11234103	1.55617051	9.68666667	-23.20000000
HCO3	4	18.47500000	2.75000000	1.37500000	7.56250000	73.90000000
TOTCO2	4	19.90000000	2.52586619	1.26293309	6.38000000	79.60000000
NAOLD	3	142.83333333	6.71441236	3.87656778	45.08333333	428.50000000
KOLD	3	4.13333333	0.15275252	0.08819171	0.02333333	12.40000000
NANEW	4	150.12500000	2.01556444	1.00778222	4.06250000	600.50000000
KNEW	4	4.50000000	0.11547005	0.05773503	0.01333333	18.00000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=5 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.34825000	0.02860507	0.01430253	0.00081825	29.39300000
PCO2	4	38.97500000	3.64451643	1.82225821	13.28250000	155.90000000
PO2	4	48.25000000	9.18930538	4.59465269	84.44333333	193.00000000
BE	4	-1.55000000	1.47986486	0.73993243	2.19000000	-6.20000000
HCO3	4	22.22500000	0.56789083	0.28394542	0.32250000	88.90000000
TOTCO2	4	23.47500000	0.52519838	0.26259919	0.27583333	93.90000000
NAOLD	1	137.00000000	.	.	.	137.00000000
KOLD	1	4.40000000	.	.	.	4.40000000
NANEW	4	149.62500000	1.88745861	0.94372930	3.56250000	598.50000000
KNEW	4	4.75000000	0.17320508	0.08660254	0.03000000	19.00000000
GROUP=5 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36500000	0.02544275	0.01272137	0.00064733	29.46000000
PCO2	4	35.27500000	3.45964834	1.72982417	11.96916667	141.10000000
PO2	4	57.27500000	13.10556498	6.55278249	171.75583333	229.10000000
BE	4	-3.72500000	1.28150056	0.64080028	1.64250000	-14.90000000
HCO3	4	19.87500000	1.24465524	0.62232762	1.54916667	79.50000000
TOTCO2	4	21.02500000	1.36473441	0.68236720	1.86250000	84.10000000
NAOLD	1	137.00000000	.	.	.	137.00000000
KOLD	1	4.50000000	.	.	.	4.50000000
NANEW	4	148.50000000	1.29099445	0.64549722	1.66666667	594.00000000
KNEW	4	5.07500000	0.17078251	0.08539126	0.02916667	20.30000000
GROUP=5 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.34250000	0.01774824	0.00887412	0.00031500	29.37000000
PCO2	4	36.80000000	2.35513623	1.17756812	5.54666667	147.20000000
PO2	4	55.37500000	6.28934284	3.14467142	39.55583333	221.50000000
BE	4	-4.42500000	0.70887234	0.35443617	0.50250000	-17.70000000
HCO3	4	19.70000000	0.71647284	0.35823642	0.51333333	78.80000000
TOTCO2	4	20.90000000	0.77028133	0.38514067	0.59333333	83.60000000
NAOLD	1	137.00000000	.	.	.	137.00000000
KOLD	1	4.40000000	.	.	.	4.40000000
NANEW	4	149.50000000	2.04124145	1.02062073	4.16666667	598.00000000
KNEW	4	4.87500000	0.18929694	0.09464847	0.03583333	19.50000000
GROUP=5 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.34025000	0.02604323	0.01302162	0.00067825	29.36100000
PCO2	4	37.62500000	2.97811462	1.48905731	8.86916667	150.50000000
PO2	4	52.20000000	12.52544078	6.26272039	156.88666667	208.80000000
BE	4	-4.12500000	0.18929694	0.09464847	0.03583333	-16.50000000
HCO3	4	19.97500000	0.38622101	0.19311050	0.14916667	79.90000000
TOTCO2	4	21.25000000	0.47958315	0.23979158	0.23000000	85.00000000
NAOLD	1	136.00000000	.	.	.	136.00000000
KOLD	1	4.60000000	.	.	.	4.60000000
NANEW	4	149.12500000	1.25000000	0.62500000	1.56250000	596.50000000
KNEW	4	4.72500000	0.12583057	0.06291529	0.01583333	18.90000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=5 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.33925000	0.02913617	0.01456809	0.00084892	29.35700000
PCO2	4	35.82500000	2.06135069	1.03067534	4.24916667	143.30000000
PO2	4	63.50000000	6.93157029	3.46578514	48.04666667	254.00000000
BE	4	-5.15000000	1.03440804	0.51720402	1.07000000	-20.60000000
HCO3	4	19.02500000	0.53150729	0.26575365	0.28250000	76.10000000
TOTCO2	4	20.20000000	0.54160256	0.27080128	0.29333333	80.80000000
NAOLD	1	137.00000000	.	.	.	137.00000000
KOLD	1	4.50000000	.	.	.	4.50000000
NANEW	4	152.12500000	3.61420807	1.80710404	13.06250000	608.50000000
KNEW	4	5.05000000	0.12909944	0.06454972	0.01666667	20.20000000
GROUP=5 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.32900000	0.02976575	0.01488288	0.00088600	29.31600000
PCO2	4	34.67500000	1.45229703	0.72614852	2.10916667	138.70000000
PO2	4	64.35000000	10.77574437	5.38787218	116.11666667	257.40000000
BE	4	-6.22500000	1.62762608	0.81381304	2.64916667	-24.90000000
HCO3	4	18.02500000	1.25266383	0.62633191	1.56916667	72.10000000
TOTCO2	4	19.17500000	1.28679188	0.64339594	1.65583333	76.70000000
NAOLD	1	137.00000000	.	.	.	137.00000000
KOLD	1	4.60000000	.	.	.	4.60000000
NANEW	4	150.62500000	2.17466473	1.08733236	4.72916667	602.50000000
KNEW	4	5.00000000	0.14142136	0.07071068	0.02000000	20.00000000
GROUP=5 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.32125000	0.04652866	0.02326433	0.00216492	29.28500000
PCO2	4	35.55000000	1.13871272	0.56935636	1.29666667	142.20000000
PO2	4	59.90000000	10.01365734	5.00682867	100.27333333	239.60000000
BE	4	-6.22500000	2.43224862	1.21612431	5.91583333	-24.90000000
HCO3	4	18.17500000	1.74236429	0.87118215	3.03583333	72.70000000
TOTCO2	4	19.35000000	1.75214155	0.87607077	3.07000000	77.40000000
NAOLD	1	136.00000000	.	.	.	136.00000000
KOLD	1	4.60000000	.	.	.	4.60000000
NANEW	4	149.00000000	1.15470054	0.57735027	1.33333333	596.00000000
KNEW	4	4.95000000	0.17320508	0.08660254	0.03000000	19.80000000
GROUP=6 TIME=1						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.37050000	0.00777817	0.00550000	0.00006050	14.74100000
PCO2	2	37.55000000	1.90918831	1.35000000	3.64500000	75.10000000
PO2	2	53.65000000	14.77853173	10.45000000	218.40500000	107.30000000
BE	2	-2.40000000	1.69705627	1.20000000	2.88000000	-4.80000000
HCO3	2	21.35000000	1.48492424	1.05000000	2.20500000	42.70000000
TOTCO2	2	22.60000000	1.55563492	1.10000000	2.42000000	45.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	143.75000000	1.76776695	1.25000000	3.12500000	287.50000000
KNEW	2	4.55000000	0.21213203	0.15000000	0.04500000	9.10000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=6 TIME=2						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.34000000	0.00141421	0.00100000	0.00000200	14.68000000
PCO2	2	35.95000000	0.91923882	0.65000000	0.84500000	71.90000000
PO2	2	71.60000000	22.06173157	15.60000000	486.72000000	143.20000000
BE	2	-5.15000000	0.63639610	0.45000000	0.40500000	-10.30000000
HCO3	2	19.10000000	0.56568542	0.40000000	0.32000000	38.20000000
TOTCO2	2	20.30000000	0.56568542	0.40000000	0.32000000	40.60000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	143.75000000	1.06066017	0.75000000	1.12500000	287.50000000
KNEW	2	5.00000000	0.28284271	0.20000000	0.08000000	10.00000000
GROUP=6 TIME=3						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.30200000	0.02687006	0.01900000	0.00072200	14.60400000
PCO2	2	37.35000000	3.60624458	2.55000000	13.00500000	74.70000000
PO2	2	65.25000000	0.21213203	0.15000000	0.04500000	130.50000000
BE	2	-6.85000000	0.21213203	0.15000000	0.04500000	-13.70000000
HCO3	2	18.15000000	0.63639610	0.45000000	0.40500000	36.30000000
TOTCO2	2	19.40000000	0.70710678	0.50000000	0.50000000	38.80000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	143.25000000	1.06066017	0.75000000	1.12500000	286.50000000
KNEW	2	5.15000000	0.21213203	0.15000000	0.04500000	10.30000000
GROUP=6 TIME=4						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.28950000	0.00777817	0.00550000	0.00006050	14.57900000
PCO2	2	39.25000000	1.76776695	1.25000000	3.12500000	78.50000000
PO2	2	48.45000000	2.05060967	1.45000000	4.20500000	96.90000000
BE	2	-6.55000000	0.35355339	0.25000000	0.12500000	-13.10000000
HCO3	2	18.55000000	0.49497475	0.35000000	0.24500000	37.10000000
TOTCO2	2	19.85000000	0.63639610	0.45000000	0.40500000	39.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	143.25000000	1.76776695	1.25000000	3.12500000	286.50000000
KNEW	2	5.00000000	0.42426407	0.30000000	0.18000000	10.00000000
GROUP=6 TIME=5						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.29100000	0.03111270	0.02200000	0.00096800	14.58200000
PCO2	2	38.90000000	3.11126984	2.20000000	9.68000000	77.80000000
PO2	2	54.35000000	5.02045815	3.55000000	25.20500000	108.70000000
BE	2	-6.75000000	0.49497475	0.35000000	0.24500000	-13.50000000
HCO3	2	18.45000000	0.21213203	0.15000000	0.04500000	36.90000000
TOTCO2	2	19.75000000	0.35355339	0.25000000	0.12500000	39.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	143.25000000	1.76776695	1.25000000	3.12500000	286.50000000
KNEW	2	4.65000000	0.49497475	0.35000000	0.24500000	9.30000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=6 TIME=6						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.29750000	0.04313351	0.03050000	0.00186050	14.59500000
PCO2	2	38.70000000	2.26274170	1.60000000	5.12000000	77.40000000
PO2	2	55.55000000	6.29325035	4.45000000	39.60500000	111.10000000
BE	2	-6.35000000	1.34350288	0.95000000	1.80500000	-12.70000000
HCO3	2	18.70000000	0.70710678	0.50000000	0.50000000	37.40000000
TOTCO2	2	19.95000000	0.63639610	0.45000000	0.40500000	39.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	144.00000000	2.12132034	1.50000000	4.50000000	288.00000000
KNEW	2	4.30000000	0.28284271	0.20000000	0.08000000	8.60000000
GROUP=6 TIME=7						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.28800000	0.06222540	0.04400000	0.00387200	14.57600000
PCO2	2	39.20000000	1.97989899	1.40000000	3.92000000	78.40000000
PO2	2	54.05000000	5.86898628	4.15000000	34.44500000	108.10000000
BE	2	-6.80000000	2.96984848	2.10000000	8.82000000	-13.60000000
HCO3	2	18.50000000	1.69705627	1.20000000	2.88000000	37.00000000
TOTCO2	2	19.60000000	1.83847763	1.30000000	3.38000000	39.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	144.25000000	1.76776695	1.25000000	3.12500000	288.50000000
KNEW	2	4.45000000	0.35355339	0.25000000	0.12500000	8.90000000
GROUP=7 TIME=1						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.35100000	0.02969848	0.02100000	0.00088200	14.70200000
PCO2	2	38.35000000	4.31335137	3.05000000	18.60500000	76.70000000
PO2	2	47.75000000	12.23294731	8.65000000	149.64500000	95.50000000
BE	2	-3.05000000	0.35355339	0.25000000	0.12500000	-6.10000000
HCO3	2	20.85000000	0.91923882	0.65000000	0.84500000	41.70000000
TOTCO2	2	22.10000000	0.98994949	0.70000000	0.98000000	44.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	148.50000000	0.70710678	0.50000000	0.50000000	297.00000000
KNEW	2	4.70000000	0.14142136	0.10000000	0.02000000	9.40000000
GROUP=7 TIME=2						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.37950000	0.01484924	0.01050000	0.00022050	14.75900000
PCO2	2	35.35000000	1.34350288	0.95000000	1.80500000	70.70000000
PO2	2	60.65000000	14.77853173	10.45000000	218.40500000	121.30000000
BE	2	-2.90000000	0.14142136	0.10000000	0.02000000	-5.80000000
HCO3	2	20.55000000	0.07071068	0.05000000	0.00500000	41.10000000
TOTCO2	2	21.75000000	0.07071068	0.05000000	0.00500000	43.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	148.25000000	0.35355339	0.25000000	0.12500000	296.50000000
KNEW	2	4.75000000	0.21213203	0.15000000	0.04500000	9.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=7 TIME=3						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.36650000	0.01909188	0.01350000	0.00036450	14.73300000
PCO2	2	35.65000000	2.47487373	1.75000000	6.12500000	71.30000000
PO2	2	59.15000000	15.76848122	11.15000000	248.64500000	118.30000000
BE	2	-3.60000000	0.14142136	0.10000000	0.02000000	-7.20000000
HCO3	2	20.15000000	0.49497475	0.35000000	0.24500000	40.30000000
TOTCO2	2	21.25000000	0.63639610	0.45000000	0.40500000	42.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	148.00000000	0.70710678	0.50000000	0.50000000	296.00000000
KNEW	2	4.80000000	0.28284271	0.20000000	0.08000000	9.60000000
GROUP=7 TIME=4						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.34850000	0.00212132	0.00150000	0.00000450	14.69700000
PCO2	2	34.90000000	0.70710678	0.50000000	0.50000000	69.80000000
PO2	2	58.15000000	16.19274529	11.45000000	262.20500000	116.30000000
BE	2	-4.95000000	0.21213203	0.15000000	0.04500000	-9.90000000
HCO3	2	18.90000000	0.56568542	0.40000000	0.32000000	37.80000000
TOTCO2	2	20.05000000	0.49497475	0.35000000	0.24500000	40.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	147.50000000	0.70710678	0.50000000	0.50000000	295.00000000
KNEW	2	5.10000000	0.28284271	0.20000000	0.08000000	10.20000000
GROUP=7 TIME=5						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.32050000	0.02333452	0.01650000	0.00054450	14.64100000
PCO2	2	33.45000000	1.34350288	0.95000000	1.80500000	66.90000000
PO2	2	63.60000000	17.67766953	12.50000000	312.50000000	127.20000000
BE	2	-7.25000000	1.62634560	1.15000000	2.64500000	-14.50000000
HCO3	2	17.00000000	1.55563492	1.10000000	2.42000000	34.00000000
TOTCO2	2	18.15000000	1.62634560	1.15000000	2.64500000	36.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	147.50000000	0.70710678	0.50000000	0.50000000	295.00000000
KNEW	2	4.95000000	0.35355339	0.25000000	0.12500000	9.90000000
GROUP=7 TIME=6						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.29550000	0.03464823	0.02450000	0.00120050	14.59100000
PCO2	2	35.90000000	3.39411255	2.40000000	11.52000000	71.80000000
PO2	2	59.05000000	11.38441918	8.05000000	129.60500000	118.10000000
BE	2	-8.50000000	1.97989899	1.40000000	3.92000000	-17.00000000
HCO3	2	16.15000000	1.20208153	0.85000000	1.44500000	32.30000000
TOTCO2	2	17.25000000	1.20208153	0.85000000	1.44500000	34.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.50000000	0.70710678	0.50000000	0.50000000	293.00000000
KNEW	2	4.95000000	0.49497475	0.35000000	0.24500000	9.90000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=7 TIME=7						
ID	2	1.50000000	0.70710678	0.50000000	0.50000000	3.00000000
PH	2	7.28400000	0.02545584	0.01800000	0.00064800	14.56800000
PCO2	2	34.50000000	3.11126984	2.20000000	9.68000000	69.00000000
PO2	2	57.70000000	0.00000000	0.00000000	0.00000000	115.40000000
BE	2	-8.85000000	0.21213203	0.15000000	0.04500000	-17.70000000
HCO3	2	16.05000000	0.49497475	0.35000000	0.24500000	32.10000000
TOTCO2	2	17.20000000	0.56568542	0.40000000	0.32000000	34.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	2	146.25000000	1.76776695	1.25000000	3.12500000	292.50000000
KNEW	2	5.05000000	0.77781746	0.55000000	0.60500000	10.10000000
GROUP=8 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39650000	0.01912241	0.00956121	0.00036567	29.58600000
PCO2	4	37.35000000	5.47144100	2.73572050	29.93666667	149.40000000
PO2	4	57.22500000	14.23712869	7.11856434	202.69583333	228.90000000
BE	4	-0.75000000	1.55456318	0.77728159	2.41666667	-3.00000000
HCO3	4	22.57500000	2.23662692	1.11831346	5.00250000	90.30000000
TOTCO2	4	23.77500000	2.37679757	1.18839878	5.64916667	95.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	150.25000000	1.19023807	0.59511904	1.41666667	601.00000000
KNEW	4	4.60000000	0.21602469	0.10801234	0.04666667	18.40000000
GROUP=8 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.41450000	0.02143984	0.01071992	0.00045967	29.65800000
PCO2	4	36.45000000	3.46265794	1.73132897	11.99000000	145.80000000
PO2	4	53.00000000	10.94074952	5.47037476	119.70000000	212.00000000
BE	4	0.07500000	1.81911150	0.90955575	3.30916667	0.30000000
HCO3	4	23.02500000	1.92764969	0.96382485	3.71583333	92.10000000
TOTCO2	4	21.70000000	3.22386931	1.61193466	10.39333333	86.80000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	149.00000000	1.08012345	0.54006172	1.16666667	596.00000000
KNEW	4	4.67500000	0.29860788	0.14930394	0.08916667	18.70000000
GROUP=8 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40325000	0.02585053	0.01292527	0.00066825	29.61300000
PCO2	4	36.37500000	1.45459043	0.72729522	2.11583333	145.50000000
PO2	4	59.75000000	11.26217859	5.63108930	126.83666667	239.00000000
BE	4	-0.80000000	1.11654228	0.55827114	1.24666667	-3.20000000
HCO3	4	22.40000000	0.78315601	0.39157800	0.61333333	89.60000000
TOTCO2	4	23.57500000	0.77620873	0.38810437	0.60250000	94.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.25000000	1.04083300	0.52041650	1.08333333	593.00000000
KNEW	4	4.65000000	0.23804761	0.11902381	0.05666667	18.60000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=8 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39600000	0.01518771	0.00759386	0.00023067	29.58400000
PCO2	4	36.52500000	1.72699160	0.86349580	2.98250000	146.10000000
PO2	4	53.82500000	9.58205789	4.79102894	91.81583333	215.30000000
BE	4	-1.10000000	0.83666003	0.41833001	0.70000000	-4.40000000
HCO3	4	22.12500000	0.78898669	0.39449335	0.62250000	88.50000000
TOTCO2	4	23.32500000	0.78898669	0.39449335	0.62250000	93.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	150.50000000	1.77951304	0.88975652	3.16666667	602.00000000
KNEW	4	4.70000000	0.21602469	0.10801234	0.04666667	18.80000000
GROUP=8 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38425000	0.03073950	0.01536975	0.00094492	29.53700000
PCO2	4	37.77500000	2.50383040	1.25191520	6.26916667	151.10000000
PO2	4	47.52500000	7.29263327	3.64631663	53.18250000	190.10000000
BE	4	-1.15000000	1.43643076	0.71821538	2.06333333	-4.60000000
HCO3	4	22.25000000	1.24498996	0.62249498	1.55000000	89.00000000
TOTCO2	4	23.47500000	1.26852933	0.63426467	1.60916667	93.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.12500000	1.03077641	0.51538820	1.06250000	592.50000000
KNEW	4	4.55000000	0.23804761	0.11902381	0.05666667	18.20000000
GROUP=8 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38675000	0.01575595	0.00787798	0.00024825	29.54700000
PCO2	4	37.20000000	3.24037035	1.62018517	10.50000000	148.80000000
PO2	4	55.30000000	19.26395598	9.63197799	371.10000000	221.20000000
BE	4	-1.32500000	1.62557682	0.81278841	2.64250000	-5.30000000
HCO3	4	22.05000000	1.78605711	0.89302855	3.19000000	88.20000000
TOTCO2	4	23.25000000	1.84481255	0.92240627	3.40333333	93.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.87500000	2.01556444	1.00778222	4.06250000	595.50000000
KNEW	4	4.60000000	0.24494897	0.12247449	0.06000000	18.40000000
GROUP=8 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38000000	0.02044505	0.01022252	0.00041800	29.52000000
PCO2	4	38.10000000	1.88856206	0.94428103	3.56666667	152.40000000
PO2	4	47.12500000	5.77140942	2.88570471	33.30916667	188.50000000
BE	4	-1.25000000	1.37234592	0.68617296	1.88333333	-5.00000000
HCO3	4	22.25000000	1.31021627	0.65510813	1.71666667	89.00000000
TOTCO2	4	23.47500000	1.31244047	0.65622024	1.72250000	93.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	149.87500000	2.65753645	1.32876823	7.06250000	599.50000000
KNEW	4	4.70000000	0.14142136	0.07071068	0.02000000	18.80000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=9 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40175000	0.00590903	0.00295452	0.00003492	29.60700000
PCO2	4	36.15000000	1.70587221	0.85293611	2.91000000	144.60000000
PO2	4	51.87500000	6.19267040	3.09633520	38.34916667	207.50000000
BE	4	-0.97500000	0.99121138	0.49560569	0.98250000	-3.90000000
HCO3	4	22.20000000	0.96263527	0.48131764	0.92666667	88.80000000
TOTCO2	4	23.37500000	0.97425185	0.48712592	0.94916667	93.50000000
NAOLD	1	141.00000000	.	.	.	141.00000000
KOLD	1	4.20000000	.	.	.	4.20000000
NANEW	2	148.00000000	2.82842712	2.00000000	8.00000000	296.00000000
KNEW	2	4.60000000	0.14142136	0.10000000	0.02000000	9.20000000
GROUP=9 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36750000	0.01438749	0.00719375	0.00020700	29.47000000
PCO2	4	37.67500000	1.81176709	0.90588355	3.28250000	150.70000000
PO2	4	44.80000000	3.58608422	1.79304211	12.86000000	179.20000000
BE	4	-2.35000000	0.82259751	0.41129876	0.67666667	-9.40000000
HCO3	4	21.37500000	0.80570880	0.40285440	0.64916667	85.50000000
TOTCO2	4	22.60000000	0.85244746	0.42622373	0.72666667	90.40000000
NAOLD	1	141.00000000	.	.	.	141.00000000
KOLD	1	3.90000000	.	.	.	3.90000000
NANEW	2	154.00000000	6.36396103	4.50000000	40.50000000	308.00000000
KNEW	2	4.35000000	0.35355339	0.25000000	0.12500000	8.70000000
GROUP=9 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.34300000	0.04035674	0.02017837	0.00162867	29.37200000
PCO2	4	35.37500000	2.74514723	1.37257362	7.53583333	141.50000000
PO2	4	51.45000000	11.05154589	5.52577295	122.13666667	205.80000000
BE	4	-4.85000000	3.78285606	1.89142803	14.31000000	-19.40000000
HCO3	4	19.10000000	3.13155978	1.56577989	9.80666667	76.40000000
TOTCO2	4	20.20000000	3.13687743	1.56843871	9.84000000	80.80000000
NAOLD	1	140.00000000	.	.	.	140.00000000
KOLD	1	4.00000000	.	.	.	4.00000000
NANEW	2	155.25000000	9.54594155	6.75000000	91.12500000	310.50000000
KNEW	2	4.50000000	0.42426407	0.30000000	0.18000000	9.00000000
GROUP=9 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35850000	0.02982728	0.01491364	0.00088967	29.43400000
PCO2	4	34.85000000	4.63501169	2.31750584	21.48333333	139.40000000
PO2	4	51.50000000	9.33416663	4.66708331	87.12666667	206.00000000
BE	4	-4.35000000	2.56190034	1.28095017	6.56333333	-17.40000000
HCO3	4	19.35000000	2.49332442	1.24666221	6.21666667	77.40000000
TOTCO2	4	20.50000000	2.59871763	1.29935882	6.75333333	82.00000000
NAOLD	1	140.00000000	.	.	.	140.00000000
KOLD	1	4.00000000	.	.	.	4.00000000
NANEW	2	148.50000000	0.70710678	0.50000000	0.50000000	297.00000000
KNEW	2	4.25000000	0.07071068	0.05000000	0.00500000	8.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=9 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35075000	0.02934138	0.01467069	0.00086092	29.40300000
PCO2	4	36.17500000	1.87149673	0.93574836	3.50250000	144.70000000
PO2	4	51.20000000	12.60476101	6.30238050	158.88000000	204.80000000
BE	4	-4.12500000	2.03695033	1.01847517	4.14916667	-16.50000000
HCO3	4	19.75000000	1.48436294	0.74218147	2.20333333	79.00000000
TOTCO2	4	20.95000000	1.47082743	0.73541372	2.16333333	83.80000000
NAOLD	1	140.00000000	.	.	.	140.00000000
KOLD	1	3.90000000	.	.	.	3.90000000
NANEW	2	148.00000000	0.00000000	0.00000000	0.00000000	296.00000000
KNEW	2	4.25000000	0.07071068	0.05000000	0.00500000	8.50000000
GROUP=9 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36350000	0.03449154	0.01724577	0.00118967	29.45400000
PCO2	4	38.25000000	2.66020049	1.33010025	7.07666667	153.00000000
PO2	4	40.97500000	3.70798688	1.85399344	13.74916667	163.90000000
BE	4	-2.22500000	1.14709779	0.57354889	1.31583333	-8.90000000
HCO3	4	21.42500000	0.66520673	0.33260337	0.44250000	85.70000000
TOTCO2	4	22.70000000	0.66833126	0.33416563	0.44666667	90.80000000
NAOLD	1	141.00000000	.	.	.	141.00000000
KOLD	1	4.00000000	.	.	.	4.00000000
NANEW	1	148.00000000	.	.	.	148.00000000
KNEW	1	4.30000000	.	.	.	4.30000000
GROUP=9 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36225000	0.03466386	0.01733193	0.00120158	29.44900000
PCO2	4	38.95000000	2.13150964	1.06575482	4.54333333	155.80000000
PO2	4	40.47500000	1.93799725	0.96899862	3.75583333	161.90000000
BE	4	-1.97500000	1.45459043	0.72729522	2.11583333	-7.90000000
HCO3	4	21.80000000	0.99331096	0.49665548	0.98666667	87.20000000
TOTCO2	4	23.05000000	0.96090235	0.48045118	0.92333333	92.20000000
NAOLD	1	141.00000000	.	.	.	141.00000000
KOLD	1	3.90000000	.	.	.	3.90000000
NANEW	1	150.00000000	.	.	.	150.00000000
KNEW	1	4.20000000	.	.	.	4.20000000
GROUP=10 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39325000	0.03091251	0.01545626	0.00095558	29.57300000
PCO2	4	35.82500000	2.13131415	1.06565707	4.54250000	143.30000000
PO2	4	61.77500000	10.86749741	5.43374871	118.10250000	247.10000000
BE	4	-1.72500000	1.37689264	0.68844632	1.89583333	-6.90000000
HCO3	4	21.57500000	1.07819293	0.53909647	1.16250000	86.30000000
TOTCO2	4	22.72500000	1.04363148	0.52181574	1.08916667	90.90000000
NAOLD	2	142.00000000	2.82842712	2.00000000	8.00000000	284.00000000
KOLD	2	4.80000000	0.14142136	0.10000000	0.02000000	9.60000000
NANEW	3	148.00000000	2.17944947	1.25830574	4.75000000	444.00000000
KNEW	3	4.90000000	0.43588989	0.25166115	0.19000000	14.70000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=10 TIME=2						
ID	3	2.00000000	1.00000000	0.57735027	1.00000000	6.00000000
PH	3	7.43400000	0.04214262	0.02433105	0.00177600	22.30200000
PCO2	3	36.03333333	3.71662930	2.14579693	13.81333333	108.10000000
PO2	3	67.66666667	20.48422157	11.82657084	419.60333333	203.00000000
BE	3	1.13333333	1.55026879	0.89504811	2.40333333	3.40000000
HCO3	3	23.76666667	1.26622799	0.73105707	1.60333333	71.30000000
TOTCO2	3	24.96666667	1.33166562	0.76883751	1.77333333	74.90000000
NAOLD	2	147.00000000	7.07106781	5.00000000	50.00000000	294.00000000
KOLD	2	4.35000000	0.21213203	0.15000000	0.04500000	8.70000000
NANEW	2	152.00000000	4.24264069	3.00000000	18.00000000	304.00000000
KNEW	2	4.65000000	0.21213203	0.15000000	0.04500000	9.30000000
GROUP=10 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44000000	0.03256788	0.01628394	0.00106067	29.76000000
PCO2	4	36.02500000	2.00229036	1.00114518	4.00916667	144.10000000
PO2	4	67.22500000	12.81467258	6.40733629	164.21583333	268.90000000
BE	4	2.37500000	1.77646653	0.88823327	3.15583333	9.50000000
HCO3	4	24.87500000	1.35984068	0.67992034	1.84916667	99.50000000
TOTCO2	4	26.07500000	1.35246688	0.67623344	1.82916667	104.30000000
NAOLD	2	146.75000000	5.30330086	3.75000000	28.12500000	293.50000000
KOLD	2	4.30000000	0.14142136	0.10000000	0.02000000	8.60000000
NANEW	3	150.33333333	1.25830574	0.72648316	1.58333333	451.00000000
KNEW	3	4.46666667	0.15275252	0.08819171	0.02333333	13.40000000
GROUP=10 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.46475000	0.03271468	0.01635734	0.00107025	29.85900000
PCO2	4	36.52500000	2.15309854	1.07654927	4.63583333	146.10000000
PO2	4	65.02500000	12.30159204	6.15079602	151.32916667	260.10000000
BE	4	3.57500000	1.25532200	0.62766100	1.57583333	14.30000000
HCO3	4	25.92500000	0.74105780	0.37052890	0.54916667	103.70000000
TOTCO2	4	27.10000000	0.76157731	0.38078866	0.58000000	108.40000000
NAOLD	2	140.50000000	7.77817459	5.50000000	60.50000000	281.00000000
KOLD	2	4.00000000	0.56568542	0.40000000	0.32000000	8.00000000
NANEW	3	146.00000000	8.78919792	5.07444578	77.25000000	438.00000000
KNEW	3	4.20000000	0.40000000	0.23094011	0.16000000	12.60000000
GROUP=10 TIME=5						
ID	5	2.80000000	1.30384048	0.58309519	1.70000000	14.00000000
PH	5	7.46480000	0.03310136	0.01480338	0.00109570	37.32400000
PCO2	5	36.48000000	2.14639232	0.95989583	4.60700000	182.40000000
PO2	5	62.98000000	10.74974418	4.80743175	115.55700000	314.90000000
BE	5	3.54000000	2.13377600	0.95425364	4.55300000	17.70000000
HCO3	5	25.92000000	1.88334808	0.84225887	3.54700000	129.60000000
TOTCO2	5	27.10000000	1.90656760	0.85264295	3.63500000	135.50000000
NAOLD	2	148.75000000	6.71751442	4.75000000	45.12500000	297.50000000
KOLD	2	4.15000000	0.07071068	0.05000000	0.00500000	8.30000000
NANEW	4	151.12500000	2.89755644	1.44877822	8.39583333	604.50000000
KNEW	4	4.30000000	0.14142136	0.07071068	0.02000000	17.20000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=10 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47200000	0.02913188	0.01456594	0.00084867	29.88800000
PCO2	4	38.15000000	2.88617394	1.44308697	8.33000000	152.60000000
PO2	4	65.50000000	13.49592531	6.74796266	182.14000000	262.00000000
BE	4	5.02500000	1.61529151	0.80764576	2.60916667	20.10000000
HCO3	4	27.50000000	1.58954920	0.79477460	2.52666667	110.00000000
TOTCO2	4	28.75000000	1.60519988	0.80259994	2.57666667	115.00000000
NAOLD	1	145.00000000	.	.	.	145.00000000
KOLD	1	4.00000000	.	.	.	4.00000000
NANEW	2	150.00000000	0.70710678	0.50000000	0.50000000	300.00000000
KNEW	2	4.10000000	0.00000000	0.00000000	0.00000000	8.20000000
GROUP=10 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47675000	0.02998194	0.01499097	0.00089892	29.90700000
PCO2	4	38.42500000	2.69613922	1.34806961	7.26916667	153.70000000
PO2	4	64.82500000	13.96886419	6.98443209	195.12916667	259.30000000
BE	4	5.55000000	1.02469508	0.51234754	1.05000000	22.20000000
HCO3	4	28.00000000	0.86794777	0.43397389	0.75333333	112.00000000
TOTCO2	4	29.25000000	0.85829288	0.42914644	0.73666667	117.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	1	149.50000000	.	.	.	149.50000000
KNEW	1	4.10000000	.	.	.	4.10000000
GROUP=11 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38175000	0.04563898	0.02281949	0.00208292	29.52700000
PCO2	4	38.47500000	4.16683333	2.08341667	17.36250000	153.90000000
PO2	4	55.80000000	21.11792288	10.55896144	445.96666667	223.20000000
BE	4	-1.02500000	1.73469498	0.86734749	3.00916667	-4.10000000
HCO3	4	22.47500000	1.49303941	0.74651970	2.22916667	89.90000000
TOTCO2	4	23.75000000	1.49777613	0.74888806	2.24333333	95.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	147.37500000	0.85391256	0.42695628	0.72916667	589.50000000
KNEW	4	4.62500000	0.05000000	0.02500000	0.00250000	18.50000000
GROUP=11 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44000000	0.02523225	0.01261613	0.00063667	29.76000000
PCO2	4	36.15000000	1.85921130	0.92960565	3.45666667	144.60000000
PO2	4	55.00000000	9.05391260	4.52695630	81.97333333	220.00000000
BE	4	1.72500000	2.46356787	1.23178394	6.06916667	6.90000000
HCO3	4	24.32500000	2.24851803	1.12425902	5.05583333	97.30000000
TOTCO2	4	25.52500000	2.24851803	1.12425902	5.05583333	102.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.37500000	1.49303941	0.74651970	2.22916667	593.50000000
KNEW	4	4.50000000	0.27080128	0.13540064	0.07333333	18.00000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=11 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44900000	0.02118175	0.01059088	0.00044867	29.79600000
PCO2	4	36.95000000	2.15483951	1.07741976	4.64333333	147.80000000
PO2	4	51.95000000	16.76196090	8.38098045	280.96333333	207.80000000
BE	4	2.92500000	2.70354705	1.35177353	7.30916667	11.70000000
HCO3	4	25.35000000	2.46779254	1.23389627	6.09000000	101.40000000
TOTCO2	4	26.55000000	2.54885595	1.27442798	6.49666667	106.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	149.75000000	2.53311403	1.26655701	6.41666667	599.00000000
KNEW	4	4.47500000	0.30956959	0.15478480	0.09583333	17.90000000
GROUP=11 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44575000	0.02479751	0.01239876	0.00061492	29.78300000
PCO2	4	37.87500000	0.89582364	0.44791182	0.80250000	151.50000000
PO2	4	47.25000000	9.75380268	4.87690134	95.13666667	189.00000000
BE	4	3.22500000	2.41712639	1.20856320	5.84250000	12.90000000
HCO3	4	25.80000000	2.08006410	1.04003205	4.32666667	103.20000000
TOTCO2	4	27.00000000	2.08006410	1.04003205	4.32666667	108.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	144.00000000	10.13245610	5.06622805	102.66666667	576.00000000
KNEW	4	4.17500000	0.49916597	0.24958299	0.24916667	16.70000000
GROUP=11 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44950000	0.01103026	0.00551513	0.00012167	29.79800000
PCO2	4	37.92500000	1.74809420	0.87404710	3.05583333	151.70000000
PO2	4	48.97500000	10.22492869	5.11246434	104.54916667	195.90000000
BE	4	3.45000000	1.93649167	0.96824584	3.75000000	13.80000000
HCO3	4	26.02500000	1.80623919	0.90311959	3.26250000	104.10000000
TOTCO2	4	27.25000000	1.90175358	0.95087679	3.61666667	109.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	150.25000000	1.65831240	0.82915620	2.75000000	601.00000000
KNEW	4	4.20000000	0.24494897	0.12247449	0.06000000	16.80000000
GROUP=11 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45350000	0.00943398	0.00471699	0.00008900	29.81400000
PCO2	4	39.10000000	2.14631467	1.07315734	4.60666667	156.40000000
PO2	4	45.22500000	11.97452156	5.98726078	143.38916667	180.90000000
BE	4	4.50000000	1.70684895	0.85342447	2.91333333	18.00000000
HCO3	4	27.07500000	1.66608323	0.83304162	2.77583333	108.30000000
TOTCO2	4	28.37500000	1.74045013	0.87022507	3.02916667	113.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	151.12500000	2.32289331	1.16144666	5.39583333	604.50000000
KNEW	4	4.20000000	0.23094011	0.11547005	0.05333333	16.80000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=11 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45750000	0.01417745	0.00708872	0.00020100	29.83000000
PCO2	4	39.72500000	2.38659451	1.19329725	5.69583333	158.90000000
PO2	4	42.77500000	9.71815312	4.85907656	94.44250000	171.10000000
BE	4	5.15000000	0.95742711	0.47871355	0.91666667	20.60000000
HCO3	4	27.70000000	1.06770783	0.53385391	1.14000000	110.80000000
TOTCO2	4	29.02500000	1.15000000	0.57500000	1.32250000	116.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	150.37500000	2.59406374	1.29703187	6.72916667	601.50000000
KNEW	4	4.22500000	0.15000000	0.07500000	0.02250000	16.90000000
GROUP=12 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40375000	0.02007278	0.01003639	0.00040292	29.61500000
PCO2	4	35.42500000	2.42813371	1.21406686	5.89583333	141.70000000
PO2	4	64.82500000	9.64136055	4.82068028	92.95583333	259.30000000
BE	4	-1.25000000	2.04205779	1.02102889	4.17000000	-5.00000000
HCO3	4	21.92500000	2.08226639	1.04113320	4.33583333	87.70000000
TOTCO2	4	23.07500000	2.13911976	1.06955988	4.57583333	92.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.62500000	2.42813371	1.21406686	5.89583333	594.50000000
KNEW	4	4.62500000	0.29860788	0.14930394	0.08916667	18.50000000
GROUP=12 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.41450000	0.00655744	0.00327872	0.00004300	29.65800000
PCO2	4	36.75000000	3.88029209	1.94014604	15.05666667	147.00000000
PO2	4	65.57500000	13.34250726	6.67125363	178.02250000	262.30000000
BE	4	0.15000000	2.24870333	1.12435167	5.05666667	0.60000000
HCO3	4	23.27500000	2.64622372	1.32311186	7.00250000	93.10000000
TOTCO2	4	24.50000000	2.73982968	1.36991484	7.50666667	98.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	154.00000000	16.29417074	8.14708537	265.50000000	616.00000000
KNEW	4	4.70000000	0.31622777	0.15811388	0.10000000	18.80000000
GROUP=12 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40175000	0.02312827	0.01156413	0.00053492	29.60700000
PCO2	4	35.52500000	3.57898962	1.78949481	12.80916667	142.10000000
PO2	4	65.07500000	10.52374300	5.26187150	110.74916667	260.30000000
BE	4	-1.20000000	3.25883415	1.62941707	10.62000000	-4.80000000
HCO3	4	22.02500000	3.34502118	1.67251059	11.18916667	88.10000000
TOTCO2	4	23.20000000	3.43608304	1.71804152	11.80666667	92.80000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	143.62500000	5.86479610	2.93239805	34.39583333	574.50000000
KNEW	4	4.45000000	0.12909944	0.06454972	0.01666667	17.80000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=12 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.41150000	0.01391642	0.00695821	0.00019367	29.64600000
PCO2	4	36.95000000	2.17025344	1.08512672	4.71000000	147.80000000
PO2	4	67.57500000	6.88591558	3.44295779	47.41583333	270.30000000
BE	4	-0.05000000	1.55456318	0.77728159	2.41666667	-0.20000000
HCO3	4	23.22500000	1.67605688	0.83802844	2.80916667	92.90000000
TOTCO2	4	24.42500000	1.75570499	0.87785249	3.08250000	97.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	144.37500000	3.44903368	1.72451684	11.89583333	577.50000000
KNEW	4	4.50000000	0.20000000	0.10000000	0.04000000	18.00000000
GROUP=12 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38500000	0.00787401	0.00393700	0.00006200	29.54000000
PCO2	4	36.45000000	3.58282942	1.79141471	12.83666667	145.80000000
PO2	4	63.75000000	13.92850794	6.96425397	194.00333333	255.00000000
BE	4	-1.97500000	1.95170865	0.97585433	3.80916667	-7.90000000
HCO3	4	21.57500000	2.22766694	1.11383347	4.96250000	86.30000000
TOTCO2	4	22.72500000	2.35566693	1.17783346	5.54916667	90.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	146.62500000	6.01906693	3.00953346	36.22916667	586.50000000
KNEW	4	4.47500000	0.17078251	0.08539126	0.02916667	17.90000000
GROUP=12 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40225000	0.01081280	0.00540640	0.00011692	29.60900000
PCO2	4	36.90000000	2.85773803	1.42886902	8.16666667	147.60000000
PO2	4	61.20000000	11.39502816	5.69751408	129.84666667	244.80000000
BE	4	-0.60000000	1.84932420	0.92466210	3.42000000	-2.40000000
HCO3	4	22.72500000	2.00727842	1.00363921	4.02916667	90.90000000
TOTCO2	4	23.92500000	2.07906229	1.03953114	4.32250000	95.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	144.12500000	2.25000000	1.12500000	5.06250000	576.50000000
KNEW	4	4.50000000	0.16329932	0.08164966	0.02666667	18.00000000
GROUP=12 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39400000	0.01585350	0.00792675	0.00025133	29.57600000
PCO2	4	36.65000000	4.34319391	2.17159695	18.86333333	146.60000000
PO2	4	65.10000000	16.98136233	8.49068117	288.36666667	260.40000000
BE	4	-1.30000000	2.34520788	1.17260394	5.50000000	-5.20000000
HCO3	4	22.12500000	2.61071510	1.30535755	6.81583333	88.50000000
TOTCO2	4	23.30000000	2.70431754	1.35215877	7.31333333	93.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	143.75000000	2.87228132	1.43614066	8.25000000	575.00000000
KNEW	4	4.50000000	0.16329932	0.08164966	0.02666667	18.00000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=13 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38375000	0.01468276	0.00734138	0.00021558	29.53500000
PCO2	4	39.65000000	2.85248430	1.42624215	8.13666667	158.60000000
PO2	4	53.72500000	10.52342625	5.26171312	110.74250000	214.90000000
BE	4	-0.52500000	0.55602758	0.27801379	0.30916667	-2.10000000
HCO3	4	23.32500000	0.92870878	0.46435439	0.86250000	93.30000000
TOTCO2	4	24.60000000	1.02306728	0.51153364	1.04666667	98.40000000
NAOLD	4	141.00000000	2.44948974	1.22474487	6.00000000	564.00000000
KOLD	4	4.25000000	0.10000000	0.05000000	0.01000000	17.00000000
NANEW	4	148.62500000	2.17466473	1.08733236	4.72916667	594.50000000
KNEW	4	4.40000000	0.29439203	0.14719601	0.08666667	17.60000000
GROUP=13 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37975000	0.03542480	0.01771240	0.00125492	29.51900000
PCO2	4	38.82500000	2.83122471	1.41561235	8.01583333	155.30000000
PO2	4	59.20000000	9.25886962	4.62943481	85.72666667	236.80000000
BE	4	-1.20000000	1.70684895	0.85342447	2.91333333	-4.80000000
HCO3	4	22.70000000	1.39761702	0.69880851	1.95333333	90.80000000
TOTCO2	4	23.95000000	1.42711831	0.71355915	2.03666667	95.80000000
NAOLD	4	139.25000000	3.20156212	1.60078106	10.25000000	557.00000000
KOLD	4	4.25000000	0.17320508	0.08660254	0.03000000	17.00000000
NANEW	4	146.87500000	2.17466473	1.08733236	4.72916667	587.50000000
KNEW	4	4.40000000	0.32659863	0.16329932	0.10666667	17.60000000
GROUP=13 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37100000	0.02092845	0.01046422	0.00043800	29.48400000
PCO2	4	38.55000000	2.48529006	1.24264503	6.17666667	154.20000000
PO2	4	57.55000000	9.24499865	4.62249932	85.47000000	230.20000000
BE	4	-1.95000000	0.80622577	0.40311289	0.65000000	-7.80000000
HCO3	4	22.00000000	0.82865353	0.41432676	0.68666667	88.00000000
TOTCO2	4	23.25000000	0.92556289	0.46278145	0.85666667	93.00000000
NAOLD	4	138.50000000	1.73205081	0.86602540	3.00000000	554.00000000
KOLD	4	4.27500000	0.23629078	0.11814539	0.05583333	17.10000000
NANEW	4	146.12500000	1.60078106	0.80039053	2.56250000	584.50000000
KNEW	4	4.45000000	0.36968455	0.18484228	0.13666667	17.80000000
GROUP=13 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35850000	0.02930870	0.01465435	0.00085900	29.43400000
PCO2	4	39.57500000	2.61326743	1.30663372	6.82916667	158.30000000
PO2	4	54.42500000	6.59260950	3.29630475	43.46250000	217.70000000
BE	4	-2.22500000	1.12361025	0.56180513	1.26250000	-8.90000000
HCO3	4	22.00000000	0.96609178	0.48304589	0.93333333	88.00000000
TOTCO2	4	23.22500000	1.03077641	0.51538820	1.06250000	92.90000000
NAOLD	4	138.25000000	2.98607881	1.49303941	8.91666667	553.00000000
KOLD	4	4.20000000	0.21602469	0.10801234	0.04666667	16.80000000
NANEW	4	145.50000000	2.38047614	1.19023807	5.66666667	582.00000000
KNEW	4	4.40000000	0.29439203	0.14719601	0.08666667	17.60000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=13 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35800000	0.02758019	0.01379009	0.00076067	29.43200000
PCO2	4	40.47500000	3.39546266	1.69773133	11.52916667	161.90000000
PO2	4	50.40000000	7.34166194	3.67083097	53.90000000	201.60000000
BE	4	-1.75000000	1.68226038	0.84113019	2.83000000	-7.00000000
HCO3	4	22.45000000	1.66833250	0.83416625	2.78333333	89.80000000
TOTCO2	4	23.75000000	1.74068952	0.87034476	3.03000000	95.00000000
NAOLD	4	137.75000000	2.62995564	1.31497782	6.91666667	551.00000000
KOLD	4	4.27500000	0.17078251	0.08539126	0.02916667	17.10000000
NANEW	4	145.12500000	2.09662427	1.04831214	4.39583333	580.50000000
KNEW	4	4.45000000	0.28867513	0.14433757	0.08333333	17.80000000
GROUP=13 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35350000	0.02406242	0.01203121	0.00057900	29.41400000
PCO2	4	41.17500000	4.75490974	2.37745487	22.60916667	164.70000000
PO2	4	49.45000000	9.26408837	4.63204419	85.82333333	197.80000000
BE	4	-1.72500000	1.92418814	0.96209407	3.70250000	-6.90000000
HCO3	4	22.55000000	2.10633964	1.05316982	4.43666667	90.20000000
TOTCO2	4	23.87500000	2.22317341	1.11158670	4.94250000	95.50000000
NAOLD	4	137.00000000	2.58198890	1.29099445	6.66666667	548.00000000
KOLD	4	4.22500000	0.18929694	0.09464847	0.03583333	16.90000000
NANEW	4	144.50000000	2.27303028	1.13651514	5.16666667	578.00000000
KNEW	4	4.40000000	0.33665016	0.16832508	0.11333333	17.60000000
GROUP=13 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35100000	0.02687006	0.01343503	0.00072200	29.40400000
PCO2	4	40.60000000	4.20079358	2.10039679	17.64666667	162.40000000
PO2	4	48.67500000	9.80216813	4.90108406	96.08250000	194.70000000
BE	4	-2.12500000	1.87860764	0.93930382	3.52916667	-8.50000000
HCO3	4	22.15000000	1.85741756	0.92870878	3.45000000	88.60000000
TOTCO2	4	23.45000000	1.98410349	0.99205175	3.93666667	93.80000000
NAOLD	4	138.00000000	3.26598632	1.63299316	10.66666667	552.00000000
KOLD	4	4.27500000	0.20615528	0.10307764	0.04250000	17.10000000
NANEW	4	144.87500000	3.11916121	1.55958061	9.72916667	579.50000000
KNEW	4	4.42500000	0.34034296	0.17017148	0.11583333	17.70000000
GROUP=14 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40150000	0.02474537	0.01237268	0.00061233	29.60600000
PCO2	4	34.57500000	0.92150240	0.46075120	0.84916667	138.30000000
PO2	4	61.30000000	6.53146232	3.26573116	42.66000000	245.20000000
BE	4	-1.85000000	1.95533458	0.97766729	3.82333333	-7.40000000
HCO3	4	21.20000000	1.64721988	0.82360994	2.71333333	84.80000000
TOTCO2	4	22.30000000	1.64721988	0.82360994	2.71333333	89.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	145.75000000	1.65831240	0.82915620	2.75000000	583.00000000
KNEW	4	4.17500000	0.27537853	0.13768926	0.07583333	16.70000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=14 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.43075000	0.01643928	0.00821964	0.00027025	29.72300000
PCO2	4	36.00000000	0.61644140	0.30822070	0.38000000	144.00000000
PO2	4	62.02500000	8.68691545	4.34345772	75.46250000	248.10000000
BE	4	0.80000000	1.21928941	0.60964471	1.48666667	3.20000000
HCO3	4	23.60000000	1.06144556	0.53072278	1.12666667	94.40000000
TOTCO2	4	24.80000000	1.06144556	0.53072278	1.12666667	99.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	149.12500000	0.25000000	0.12500000	0.06250000	596.50000000
KNEW	4	3.87500000	0.17078251	0.08539126	0.02916667	15.50000000
GROUP=14 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45275000	0.01785824	0.00892912	0.00031892	29.81100000
PCO2	4	36.75000000	1.99081223	0.99540611	3.96333333	147.00000000
PO2	4	55.50000000	10.01765109	5.00882554	100.35333333	222.00000000
BE	4	2.85000000	1.11205515	0.55602758	1.23666667	11.40000000
HCO3	4	25.35000000	1.12101145	0.56050572	1.25666667	101.40000000
TOTCO2	4	26.52500000	1.18427193	0.59213596	1.40250000	106.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	150.87500000	1.54784797	0.77392398	2.39583333	603.50000000
KNEW	4	4.00000000	0.11547005	0.05773503	0.01333333	16.00000000
GROUP=14 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.46425000	0.01322561	0.00661280	0.00017492	29.85700000
PCO2	4	37.37500000	2.29981883	1.14990942	5.28916667	149.50000000
PO2	4	55.35000000	8.38828548	4.19414274	70.36333333	221.40000000
BE	4	4.00000000	1.36137186	0.68068593	1.85333333	16.00000000
HCO3	4	26.45000000	1.47986486	0.73993243	2.19000000	105.80000000
TOTCO2	4	27.65000000	1.52643375	0.76321688	2.33000000	110.60000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	152.50000000	2.73861279	1.36930639	7.50000000	610.00000000
KNEW	4	3.97500000	0.05000000	0.02500000	0.00250000	15.90000000
GROUP=14 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47325000	0.00665207	0.00332603	0.00004425	29.89300000
PCO2	4	38.32500000	1.71148084	0.85574042	2.92916667	153.30000000
PO2	4	47.65000000	10.66723957	5.33361978	113.79000000	190.60000000
BE	4	5.42500000	1.56498136	0.78249068	2.44916667	21.70000000
HCO3	4	27.70000000	1.43061758	0.71530879	2.04666667	110.80000000
TOTCO2	4	28.95000000	1.51986842	0.75993421	2.31000000	115.80000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	154.87500000	2.86865241	1.43432621	8.22916667	619.50000000
KNEW	4	3.87500000	0.12583057	0.06291529	0.01583333	15.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=14 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47475000	0.01436141	0.00718070	0.00020625	29.89900000
PCO2	4	38.70000000	2.49666444	1.24833222	6.23333333	154.80000000
PO2	4	51.97500000	15.39943181	7.69971590	237.14250000	207.90000000
BE	4	5.72500000	1.82460041	0.91230021	3.32916667	22.90000000
HCO3	4	28.05000000	1.75214155	0.87607077	3.07000000	112.20000000
TOTCO2	4	29.30000000	1.83121089	0.91560545	3.35333333	117.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	156.00000000	3.34165628	1.67082814	11.16666667	624.00000000
KNEW	4	3.85000000	0.12909944	0.06454972	0.01666667	15.40000000
GROUP=14 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47125000	0.00704154	0.00352077	0.00004958	29.88500000
PCO2	4	38.57500000	3.15950946	1.57975473	9.98250000	154.30000000
PO2	4	49.97500000	12.24809509	6.12404754	150.01583333	199.90000000
BE	4	5.35000000	2.04857674	1.02428837	4.19666667	21.40000000
HCO3	4	27.72500000	2.28673712	1.14336856	5.22916667	110.90000000
TOTCO2	4	28.97500000	2.34147389	1.17073695	5.48250000	115.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	157.87500000	2.46221445	1.23110723	6.06250000	631.50000000
KNEW	4	3.80000000	0.08164966	0.04082483	0.00666667	15.20000000
GROUP=14 TIME=8						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.46650000	0.01014889	0.00507445	0.00010300	29.86600000
PCO2	4	39.05000000	2.95803989	1.47901995	8.75000000	156.20000000
PO2	4	50.72500000	12.07183361	6.03591680	145.72916667	202.90000000
BE	4	5.20000000	2.04124145	1.02062073	4.16666667	20.80000000
HCO3	4	27.75000000	2.16717943	1.08358971	4.69666667	111.00000000
TOTCO2	4	29.05000000	2.23383079	1.11691540	4.99000000	116.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	158.55000000	1.54164414	0.77082207	2.37666667	634.20000000
KNEW	4	3.72500000	0.18929694	0.09464847	0.03583333	14.90000000
GROUP=14 TIME=9						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.46150000	0.01109054	0.00554527	0.00012300	29.84600000
PCO2	4	39.77500000	2.66505159	1.33252580	7.10250000	159.10000000
PO2	4	47.67500000	14.93081266	7.46540633	222.92916667	190.70000000
BE	4	5.40000000	2.20605228	1.10302614	4.86666667	21.60000000
HCO3	4	27.97500000	2.15154983	1.07577491	4.62916667	111.90000000
TOTCO2	4	29.30000000	2.23159136	1.11579568	4.98000000	117.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	160.17500000	1.97209702	0.98604851	3.88916667	640.70000000
KNEW	4	3.77500000	0.22173558	0.11086779	0.04916667	15.10000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=14 TIME=10						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45900000	0.01211060	0.00605530	0.00014667	29.83600000
PCO2	4	38.65000000	1.23423391	0.61711695	1.52333333	154.60000000
PO2	4	49.05000000	16.59347261	8.29673631	275.34333333	196.20000000
BE	4	4.55000000	1.84842275	0.92421138	3.41666667	18.20000000
HCO3	4	27.02500000	1.53487242	0.76743621	2.35583333	108.10000000
TOTCO2	4	28.27500000	1.59243001	0.79621500	2.53583333	113.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	160.12500000	3.32603367	1.66301684	11.06250000	640.50000000
KNEW	4	3.62500000	0.22173558	0.11086779	0.04916667	14.50000000
GROUP=14 TIME=11						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45525000	0.02163909	0.01081954	0.00046825	29.82100000
PCO2	4	38.47500000	0.35939764	0.17969882	0.12916667	153.90000000
PO2	4	58.75000000	12.74846396	6.37423198	162.52333333	235.00000000
BE	4	3.95000000	1.46173413	0.73086706	2.13666667	15.80000000
HCO3	4	26.65000000	1.11504858	0.55752429	1.24333333	106.60000000
TOTCO2	4	27.90000000	1.16045968	0.58022984	1.34666667	111.60000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	159.37500000	3.37577152	1.68788576	11.39583333	637.50000000
KNEW	4	3.57500000	0.09574271	0.04787136	0.00916667	14.30000000
GROUP=14 TIME=12						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45225000	0.02179258	0.01089629	0.00047492	29.80900000
PCO2	4	38.77500000	2.15773801	1.07886901	4.65583333	155.10000000
PO2	4	62.12500000	5.45244593	2.72622297	29.72916667	248.50000000
BE	4	3.75000000	0.99833194	0.49916597	0.99666667	15.00000000
HCO3	4	26.65000000	0.93273791	0.46636895	0.87000000	106.60000000
TOTCO2	4	27.90000000	0.99666109	0.49833055	0.99333333	111.60000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	158.87500000	2.95451632	1.47725816	8.72916667	635.50000000
KNEW	4	3.57500000	0.15000000	0.07500000	0.02250000	14.30000000
GROUP=14 TIME=13						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.45950000	0.03376882	0.01688441	0.00114033	29.83800000
PCO2	4	37.05000000	3.52940033	1.76470016	12.45666667	148.20000000
PO2	4	60.17500000	11.00496100	5.50248050	121.10916667	240.70000000
BE	4	3.37500000	1.37204227	0.68602114	1.88250000	13.50000000
HCO3	4	25.85000000	1.29743336	0.64871668	1.68333333	103.40000000
TOTCO2	4	27.02500000	1.49303941	0.74651970	2.22916667	108.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	158.12500000	2.09662427	1.04831214	4.39583333	632.50000000
KNEW	4	3.62500000	0.17078251	0.08539126	0.02916667	14.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=14 TIME=14						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.47375000	0.03606822	0.01803411	0.00130092	29.89500000
PCO2	4	35.62500000	3.51793026	1.75896513	12.37583333	142.50000000
PO2	4	56.22500000	8.78383933	4.39191966	77.15583333	224.90000000
BE	4	3.67500000	1.53269914	0.76634957	2.34916667	14.70000000
HCO3	4	25.67500000	1.43845982	0.71922991	2.06916667	102.70000000
TOTCO2	4	26.87500000	1.50637534	0.75318767	2.26916667	107.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	157.25000000	1.93649167	0.96824584	3.75000000	629.00000000
KNEW	4	3.60000000	0.16329932	0.08164966	0.02666667	14.40000000
GROUP=14 TIME=15						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.46050000	0.02106340	0.01053170	0.00044367	29.84200000
PCO2	4	35.82500000	2.75847180	1.37923590	7.60916667	143.30000000
PO2	4	62.90000000	7.61577311	3.80788655	58.00000000	251.60000000
BE	4	2.80000000	1.80923557	0.90461778	3.27333333	11.20000000
HCO3	4	25.12500000	1.93283039	0.96641520	3.73583333	100.50000000
TOTCO2	4	26.27500000	1.98725103	0.99362552	3.94916667	105.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	156.37500000	1.60078106	0.80039053	2.56250000	625.50000000
KNEW	4	3.55000000	0.10000000	0.05000000	0.01000000	14.20000000
GROUP=14 TIME=16						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.44200000	0.01254326	0.00627163	0.00015733	29.76800000
PCO2	4	37.20000000	1.19163753	0.59581876	1.42000000	148.80000000
PO2	4	66.60000000	5.52760697	2.76375349	30.55333333	266.40000000
BE	4	2.22500000	1.37204227	0.68602114	1.88250000	8.90000000
HCO3	4	25.05000000	1.40118997	0.70059499	1.96333333	100.20000000
TOTCO2	4	26.25000000	1.40118997	0.70059499	1.96333333	105.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	155.12500000	1.43614066	0.71807033	2.06250000	620.50000000
KNEW	4	3.50000000	0.37416574	0.18708287	0.14000000	14.00000000
GROUP=14 TIME=17						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.41925000	0.03685444	0.01842722	0.00135825	29.67700000
PCO2	4	38.80000000	1.19721900	0.59860950	1.43333333	155.20000000
PO2	4	64.07500000	10.86596368	5.43298184	118.06916667	256.30000000
BE	4	1.50000000	2.57811301	1.28905650	6.64666667	6.00000000
HCO3	4	24.80000000	2.10237960	1.05118980	4.42000000	99.20000000
TOTCO2	4	26.07500000	2.07906229	1.03953114	4.32250000	104.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	154.87500000	1.43614066	0.71807033	2.06250000	619.50000000
KNEW	4	3.37500000	0.18929694	0.09464847	0.03583333	13.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=15 TIME=1						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.40075000	0.01645955	0.00822977	0.00027092	29.60300000
PCO2	4	36.15000000	1.27148207	0.63574104	1.61666667	144.60000000
PO2	4	52.00000000	2.40970261	1.20485130	5.80666667	208.00000000
BE	4	-0.97500000	1.56710987	0.78355493	2.45583333	-3.90000000
HCO3	4	22.17500000	1.47280911	0.73640455	2.16916667	88.70000000
TOTCO2	4	23.35000000	1.48436294	0.74218147	2.20333333	93.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.12500000	1.10867789	0.55433895	1.22916667	592.50000000
KNEW	4	4.52500000	0.33040379	0.16520190	0.10916667	18.10000000
GROUP=15 TIME=2						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38375000	0.00505800	0.00252900	0.00002558	29.53500000
PCO2	4	38.42500000	2.80639151	1.40319576	7.87583333	153.70000000
PO2	4	41.52500000	5.89540782	2.94770391	34.75583333	166.10000000
BE	4	-0.75000000	1.64418166	0.82209083	2.70333333	-3.00000000
HCO3	4	22.65000000	1.75404295	0.87702147	3.07666667	90.60000000
TOTCO2	4	23.87500000	1.84639288	0.92319644	3.40916667	95.50000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	147.12500000	0.47871355	0.23935678	0.22916667	588.50000000
KNEW	4	4.37500000	0.22173558	0.11086779	0.04916667	17.50000000
GROUP=15 TIME=3						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39275000	0.00850000	0.00425000	0.00007225	29.57100000
PCO2	4	38.00000000	1.92006944	0.96003472	3.68666667	152.00000000
PO2	4	45.25000000	8.26740588	4.13370294	68.35000000	181.00000000
BE	4	-0.47500000	1.28419884	0.64209942	1.64916667	-1.90000000
HCO3	4	22.80000000	1.38804419	0.69402209	1.92666667	91.20000000
TOTCO2	4	24.00000000	1.42126704	0.71063352	2.02000000	96.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	146.62500000	0.47871355	0.23935678	0.22916667	586.50000000
KNEW	4	4.35000000	0.28867513	0.14433757	0.08333333	17.40000000
GROUP=15 TIME=4						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38575000	0.01342572	0.00671286	0.00018025	29.54300000
PCO2	4	37.95000000	2.46238367	1.23119183	6.06333333	151.80000000
PO2	4	47.15000000	8.62882765	4.31441383	74.45666667	188.60000000
BE	4	-0.97500000	0.71821538	0.35910769	0.51583333	-3.90000000
HCO3	4	22.42500000	0.96046864	0.48023432	0.92250000	89.70000000
TOTCO2	4	23.67500000	1.00124922	0.50062461	1.00250000	94.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	145.75000000	1.04083300	0.52041650	1.08333333	583.00000000
KNEW	4	4.20000000	0.21602469	0.10801234	0.04666667	16.80000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=15 TIME=5						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38750000	0.01337909	0.00668954	0.00017900	29.55000000
PCO2	4	37.62500000	2.32289331	1.16144666	5.39583333	150.50000000
PO2	4	46.75000000	4.87544870	2.43772435	23.77000000	187.00000000
BE	4	-1.10000000	1.07393358	0.53696679	1.15333333	-4.40000000
HCO3	4	22.30000000	1.15758369	0.57879185	1.34000000	89.20000000
TOTCO2	4	23.52500000	1.25797456	0.62898728	1.58250000	94.10000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	145.87500000	0.25000000	0.12500000	0.06250000	583.50000000
KNEW	4	4.27500000	0.09574271	0.04787136	0.00916667	17.10000000
GROUP=15 TIME=6						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38175000	0.02117192	0.01058596	0.00044825	29.52700000
PCO2	4	38.27500000	2.38659451	1.19329725	5.69583333	153.10000000
PO2	4	47.42500000	6.27501660	3.13750830	39.37583333	189.70000000
BE	4	-1.20000000	1.06144556	0.53072278	1.12666667	-4.80000000
HCO3	4	22.35000000	1.01488916	0.50744458	1.03000000	89.40000000
TOTCO2	4	23.57500000	1.06262254	0.53131127	1.12916667	94.30000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	146.75000000	0.86602540	0.43301270	0.75000000	587.00000000
KNEW	4	4.30000000	0.29439203	0.14719601	0.08666667	17.20000000
GROUP=15 TIME=7						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38625000	0.01732772	0.00866386	0.00030025	29.54500000
PCO2	4	37.05000000	2.61087469	1.30543735	6.81666667	148.20000000
PO2	4	48.45000000	8.61336171	4.30668086	74.19000000	193.80000000
BE	4	-1.47500000	0.49916597	0.24958299	0.24916667	-5.90000000
HCO3	4	21.90000000	0.80415587	0.40207794	0.64666667	87.60000000
TOTCO2	4	23.10000000	0.87177979	0.43588989	0.76000000	92.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	147.62500000	1.25000000	0.62500000	1.56250000	590.50000000
KNEW	4	4.50000000	0.08164966	0.04082483	0.00666667	18.00000000
GROUP=15 TIME=8						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38400000	0.02267157	0.01133578	0.00051400	29.53600000
PCO2	4	37.95000000	2.10000000	1.05000000	4.41000000	151.80000000
PO2	4	44.27500000	3.88790861	1.94395430	15.11583333	177.10000000
BE	4	-1.07500000	1.44308697	0.72154348	2.08250000	-4.30000000
HCO3	4	22.35000000	1.26622799	0.63311400	1.60333333	89.40000000
TOTCO2	4	23.60000000	1.30384048	0.65192024	1.70000000	94.40000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	147.75000000	0.95742711	0.47871355	0.91666667	591.00000000
KNEW	4	4.37500000	0.12583057	0.06291529	0.01583333	17.50000000

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VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
GROUP=15 TIME=9						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38525000	0.01021029	0.00510514	0.00010425	29.54100000
PCO2	4	38.80000000	2.25388553	1.12694277	5.08000000	155.20000000
PO2	4	39.45000000	6.90917265	3.45458632	47.73666667	157.80000000
BE	4	-0.35000000	1.34783777	0.67391889	1.81666667	-1.40000000
HCO3	4	22.90000000	1.25698051	0.62849025	1.58000000	91.60000000
TOTCO2	4	24.17500000	1.32759180	0.66379590	1.76250000	96.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.12500000	1.31497782	0.65748891	1.72916667	592.50000000
KNEW	4	4.52500000	0.09574271	0.04787136	0.00916667	18.10000000
GROUP=15 TIME=10						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.38550000	0.01429452	0.00714726	0.00020433	29.54200000
PCO2	4	38.35000000	2.66645833	1.33322916	7.11000000	153.40000000
PO2	4	51.92500000	19.02215813	9.51107907	361.84250000	207.70000000
BE	4	-0.82500000	1.75570499	0.87785249	3.08250000	-3.30000000
HCO3	4	22.65000000	1.63605216	0.81802608	2.67666667	90.60000000
TOTCO2	4	23.90000000	1.67132682	0.83566341	2.79333333	95.60000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	147.87500000	1.43614066	0.71807033	2.06250000	591.50000000
KNEW	4	4.50000000	0.35590261	0.17795130	0.12666667	18.00000000
GROUP=15 TIME=11						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.39050000	0.02690105	0.01345053	0.00072367	29.56200000
PCO2	4	37.65000000	3.21403174	1.60701587	10.33000000	150.60000000
PO2	4	48.57500000	20.35065519	10.17532760	414.14916667	194.30000000
BE	4	-0.75000000	1.71369562	0.85683526	2.93666667	-3.00000000
HCO3	4	22.45000000	1.41774469	0.70887234	2.01000000	89.80000000
TOTCO2	4	23.70000000	1.49888848	0.74944424	2.24666667	94.80000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.00000000	1.35400640	0.67700320	1.83333333	592.00000000
KNEW	4	4.25000000	0.10000000	0.05000000	0.01000000	17.00000000
GROUP=15 TIME=12						
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37400000	0.01525341	0.00762671	0.00023267	29.49600000
PCO2	4	37.82500000	3.56499182	1.78249591	12.70916667	151.30000000
PO2	4	51.35000000	20.04436745	10.02218373	401.77666667	205.40000000
BE	4	-1.75000000	2.19772610	1.09886305	4.83000000	-7.00000000
HCO3	4	21.77500000	2.06458228	1.03229114	4.26250000	87.10000000
TOTCO2	4	23.00000000	2.14631467	1.07315734	4.60666667	92.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.50000000	1.68325082	0.84162541	2.83333333	594.00000000
KNEW	4	4.42500000	0.22173558	0.11086779	0.04916667	17.70000000

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GROUP=15 TIME=13

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36100000	0.02310844	0.01155422	0.00053400	29.44400000
PCO2	4	39.32500000	2.29836899	1.14918449	5.28250000	157.30000000
PO2	4	53.60000000	21.21430335	10.60715168	450.04666667	214.40000000
BE	4	-1.95000000	2.62868789	1.31434394	6.91000000	-7.80000000
HCO3	4	21.95000000	2.22186108	1.11093054	4.93666667	87.80000000
TOTCO2	4	23.25000000	2.28983260	1.14491630	5.24333333	93.00000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.37500000	1.49303941	0.74651970	2.22916667	593.50000000
KNEW	4	4.45000000	0.20816660	0.10408330	0.04333333	17.80000000

GROUP=15 TIME=14

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.37050000	0.03802192	0.01901096	0.00144567	29.48200000
PCO2	4	36.85000000	3.74655397	1.87327699	14.03666667	147.40000000
PO2	4	42.45000000	35.35708321	17.67854161	1250.12333333	169.80000000
BE	4	-2.45000000	2.86414618	1.43207309	8.20333333	-9.80000000
HCO3	4	21.00000000	2.35937845	1.17968922	5.56666667	84.00000000
TOTCO2	4	22.22500000	2.40468293	1.20234147	5.78250000	88.90000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.37500000	1.79698822	0.89849411	3.22916667	593.50000000
KNEW	4	4.42500000	0.33040379	0.16520190	0.10916667	17.70000000

GROUP=15 TIME=15

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.36925000	0.02182315	0.01091158	0.00047625	29.47700000
PCO2	4	36.60000000	2.21058062	1.10529031	4.88666667	146.40000000
PO2	4	56.92500000	20.46727062	10.23363531	418.90916667	227.70000000
BE	4	-2.77500000	2.04022058	1.02011029	4.16250000	-11.10000000
HCO3	4	20.85000000	1.70977581	0.85488791	2.92333333	83.40000000
TOTCO2	4	22.05000000	1.73877351	0.86938676	3.02333333	88.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.12500000	2.09662427	1.04831214	4.39583333	592.50000000
KNEW	4	4.20000000	0.14142136	0.07071068	0.02000000	16.80000000

GROUP=15 TIME=16

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35975000	0.02850000	0.01425000	0.00081225	29.43900000
PCO2	4	38.77500000	1.48183445	0.74091722	2.19583333	155.10000000
PO2	4	50.12500000	11.02402679	5.51201340	121.52916667	200.50000000
BE	4	-2.37500000	1.55000000	0.77500000	2.40250000	-9.50000000
HCO3	4	21.57500000	0.92150240	0.46075120	0.84916667	86.30000000
TOTCO2	4	22.80000000	0.95568475	0.47784237	0.91333333	91.20000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.75000000	1.65831240	0.82915620	2.75000000	595.00000000
KNEW	4	4.30000000	0.20000000	0.10000000	0.04000000	17.20000000

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GROUP=15 TIME=17

VARIABLE	N	MEAN	STANDARD DEVIATION	STD ERROR OF MEAN	VARIANCE	SUM
ID	4	2.50000000	1.29099445	0.64549722	1.66666667	10.00000000
PH	4	7.35625000	0.03232517	0.01616259	0.00104492	29.42500000
PCO2	4	40.20000000	3.54306835	1.77153418	12.55333333	160.80000000
PO2	4	49.12500000	24.66392440	12.33196220	608.30916667	196.50000000
BE	4	-1.72500000	2.29110599	1.14555300	5.24916667	-6.90000000
HCO3	4	22.17500000	1.71731379	0.85865690	2.94916667	88.70000000
TOTCO2	4	23.42500000	1.82094298	0.91047149	3.31583333	93.70000000
NAOLD	0	.	.	.	.	.
KOLD	0	.	.	.	.	.
NANEW	4	148.75000000	1.55456318	0.77728159	2.41666667	595.00000000
KNEW	4	4.15000000	0.31091264	0.15545632	0.09666667	16.60000000