

NEWER AND 'BETTER' INHALATION

ANESTHETIC AGENTS

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INTRODUCTION

IN A CLASSIC PAPER APPROXIMATELY FORTY YEARS AGO, THE
OUTSTANDING PIONEER, LEADER AND GENIUS IN AMERICAN ANESTHESIOLOGY,
PROFESSOR RALPH M. WATERS, PUT FORWARD THE PROPOSITION THAT THE IDEAL
ANESTHETIC AGENT SHOULD HAVE, AMONG OTHERS, THESE IMPORTANT
QUALITIES.

1. IT SHOULD BE AN INHALATION AGENT, SO THAT IT IS
READILY CONTROLLABLE.
2. IT SHOULD BE NON-FLAMMABLE AND EASY TO PREPARE, MANUFACTURE
AND STORE IN APPROPRIATE CYLINDERS. (THIS WAS THE DAY
BEFORE MASS RESERVOIRS OF GASES WERE KNOWN)
3. IT SHOULD NOT BE METABOLIZED IN THE BODY - IT WAS THEN

BELIEVED THAT INHALATION AGENTS WERE NOT METABOLIZED AND WERE BIOCHEMICALLY 'INERT'.

4. IT SHOULD PREFERABLY BE A GAS.

DR. WATERS AND HIS ASSOCIATES BELIEVED THAT THEY CAME AS CLOSE TO THE IDEAL AS WAS, AT THAT TIME SCIENTIFICALLY POSSIBLE, WITH THE DEVELOPMENT OF CYCLOPROPANE DESPITE ITS FLAMMABILITY. IT CERTAINLY DID NOT FIT IN MANY WAYS THE CRITERIA I HAVE CITED, BUT IT WAS THE STIMULUS TO THE DEVELOPMENT OF CONTROLLABLE INHALATION ANESTHESIA. IT INTRODUCED THE CONCEPT OF TRYING TO PRESERVE NORMAL PHYSIOLOGICAL ACTIVITY DURING ANESTHESIA. IT MADE NECESSARY THE USE OF CONTROLLED RESPIRATION AND THE CARBON DIOXIDE ABSORPTION TECHNIQUES AND ITS VARIOUS MODIFICATIONS. THESE REVOLUTIONARY CHANGES IN SCIENTIFIC CONCEPT AND CLINICAL PRACTICE WERE ESSENTIAL PRECURSORS TO THE MAJOR DEVELOPMENTS IN EFFICIENT ANESTHETIC CARE AND IN THE USE OF ALL MODERN ANESTHETIC DRUGS, INCLUDING MUSCLE RELAXANTS AND THE NEWEST AGENTS.

IN THE YEARS THAT FOLLOWED, THERE WAS AN ATTEMPT TO GET CLOSER TO THE IDEALS PROPOSED WITH THE DEVELOPMENT OF OTHER ANESTHETIC AND ADJUVANT AGENTS. THE MOST COMMONLY USED OF THESE NEWER AGENTS THROUGHOUT THE WORLD WAS HALOTHANE, USUALLY GIVEN WITH NITROUS OXIDE AND OXYGEN. HALOTHANE'S WIDE SPREAD ACCEPTANCE WAS NOT DUE ENTIRELY

TO MEETING PROFESSOR WATERS' CRITERIA BUT TO THE FACT THAT IT WAS NON-FLAMMABLE, HAD A HIGH ACCEPTABILITY TO PATIENTS, APPEARED TO CAUSE FEW PHYSIOLOGICAL DERANGEMENTS DURING ANESTHESIA AND PRODUCED A BENIGN POST OPERATIVE RECOVERY. THIS BRIGHT PICTURE WAS SOON MARRED BY THE FACT THAT HALOTHANE DOES NOT IN ITSELF PROVIDE GOOD ANALGESIA; IT APPEARS NOT TO BE AN EFFECTIVE MUSCLE RELAXANT, AND IT DOES SENSITIZE THE MYOCARDIUM TO CATECHOLAMINES AND ARRHYTHMIAS. PROBABLY, THE MOST IMPORTANT AND DAMAGING PROPERTY OF ALL IS THE UNPROVED BUT HIGHLY SUGGESTIVE RELATIONSHIP BETWEEN THE INCIDENCE OF HEPATITIS AND THE USE OF HALOTHANE.

METHOXYFLURANE (PENTHRANE) CAME INTO POPULAR USE IN PART AS A REMEDY OF THESE DEFECTS OF HALOTHANE. IT DOES NOT SENSITIZE THE MYOCARDIUM TO CATECHOLAMINES, IT DOES PROVIDE BETTER ANALGESIA THAN HALOTHANE, BUT IT IS SO SOLUBLE IN BLOOD THAT INDUCTION AND EMERGENCE FROM ANESTHESIA ARE RELATIVELY PROLONGED AND SPECIAL CLINICAL MEANS OF ADMINISTRATION HAVE TO BE TAKEN TO COUNTERACT THESE INHERENT DISABILITIES. THE DRUG ALSO REMAINS IN THE BODY FOR A CONSIDERABLE LENGTH OF TIME. RECENTLY, THE QUESTION OF RENAL INTOXICATION WITH THIS AGENT HAS ALSO BEEN RAISED. FOR ALL OF THESE REASONS AN INTENSIVE REINVESTIGATION TO DEVELOP NEW INHALATION ANESTHETIC AGENTS TOOK PLACE ONCE AGAIN.

II. ETHRANE AND FLURANE

SLIDE 1 - STRUCTURAL FORMULA OF ETHRANE

ETHRANE IS A HIGHLY HALOGENATED ETHER. IT IS A VOLATILE LIQUID AND NOT A GAS. ITS PHYSICAL CHEMICAL CHARACTERISTICS ARE:

SLIDE 2 - PHYSICAL AND CHEMICAL CHARACTERISTICS OF ETHRANE

ALTHOUGH THE CHEMICAL CONFIGURATION OF ETHRANE MORE CLOSELY RESEMBLES THAT OF METHOXYFLURANE, IT SEEMS TO BEHAVE BOTH PHARMACOLOGICALLY AND CHEMICALLY SOMEWHAT MORE LIKE HALOTHANE. THIS SIMILARITY IS POSSIBLY DUE TO THE TOO HIGHLY ELECTRO NEGATIVE FLURINE ATOMS ON THE CARBON ATOMS AT EITHER SIDE OF THE OXYGEN ATOMS WHICH DOES TEND TO REDUCE THE INFLUENCE OF THE ETHER OXYGEN AND MAKES ETHRANE BEHAVE MORE LIKE A HYDROCARBON THAN AN ETHER. THESE CHEMICAL PROPERTIES ARE LARGELY RESPONSIBLE FOR PROVIDING RELATIVE FREEDOM FROM CARDIAC ARRHYTHMIAS, BETTER MUSCLE RELAXATION AND ANALGESIA, AND GREATER CHEMICAL STABILITY THAN WITH HALOTHANE.

THE VAPOR OF ETHRANE IS PLEASANT AND PRODUCES INDUCTION OF ANESTHESIA WITHIN THREE MINUTES OF INHALATION, IF THREE TO FIVE PERCENT CONCENTRATION IS INHALED IN A NITROUS OXIDE-OXYGEN MIXTURE OF SIXTY TO FORTY PERCENT. THE CONCENTRATION OF ETHRANE SHOULD BE INCREASED GRADUALLY IN 0.5% INCREMENTS TO AVOID EXCITEMENT, BUT ONCE

SURGICAL ANESTHESIA IS ESTABLISHED, IT CAN BE REDUCED TO 1% TO 1.5% FOR REASONABLE MAINTENANCE.

ASSISTANCE OR CONTROL OF RESPIRATION NEEDS TO TAKE PLACE BECAUSE OF THE DIMINISHED TIDAL VOLUME. SINCE THE TRACHEAL-BRONCHEAL REFLEXES APPEAR TO BE GENERALLY DIMINISHED DURING ETHRANE ANESTHESIA, THE LUNGS CAN EASILY BE INFLATED ASSUMING NO MECHANICAL OBSTRUCTION. CONTROLLED VENTILATION WITH 0.5% TO 1.5% ETHRANE DOES NOT CAUSE ANY CARDIOVASCULAR DANGERS.

MOST OBSERVERS WHO HAVE USED THIS ANESTHETIC AGENT, FIND THAT THE ONLY DRAWBACK OF SOME IMPORTANCE IS THE APPEARANCE OF CENTRAL NERVOUS SYSTEM EXCITABILITY IN APPROXIMATELY 2% OF THE PATIENTS TO WHOM THE AGENT HAS BEEN GIVEN.

THIS CENTRAL NERVOUS SYSTEM HYPERACTIVITY SEEMS NOT TO HAVE CAUSED CLINICAL HARM BUT IT IS HARD FOR THIS OBSERVER TO ACCEPT TOTALLY AN AGENT THAT HAS THIS PROPERTY BOTH IN GROSS CLINICAL MANIFESTATIONS AND THE MORE SUBTLE FORM SEEN IN THE ELECTRO ENCEPHALOGRAM UNLESS IT IS UNEQUIVOCALLY SHOWN TO BE HARMLESS TO PATIENTS.

A SAVING GRACE OF THE ANESTHETIC AGENT'S DIFFICULTY IS THE FACT THAT THIS KIND OF EXCITATION IS EASILY TERMINATED BY LIGHTENING THE LEVEL, BY REDUCING THE MINUTE VENTILATION OR BY CHANGING ANESTHETIC

AGENTS. NO OBSERVERS HAVE AS YET REPORTED POST OPERATIVE DAMAGE FROM THIS MANIFESTATION.

THESE STUDIES HAVE RAISED CERTAIN QUESTIONS IN THE MINDS OF MANY. FOR INSTANCE, SHOULD ONE ACCEPT THIS DISABILITY OF AN OTHERWISE SUPERB ANESTHETIC AGENT, AND SIMPLY BLOCK THE ABNORMAL MOTOR ACTIVITY IF IT OCCURS WITH A MUSCLE RELAXANT? THIS APPROACH OR SIMILAR ONES WOULD MORE CLOSELY RESEMBLE THE NATURAL WAY IN WHICH MOST ANESTHETICS ARE GIVEN CLINICALLY IN ANY EVENT.

IT IS HIGHLY LIKELY THAT ANESTHESIOLOGISTS AND THEIR COLLEAGUES IN SURGERY AND MEDICINE WOULD BE HAPPIER WITH AN ANESTHETIC AGENT THAT HAD NO CENTRAL NERVOUS SYSTEM MOTOR PROBLEM, BUT THIS PROBLEM IS MORE ACCEPTABLE TO CLINICIANS THAN AN AGENT WHOSE INFLUENCE IS HARMFUL UPON EITHER THE LIVER OR KIDNEY AND ESPECIALLY IF THE POTENTIAL DAMAGE IS NEITHER PREDICTABLE NOR MANAGEABLE.

SATISFACTORY ANESTHESIA CAN BE PROVIDED WITH ETHRANE ALONE OR IN COMBINATION WITH OTHER DRUGS USED IN ANESTHESIA. THE PHYSICAL CHEMICAL CHARACTERISTICS ACCOUNT FOR AN INDUCTION WHICH IS RAPID AND SMOOTH AND RECOVERY WHICH IS EQUALLY RAPID AND BENIGN.

SLIDES 3,4,5,6 - COMPARISONS OF ETHRANE AND HALOTHANE.

THE UPTAKE AND ELIMINATION CURVES OF ETHRANE IN MAN IN TRACE DOSES CORROBORATE THE PREDICTION OF SPEED FROM THEIR PHYSICAL

CHARACTERISTICS AND SHOW RAPID SMOOTH INDUCTION AND RECOVERY.

SLIDES 7, 8, AND 8. #7 ENFLURANE UPTAKE CURVE OBTAINED FROM FOUR SUBJECTS EXPOSED TO 0.5% ENFLURANE CONCENTRATION FOR 60 MINUTES AND FOUR SUBJECTS FOR 30 MINUTES. VALUES OF THE ORDINATE REPRESENT THE RATIO BETWEEN ALVEOLAR ANAESTHETIC FRACTION (FA) AND INSPIRED FRACTION (FI). #8 & 9 - ELIMINATION CURVE OF ENFLURANE OBTAINED IN FOUR PATIENTS AFTER 30 MINUTES OF BODY EQUILIBRATION AND IN FOUR AFTER 60 MINUTES. VALUES OF THE ORDINATES REPRESENT THE RATIO BETWEEN ALVEOLAR ANAESTHETIC FRACTION (FA) AND THE VALUE OF ALVEOLAR FRACTION AT THE START OF THE ELIMINATION.

A FINAL WORD ON THE UPTAKE AND ELIMINATION OF ETHRANE IN MAN IS INDICATED. THE RATE OF INCREASE OF ALVEOLAR CONCENTRATION OF ETHRANE WAS STUDIED BY TORRI AND HIS COLLEAGUES IN MILAN. SIMULTANEOUS COMPARISON MEASUREMENTS WITH HALOTHANE INDICATE THAT UPTAKE WITH ETHRANE WAS MORE RAPID THAN HALOTHANE IN THE FIRST FIFTEEN MINUTES, BUT THAT AFTER FIFTEEN MINUTES THEY WERE APPROXIMATELY THE SAME. WHEN ONE ANALYZES THE VARIOUS COMPARTMENTS OF THE UPTAKE AND ELIMINATION OF THE TWO ANESTHETICS, THERE IS A LARGE DIFFERENCE IN THE SLOPE OF THE SLOWEST COMPARTMENT. IT IS BELIEVED THAT THIS

DIFFERENCE CAN BE ACCOUNTED FOR LARGELY BY THE LOWER FAT SOLUBILITY OF ETHRANE COMPARED WITH HALOTHANE.

SLIDE 10 - CARDIAC RHYTHM - COMPARISONS OF ETHRANE & HALOTHANE

CARDIAC RHYTHM WITH ETHRANE IS VERY STABLE AND ARRHYTHMIAS ARE MOST UNUSUAL. THERE IS MILD HYPOTENSION DURING INDUCTION AND A RETURN TO NEAR NORMAL LEVELS WHEN SURGICAL STIMULATION TAKES PLACE. WITH DEEPER ANESTHESIA, HYPOTENSION CAN INCREASE. CARDIAC OUTPUT IS GREATER WITH ETHRANE THAN WITH HALOTHANE AND DOES INCREASE WITH DEPTH OF ANESTHESIA, WHILE OUTPUT OF THE HEART WITH HALOTHANE REMAINS ESSENTIALLY UNCHANGED. IN DEEP ANESTHESIA, THERE IS A DIMINISHED PERIPHERAL VASCULAR RESISTANCE WITH ETHRANE AS COMPARED WITH HALOTHANE SUGGESTING THAT A GIVEN DEGREE OF HYPOTENSION WOULD BE LESS HARMFUL TO PATIENTS WITH ETHRANE THAN WITH HALOTHANE. ETHRANE IN LIGHT LEVELS IS LESS OF A DEPRESSANT UPON THE HEART AND THERE IS LESS CATECHOLAMINE RELEASE THAN EITHER HALOTHANE OR METHOXYFLURANE.

INCREASING THE TENSION OF CARBON DIOXIDE DOES NOT APPEAR TO ALTER THE RHYTHM AS IT DOES WITH HALOTHANE. BRADYCARDIA CAN FOLLOW REPEATED DOSES OF SUCCINYLCHOLINE BUT IS LESS MARKED WITH ETHRANE THAN WITH MANY OTHER INHALATION ANESTHETICS. THE STABILITY OF RHYTHM AND RATE AND THE ABSENCE OF ARRHYTHMIAS HAVE ENCOURAGED A WIDERSPREAD USE OF THIS AGENT IN PATIENTS SUSCEPTIBLE TO THESE CARDIOVASCULAR PROBLEMS.

SLIDE 11 & 12 - CARDIOVASCULAR PHARMACOLOGIC PROPERTIES -
COMPARISONS OF ETHRANE & HALOTHANE

MUSCLE RELAXATION WITH ETHRANE IS EXCELLENT, IT APPEARS TO POTENTIATE THE EFFECT OF NONDEPOLARIZING MUSCLE RELAXANTS, THUS PERMITTING THE USE OF SMALLER DOSES OF THESE MUSCLE RELAXANTS. THE PRECISE MECHANISM OF THIS ACTION HAS NOT AS YET BEEN WORKED OUT, BUT IT IS NOT AT THE NEURO-MUSCULAR JUNCTION.

ETHRANE, LIKE OTHER ANESTHETIC AGENTS WHICH ARE HALOGENATED, DOES DEPRESS RESPIRATION. IN THE CASE OF ETHRANE, THE RESPIRATORY RATE SEEMS TO REMAIN ESSENTIALLY UNCHANGED, BUT THERE IS A CONSIDERABLY DECREASED DEPTH IN BOTH MINUTE AND ALVEOLAR VENTILATION RESULTING IN A RELATIVE HYPERCAPNIA.

NAUSEA AND VOMITING ARE MINIMAL AFTER ETHRANE IN THE POSTOPERATIVE PERIOD.

LABORATORY STUDIES ON PATIENTS SHOW NO EVIDENCE OF HEPATIC AND RENAL INTOXICATION ALTHOUGH LONG TERM STUDIES IN LARGER NUMBERS CERTAINLY MIGHT REVEAL SUCH A POSSIBILITY AS BEING FACTUAL.

SLIDE 13 - OTHER COMPARISONS OF ETHRANE & HALOTHANE

THE PATIENTS SEEM TO HAVE GOOD ACCEPTANCE FOR ETHRANE. RECOVERY OCCURS RAPIDLY AS ONE MIGHT EXPECT FROM THE PHYSICOCHEMICAL CHARACTERISTICS, AND DIZZINESS AND UNPLEASANT SENSATIONS ARE REMARKABLE FOR

THEIR ABSENCE. THE PATIENT'S APPETITE SEEMS TO RETURN FAIRLY EARLY.

THE MAIN PROBLEM REMAINS THE HIGH FREQUENCY HIGH VOLTAGE EEG PATTERN WHICH IS RARELY BUT OCCASIONALLY ACCOMPANIED BY LOCALIZED MUSCLE TWITCHING. THERE HAS BEEN NO EVIDENCE OF POSTANESTHETIC NEUROLOGICAL DAMAGE THUS FAR.

THERE APPEARS TO BE NO INFLUENCE ON PREGNANT ANIMALS EITHER IN MOTHER OR IN THE FETUS OR NEWBORN IN ANY STUDIES REPORTED.

THE POTENTIATION OF NEUROMUSCULAR BLOCKADE WITH ETHRANE SEEMS TO BE DUE TO A DEPRESSANT EFFECT UPON THE CENTRAL NERVOUS SYSTEM PROBABLY AT THE LEVEL OF THE SPINAL CORD. IT DOES NOT RESPOND IN ANY WAY TO PROSTIGMIN AND IT CERTAINLY DOES NOT OCCUR AT THE MYONEURAL JUNCTION.

ONE OF THE IMPORTANT QUALITIES OF AN INHALATION ANESTHETIC AGENT IS THAT IT SHOULD BE RELATIVELY INERT IN THE BODY AND NOT BE METABOLISED. ETHRANE DOES NOT FULFILL THIS REQUIREMENT COMPLETELY IN THAT ITS BIOTRANSFORMATION, STUDIED BY HOLADAY AND HIS COLLEAGUES, SHOWS A URINARY FLUORINE EXCRETION WHICH CAN BE MEASURED.

SLIDE 14 - (HOLADAY) METABOLISM OF ETHRANE

THE TOTAL AMOUNT OF ETHRANE RECOVERED AVERAGED 85.1% IN SEVEN FEMALE PATIENTS WHO WERE STUDIED. THE AMOUNT OF NONVOLATILE FLUORINATED METABOLITES IN URINE AVERAGED 2.4%. OF THIS MATERIAL

0.5% WAS EXCRETED IN INORGANIC FORM AND 1.9% IN ORGANIC FORM.

THE MAXIMUM URINARY EXCRETION RATE OF FLUORIDE ION REACHED ITS PEAK IN SEVEN HOURS AFTER THE END OF ANESTHESIA. THE MAXIMUM EXCRETION OF ORGANIC FLUORINE METABOLITES WAS REACHED ON THE SECOND DAY. SUBSEQUENTLY, IN BOTH INSTANCES THE URINARY EXCRETION DECLINED IN A SIMPLE EXPONENTIAL DECAY FASHION.

EGER AND HIS ASSOCIATES SHOWED IN MINIATURE SWINE THAT THE SITE OF METABOLISM FOR ETHRANE WAS UNLIKELY TO BE IN THE LIVER. THESE OBSERVATIONS ARE OF IMPORTANCE BECAUSE DRUG METABOLITES OFTEN CAUSE INTOXICATION. IN CONTRAST, HALOTHANE AND METHOXYFLURANE EXHIBIT CONSIDERABLE HEPATIC METABOLISM. ETHRANE SHARES THE NON-METABOLIC ACTIVITY IN THE LIVER WITH CYCLOPROPANE AND WITH FORANE.

ETHRANE HAS NO INFLUENCE ON HEMOGLOBIN FUNCTION IN VITRO. IT SHARES THIS PROPERTY WITH NITROUS OXIDE AND HALOTHANE. THE BOHR EFFECT OF HEMOGLOBIN IS NOT ALTERED BY ETHRANE.

WITH RESPECT TO CARBOHYDRATE AND FAT METABOLISM, YOUR COLLEAGUE IN JAPAN, DR. OYAMA AND HIS ASSOCIATES DETERMINED THAT ETHRANE IN MAN APPEARED TO HAVE NO IMPORTANT EFFECT ON PLASMA GROWTH HORMONE, INSULIN, BLOOD GLUCOSE, AND FREE FATTY ACIDS UNTIL APPROXIMATELY TWO HOURS AFTER THE START OF OPERATION. AS IS COMMON WITH MANY ANESTHETIC AGENTS, BLOOD GLUCOSE DID NOT CHANGE DURING ANESTHESIA

ALONE, BUT IT INCREASED MARKEDLY DURING THE TRAUMA THAT GOES WITH SURGICAL OPERATION. PLASMA INSULIN LEVELS TENDED TO REMAIN CONSTANT DURING ANESTHESIA, BUT ALSO WERE INCREASED WITH OPERATION. THE PLASMA FREE FATTY ACID LEVELS FELL SIGNIFICANTLY DURING ANESTHESIA ALONE BUT TENDED TO RISE DURING RECOVERY. DR. OYAMA SUGGESTED THAT ETHRANE MAY BE THE AGENT OF CHOICE FOR DIABETICS, BECAUSE OF THESE QUALITIES.

ETHRANE HAS BEEN STUDIED IN SIX COUNTRIES IN EUROPE, TWO COUNTRIES IN LATIN AMERICA, THREE COUNTRIES IN THE ORIENT, AND ONE COUNTRY IN AFRICA. AS OF MAY 1973, MORE THAN THIRTY FIVE HUNDRED PATIENTS HAD RECEIVED THE ANESTHETIC AGENT.

ALTHOUGH THERE WERE SOME VARIATIONS, A SIMILAR TECHNIQUE WAS USED BY ALL OBSERVERS. A SEMI-CLOSED CIRCUIT WAS USED BY FIFTY NINE PER CENT OF THE INVESTIGATORS AND ONLY EIGHT PER CENT OF THEM USED AN ENTIRELY CLOSED CIRCUIT.

FORANE

IN THE CONTINUED SEARCH FOR A BETTER AND HOPEFULLY IDEAL ANESTHETIC AGENT, THE KNOWLEDGE OF FLUORINE CHEMICAL TECHNOLOGY AND THE SYNTHESIS OF NONFLAMMABLE AGENTS PRODUCED THE MOST MODERN OF THE INHALATION ANESTHETICS. THE SKILL OF JAPANESE SCIENTISTS IN THIS FIELD IS RECOGNIZED EVERYWHERE IN THE WORLD.

SLIDE 15 - FORANE FORMULA

MOST RECENTLY DISCOVERED OF THESE AND SYNTHESIZED IS AN AGENT KNOWN AS FORANE. THE SAME CRITERIA WHICH WERE IN THE MINDS OF SOME OBSERVERS NOT TOTALLY SATISFIED WITH THE PRESENT ANESTHETIC AGENTS WERE NON-FLAMMABILITY, STRONG CHEMICAL STABILITY, (TO REDUCE THE POSSIBILITY OF METABOLISM OF THE AGENT) MINIMAL RESPIRATORY AND CARDIOVASCULAR DEPRESSION, RAPID AND PLEASANT INDUCTION AND RECOVERY, GOOD MUSCLE RELAXATION AND LACK OF SENSITIVITY OF THE MYOCARDIUM TO CATECHOLAMINES. THE COMPOUND SHOULD ALSO SHOW NO CELLULAR INTOXICATION AND THAT IT WOULD BE ECONOMICAL TO PRODUCE.

HALOGENATION IS ESSENTIAL TO NONFLAMMABILITY. HOWEVER, TOTALLY FLUORINATED COMPOUNDS HAD NO ANESTHETIC EFFECT. COMPOUNDS WITH IODINE AND BROMINE TENDED TO BE UNSTABLE. IN GENERAL, THE ALKANES TENDED TO REPRODUCE ARRHYTHMIAS. SOME OF THESE WERE TRIED AND ABANDONED.

ETHERS SEEM TO HOLD AN INCREASED PROMISE ONCE AGAIN BECAUSE THEY DO PROVIDE BETTER MUSCLE RELAXATION, AND STABILITY OF CARDIAC RHYTHM AND A DIMINUTION OF CARDIORESPIRATORY DEPRESSION. SOME OF THE ETHER SERIES APPEARED TO BE MORE PROMISING THAN OTHERS. THE DIMETHYL SERIES TENDED TO BE UNSTABLE. INSTABILITY ALSO WAS A PROBLEM WITH ISOPROPYL METHYL AND ISOPROPYL ETHYL ETHERS. THE DIETHYL SERIES WERE

NOT QUITE SUCCESSFUL — ALMOST HISTORY REPEATING ITSELF IN A MODERN VERSION OF THE FIRST INHALATION AGENT, I.E., DIETHYL ETHER.

THE MOST PROMISING SEEMED TO BE THE METHYL ETHYL ETHERS. ENFLURANE (ETHRANE) AND ITS ISOMER FORANE ARE BOTH METHYL ETHYL ETHERS. THEY WERE DISCOVERED BY R.C. TERRELL IN 1963 AND 1965 RESPECTIVELY.

ETHRANE IS EASIER TO SYNTHESIZE THAN FORANE AND THEREFORE PRECEDED FORANE IN THE STUDIES DESIGNED FOR ULTIMATE CLINICAL APPLICATION. THE PROBLEM OF PURIFYING FORANE WAS SUFFICIENTLY GREAT SO THAT, FOR A TIME, THE COMPOUND WAS ACTUALLY ALMOST ABANDONED. HOWEVER, THE BRILLIANT CHEMICAL WORK OF LOUISE SPEERS AND OTHERS SOLVED THE PROBLEM OF SYNTHESIS STABILITY AND PERMITTED THE BIOLOGICAL AND CLINICAL TESTING OF FORANE TO TAKE PLACE.

SLIDE 16, 17, 18 AND 19 — PHYSICAL AND CHEMICAL PROPERTIES OF FORANE

THERE IS SOME MILD PUNGENCY OF FORANE, UNLIKE ETHRANE, AND IT DOES LIMIT THE RATE AT WHICH INDUCTION MAY BE ACHIEVED BUT, OF COURSE, IT HAS NO INFLUENCE ON THE RATE OF RECOVERY. FORANE AND ETHRANE COMPARED WITH HALOTHANE AND METHOXYFLURANE ARE REMARKABLE FOR THEIR CHEMICAL STABILITY.

INITIAL STUDIES WITH FORANE IN ANIMALS SHOWED EASY INDUCTION AND

RECOVERY WITH NO CHANGES IN KIDNEY OR LIVER FUNCTION AT LEAST IN THE EARLY STUDIES.

SLIDE 20, 21, & 22 - CARDIOVASCULAR COMPARISON OF FORANE & HALOTHANE

THE EARLY RESULTS IN CLINICAL TRIAL INDICATE THAT FORANE NEITHER DEPRESSES THE HUMAN HEART NOR PREDISPOSES TO ARRHYTHMIAS. IN MINIATURE SWINE THE METABOLISM OF FORANE IS LESS MARKED THAN THAT OF HALOTHANE OR METHOXYFLURANE. MUSCLE RELAXATION IS GOOD COMPARED WITH HALOTHANE. FORANE MARKEDLY POTENTIATES THE EFFECTS OF D-TUBOCURARINE. AS A DISADVANTAGE, BUT NOT TO THE EXPERT CLINICIAN, IS THE FACT THAT FORANE IS A PROFOUND RESPIRATORY DEPRESSANT.

SLIDE 23 & 24 - FORANE AND TWITCH DEPRESSION - COMPARISON WITH HALOTHANE

NOT ENOUGH CLINICAL TRIALS HAVE BEEN PERFORMED TO ANSWER THE CRUCIAL QUESTIONS ABOUT SENSITIZATION OR PROLONGED INTOXICATION. THERE ARE STILL MANY UNANSWERED QUESTIONS, BUT STUDIES ARE PROCEEDING APACE.

SLIDE 25 - OTHER COMPARISONS OF FORANE & HALOTHANE

FORANE DIFFERS FROM ETHRANE IN THAT IT DOES NOT DISPLAY ABNORMAL ELECTROENCEPHALOGRAPHIC PATTERNS AND DOES NOT SEEM TO PRODUCE IRRITABILITY OF THE CENTRAL NERVOUS SYSTEM.

IT COULD BE THAT THE CONCENTRATION OR THE DOSE OF THE AGENT MAY BE RESPONSIBLE FOR SOME OF THESE DIFFERENCES, BUT EVIDENCE IS NOT AT HAND AS YET TO BE SECURE ON THIS POINT.

SOME OF THE UNDESIRABLE EFFECTS WITH FORANE ARE AN OCCASIONAL HYPOTENSIVE EPISODE AFTER INDUCTION, WHICH IS REVERSED WHEN OPERATION IS BEGUN. THERE IS A RISE OF BLOOD GLUCOSE IN THE LARGE MAJORITY OF PATIENTS. PLASMA CORTISONE IS ALWAYS INCREASED AS ARE TOTAL CATECHOLAMINES, THERE IS RESPIRATORY DEPRESSION, WHICH IS RELATED TO THE CONCENTRATION AND THERE APPEARS ALSO TO BE INCREASED UTERINE BLEEDING.

SLIDE 26 - POTENCY OF ALL ANESTHETICS

RELATIONSHIP BETWEEN IN VITRO POTENCY AND LIPID SOLUBILITY.

SUMMARY

- 1) DISCUSSION OF "IDEAL" ANESTHETIC AND THE THRUST OF CURRENT RESEARCH TOWARD THAT OBJECTIVE WAS PRESENTED.
- 2) CLINICAL AND BASIC PHARMACOLOGY OF ETHRANE AND FORANE WERE SUMMARIZED.
- 3) BOTH ARE EXCELLENT AGENTS AND WORTHY OF CLINICAL USE.
- 4) THERE ARE THOSE WHO ARE SATISFIED WITH ETHRANE - AND OTHERS WHO BELIEVE FORANE WILL BE SUPERIOR.