

**INHALATION ANESTHESIA: A LEGACY**  
**OF THE FIRST PUBLIC DEMONSTRATION OF ETHER**  
**AT THE**  
**MASSACHUSETTS GENERAL HOSPITAL**

FIRST WILLIAM T.G. MORTON HONORARY LECTURE  
KENNEDY LIBRARY, BOSTON MASSACHUSETTS

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BY

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1. INTRODUCTION

I DEEM IT A VERY GREAT PRIVILEGE AND AN EQUALLY GREAT PLEASURE TO MEET WITH ALL OF YOU IN THE HARVARD COMMUNITY OF DISTINGUISHED ANAESTHESIA DEPARTMENTS TO PRESENT THIS FIRST MORTON LECTURE, ONE HUNDRED AND THIRTY-SIX YEARS AFTER THE FIRST PUBLIC DEMONSTRATION OF THE USE OF ETHER AT THE MASSACHUSETTS GENERAL HOSPITAL. IT IS AN EXTRAORDINARY ADDED PLEASURE TO PARTICIPATE IN THE 200TH ANNIVERSARY OF THE NATION'S NATIONAL TREASURE IN MEDICAL

EDUCATION AND MEDICAL RESEARCH, THE HARVARD MEDICAL SCHOOL. THIS OCCASION IS DIFFERENTLY SET, AND APPROPRIATELY SO, FROM THE LAST IMPORTANT CELEBRATION OF "ETHER DAY" WHICH I WAS PRIVILEGED ALSO TO ATTEND, BUT AS A JUNIOR LISTENER, TO THE DISTINGUISHED SCIENTISTS AND CLINICIANS OF THE DAY, I.E. THE 100TH ANNIVERSARY OF THE FIRST PUBLIC DEMONSTRATION IN 1946, IN A BEAUTIFUL SETTING UNDER TENTS ON A LOVELY FALL DAY IN BOSTON. DR. HENRY K. BEECHER, THE THEN DORR PROFESSOR OF ANAESTHESIA AT HARVARD AND ANAESTHETIST-IN-CHIEF OF THE MASSACHUSETTS GENERAL HOSPITAL, WHO WAS A REMARKABLY INNOVATIVE AND ABLE PERSON, INVITED A SUPERB GROUP OF DISTINGUISHED SCIENTISTS AND CLINICIANS AS SPEAKERS TO MARK THIS IMPORTANT OCCASION.

IN THE PRESENCE OF ALL OF YOU STEEPED IN THE HARVARD TRADITION AND PARTICULARLY IN THE PRESENCE OF OUR SPECIALTY'S MOST ABLE AND LITERATE HISTORIAN, DR. LEROY VANDAM, IT IS NOT SEEMING FOR ME TO ATTEMPT TO TELL YOU A HISTORY THAT YOU KNOW BETTER THAN I. AS DR. VANDAM SO ABLY POINTED OUT TO MANY OF YOU DURING THE ANNUAL MEETING THIS YEAR OF THE ASSOCIATION OF UNIVERSITY ANAESTHETISTS, THE INTRODUCTION OF ETHER AS AN ANESTHETIC AGENT IN THIS COMMUNITY HAD MUCH THAT WENT BEFORE IT, ESPECIALLY IN BRITAIN AND FRANCE, WHICH ULTIMATELY LED, BY THE BUILDING OF IDEAS, TO THIS GREAT EVENT. THE DISCOVERY OF ANESTHESIA AND PARTICULARLY, THE CONTRIBUTIONS OF MORTON AND THE DISTINGUISHED SURGEONS, BIGELOW AND WARREN MAKE THIS OUTSTANDING MEDICAL CONTRIBUTION A UNIQUELY AMERICAN GIFT TO WORLD

WELFARE AND TO THE SCIENCE AND ART OF THERAPEUTICS IN ANY FIELD. IT IS FITTING, ALSO, THAT IT TOOK PLACE AS THE RESULT OF THE GENIUS OF NEW ENGLAND AND OF HARVARD SPECIFICALLY.

A REMARKABLE TALE COULD BE TOLD OF THE EARLY INHALATION ANESTHETICS WHICH WERE, OF COURSE, NITROUS OXIDE, ETHER AND CHLOROFORM DEVELOPED SO LONG AGO. THIS PERIOD OF DISCOVERED USAGE WAS FOLLOWED BY AN UNUSUAL GAP OF SOME EIGHTY OR MORE YEARS DURING WHICH NO IMPORTANT ADDITION TO THE GROUP OF INHALATION ANESTHETIC AGENTS WAS INTRODUCED. I HAVE PONDERED ON THIS STRANGE FACT AND CAME TO SEVERAL POSSIBLE EXPLANATIONS. THE FIRST OF THESE IS THE UNUSUAL HIGH QUALITY AND FLEXIBILITY OF ETHER, WHOSE ANNIVERSARY WE CELEBRATE TODAY, WHICH SATISFIED SO MANY OF THE SURGICAL REQUIREMENTS OF THE SECOND HALF OF THE NINETEENTH CENTURY AND THE FIRST QUARTER OF THE TWENTIETH CENTURY OR, PERHAPS, EVEN THE FIRST HALF OF THE TWENTIETH CENTURY; THAT THE MOTIVATION FOR THE DEVELOPMENT OF NEW ANESTHETIC INHALANTS MAY HAVE BEEN RELATIVELY SMALL.

NITROUS OXIDE'S EXCELLENCE IS BEST BESPOKEN BY ITS CURRENT CONTINUED USE TODAY, INHIBITED CHIEFLY BY ITS LACK OF POTENCY FOR MANY PURPOSES. THAT DEFICIENCY WAS COMPENSATED AND ATTEMPTS WERE MADE TO MAKE ANESTHESIA MORE NEARLY "PERFECT" BY THE USE OF SUPPLEMENTARY NON-VOLATILE SUBSTANCES WHICH WERE SEDATIVE, HYPNOTIC, ANALGESIC AND RELAXANT IN TYPE. HOWEVER, THIS YEAR, QUESTIONS ARE

BEING RAISED BY EGER AND OTHERS ABOUT NITROUS OXIDE'S SAFETY AND ITS FUTURE. ENOUGH QUESTIONS ABOUT NITROUS OXIDE ARE PROPERLY BEING RAISED AS TO WHETHER ITS PRESENT ROLE IN BALANCED ANESTHESIA SHOULD NOT BE RE-EVALUATED.

THE IMPLICATION IN THESE QUESTIONS IS THAT NITROUS OXIDE MAY CARRY TOO MANY LIABILITIES, E.G. HYPOXIA, BODY COMPARTMENT GAS EXPANSION PROBLEMS, MUTAGENICITY AND POSSIBLY EVEN CARCINOGENICITY AND THAT ITS USEFULNESS SHOULD BE RECONCILED WITH ITS PROBLEMS. IT IS EVEN POSSIBLE THAT IF ETHER WERE NONFLAMMABLE AND, PERHAPS, LESS SOLUBLE IN THE BLOOD, IT MIGHT STILL BE USED TODAY.

WITH THE SCIENTIFIC AND CLINICAL FERMENT STIMULATED, AS I VIEW IT, BY THE EXPERIENCES OF THE SECOND WORLD WAR AND THE POST WAR PERIOD, A TREMENDOUS EXPANSION IN SCIENTIFIC INFORMATION LED TO GREATER REQUIREMENTS FOR ANESTHETIC CARE ON THE PART OF THOSE WHO PERFORM SURGERY, AND LED TO GREATER COMPETENCE AND RESPONSIVENESS OF THOSE WHO ADMINISTER ANESTHESIA.

THE CATALYST OF CREATIVE IMAGINATION, ALONG WITH THE ECONOMIC POWER OF THE TIMES, CERTAINLY PUSHED THOSE INVOLVED IN THE SURGICAL CARE OF PATIENTS TO FIND ANESTHETIC AGENTS OR SYSTEMS THAT HAD FEWER SIDE EFFECTS OR DAMAGING POTENTIAL THAN ETHER OR CHLOROFORM.

THE PHARMACOLOGISTS WERE BUSY IN THIS PERIOD PRODUCING A WHOLE VARIETY OF ANESTHETIC AGENTS, INCLUDING THE MOST INTERESTING DEVELOPMENT OF CYCLOPROPANE WHICH WAS POTENT AND

HAD A LOW SOLUBILITY IN THE BLOOD AND, THEREFORE, WAS MORE CONTROLLABLE THAN ETHER. ITS APPARENT SUPPORT OF CIRCULATORY FUNCTION DIMINISHED THAT TYPE OF UNDERSIRABLE SIDE EFFECT, BUT ITS POTENTIAL FOR PRODUCING CARDIAC ARRHYTHMIAS AND FIRE AND EXPLOSION, ULTIMATELY DOOMED IT TO BECOME AN AGENT WHICH WOULD BECOME OBSOLETE. THOSE WHO QUARRELED ABOUT THE RELATIVE MERITS OF ETHER AND CYCLOPROPANE IN THOSE DAYS, WERE HANDICAPPED BY AN INADEQUATE KNOWLEDGE OF THE PHYSICAL CHEMISTRY OF ANESTHETIC AGENTS WHICH WAS TO COME SOMEWHAT LATER AND WHICH IN TURN LED TO A BETTER UNDERSTANDING OF PHARMACOKINETICS AND THE UPTAKE AND DISTRIBUTION OF THESE DRUGS. IF THAT KNOWLEDGE HAD BEEN AVAILABLE, THE ARGUMENTS MIGHT HAVE BECOME SOMEWHAT MORE RATIONAL THAN THEY WERE IN THE IMMEDIATE PRE AND POST WAR PERIODS SINCE BOTH THE "CHAMPAGNE" OF GENERAL ANESTHETICS, CYCLOPROPANE, AND THE "BEER" OF ANESTHETICS, ETHER, AS ROVENSTINE DESCRIBED THEM, WERE BOTH SLATED FOR ULTIMATE DEPARTURE INTO HISTORY RATHER THAN PRESERVATION IN CURRENT USAGE.

DESPITE ALL THAT WAS AVAILABLE, BY 1950 IT BECAME VERY OBVIOUS THAT EVEN THE BEST OF AGENTS, ETHER AND CYCLOPROPANE WHICH WERE EXPLOSIVE, RELATIVELY INFLEXIBLE OR TOXIC TO IMPORTANT ORGANIC SYSTEMS REQUIRED THAT A REPLACEMENT SEARCH HAD TO BE PERSUED VIGOROUSLY.

AS IS OCCASIONALLY THE CASE, AN EVIL OF THE PERIOD ALSO HARBORED MUCH THAT WAS GOOD. IN ORDER TO DEVELOP A SOUND TECHNOLOGY

OF SEPARATION OF URANIUM ISOTOPES FOR ATOMIC WARFARE, IT WAS NECESSARY TO DEVELOP A HIGHLY SOPHISTICATED TECHNOLOGY FOR FLUORINATED COMPOUNDS. FLAMMABILITY WAS QUENCHED BY ADDING FLUORINE AND STABILIZATION OF COMPOUNDS WAS ENHANCED AS WELL. THESE TWO PROPERTIES DEVISED FROM MILITARY USAGE WERE APPLIED TO ANESTHETIC RESEARCH AND LED TO THE SYNTHESIS OF A NEW GENERATION OF INHALATION ANESTHETIC AGENTS, WHICH WAS TO BE BASED UPON HALOGENATION, AND MORE SPECIFICALLY, UPON FLUORINATION. ALTHOUGH THERE WERE SEVERAL NEW HALOGENATED ANESTHETIC AGENTS DEVELOPED PRIOR TO THE DISCOVERY OF HALOTHANE, IT WAS THE SYNTHESIS OF THAT COMPOUND BY RAVENTOS AND HIS COLLEAGUES WHICH WAS THE RESULT OF CAREFUL AND EXQUISITE PHYSICAL CHEMICAL PREDICTIONS ABOUT MOLECULAR STRUCTURE THAT WOULD PROVIDE THE QUALITIES OF NON-FLAMMABILITY, ACCEPTABLE SOLUBILITY IN THE BLOOD AND MOLECULAR STABILITY. ANESTHETIC POTENCY WAS ALSO ENHANCED BY OTHER TINKERING WITH THE MOLECULE.

THIS MAGNIFICENT DEVELOPMENT IN INHALATION ANESTHESIA FOR ALL TIME ENDED THE USE OF ANESTHETIC AGENTS THAT WERE FLAMMABLE AND GREATLY ENHANCED THE ABILITY OF OUR SURGICAL COLLEAGUES TO DO MORE THINGS FOR MORE PATIENTS WITHOUT THE CONCERNS THAT THE FLAMMABLE AGENTS CAUSED.

UNFORTUNATELY, HUMAN ENTHUSIASM IS RARELY REASONABLY BALANCED. THE DEVELOPMENT OF HALOTHANE, EVEN THOUGH A MAJOR ADVANCE, WAS HALLED AS THE PERFECT ANESTHETIC AGENT; BUT, IT DID NOT TAKE LONG

UNTIL IT WAS EVIDENT THAT IT DID PRODUCE DEPRESSION OF BREATHING, COULD CAUSE CARDIAC ARRHYTHMIAS AND DID INTERFERE WITH CIRCULATORY FUNCTION. THESE DISABILITIES WERE REASONABLY WELL TOLERATED BY THE SCIENTIFIC AND CLINICAL PUBLIC AND THEIR PATIENTS UNTIL REPORTS OF HEPATIC DAMAGE, ALTHOUGH ON RARE OCCASIONS, SEEMED SPECTACULAR ENOUGH TO STIMULATE THE SEARCH FOR REPLACEMENT OF SUCCESSOR DRUGS FOR HALOTHANE.

THE WORK OF VANDYKE AND OTHERS DEMONSTRATED THAT EVEN THE PREVIOUSLY BELIEVED NON-METABOLIZABLE INHALANT DRUGS WERE DEGRADED AND IN THE CASE OF HALOTHANE, PRODUCED DEGRADATION PRODUCTS THAT COULD POSSIBLY EXPLAIN THE TOXIC EFFECTS ON THE LIVER. THE HALOGENATED DEGRADATION PRODUCTS OF OTHER COMPOUNDS, E.G. METHOXYFLURANE, AFFECTED MOSTLY THE KIDNEYS. ACCORDINGLY, IT SEEMED DESIRABLE TO LOOK AGAIN AT THE ETHERS FOR THE DEVELOPMENT OF ANESTHETIC COMPOUNDS THAT HAD LITTLE OR NONE OF THE DISADVANTAGES OF HALOTHANE AND CERTAINLY, NONE OF THE DISADVANTAGES OF THE ORIGINAL DIETHYL ETHER OF MORTON'S DEMONSTRATION WHICH WAS DIGNIFIED BY THE USE OF THE SIMPLE NAME, ETHER, AND UNDERSTOOD BY ALL EVEN TODAY.

WITH THE DEVELOPMENT OF HALOGENATED METHYLETHYL ETHERS, NEW PERCEPTIONS BECAME POSSIBLE. THE FIRST OF THESE, METHOXYFLURANE, WHICH WAS ACCEPTED, TURNED OUT TO BE BIODEGRADABLE AND PRODUCED BOTH RENAL AND HEPATIC INJURY. IT WAS ALSO LESS FLEXIBLE THAN DESIRED.

THE NEXT IMPORTANT TWO COMPOUNDS IN THIS SERIES, ENFLURANE AND

ITS ISOMER, ISOFLURANE WERE DEVELOPMENTS OF GREAT NOTE IN THE DIRECTION OF MINIMIZING TOXICITY AND PROVIDING FOR MANY OF THE DESIRABLE EFFECTS OF GENERAL ANESTHETIC AGENTS.

UNFORTUNATELY, ISOFLURANE WAS DIFFICULT TO SYNTHESIZE AND HAD A MORE CHECKERED CAREER IN ITS EARLY DAYS AFTER ITS ORIGINAL SYNTHESIS BY TERRELL IN 1963, INCLUDING AN EPISODE OF ALLEGED CARCINOGENICITY IN ANIMALS.

ENFLURANE BECAME A SUCCESSOR HALOGENATED COMPOUND AND PROVIDED THE ANESTHESIOLOGIST WITH MUCH OF WHAT HE DESIRED FOR INHALATION ANESTHESIA. WHEN ISOFLURANE'S SYNTHESIS BECAME EASIER AND MORE PRACTICAL, IT WAS USED IN SEVERAL COUNTRIES ABROAD AND THEN FINALLY APPROVED FOR USE IN THE UNITED STATES AND IN CANADA, EARLY IN 1982. ITS POPULARITY AMONG CLINICIANS SEEMED WELL DESERVED; IT TOOK HOLD RAPIDLY.

ISOFLURANE, FROM THE LATEST DATA AVAILABLE IN THE UNITED STATES, IS USED IN MORE THAN FIFTY PERCENT OF ALL INHALATION ANESTHESIAS GIVEN IN OUR COUNTRY IN 1982. WE APPEAR TO BE IN AN ERA OF HALOGENATED INHALATION ANESTHETICS AND ONE IN WHICH NITROUS OXIDE, REINFORCED BY DEFICIENCY CORRECTIVE DRUGS, ARE THE COEXISTENT MAINSTAY, SUCCESSOR TO THE FLAMMABLE AGENTS, ETHER AND CYCLOPROPANE. THIS METHOD TERMED "BALANCED ANESTHESIA" IS ALSO A SUCCESSOR SYSTEM OF NEW NONVOLATILE MATERIALS AND DRUGS TO AN OLDER ONE - BOTH EMPLOYING NITROUS OXIDE.

ACCORDINGLY, WITH THIS SHORT DESCRIPTION OF THE WAY THINGS BEGAN AND ARE EVOLVING, IT SEEMED OF INTEREST TO ME TO EXAMINE WITH YOU SOMETHING ABOUT INHALATION ANESTHESIA IN CONCEPT; WHY IT IS SO IMPORTANT AND WHAT THE PROBLEMS THEN AND NOW WERE AND WHAT SOME OF THEM MIGHT BE FOR THE FUTURE IN ITS FURTHER EVOLUTION.

WE HAVE ALSO EVOLVED IN RECOGNITION TERMINOLOGY. ETHER, OF THE MORTON DAYS, WAS, OF COURSE, DIETHYLETHER. THE ETHER OF OUR PRESENT DAY IS ONE OF TWO METHYLETHYL HALOGENATED ETHERS AND IT IS KNOWN, DEPENDING ON WHICH ISOMER ONE USES AS ENFLURANE OR ISOFLURANE.

I DO NOT CLAIM ORIGINALITY FOR MANY OF THESE VIEWS BUT FEEL IT APPROPRIATE FOR ME TO EXPRESS TO YOU SOME ATTITUDES I HAVE DEVELOPED OVER A LONG CAREER IN OUR SPECIALTY AND SOME OF THE PERSPECTIVES WHICH MAY SEEM STRANGE TO SOME OF OUR YOUNGER COLLEAGUES. I AM GOING TO, NONETHELESS, MAKE AN ATTEMPT TO DEAL WITH THE SUBJECT THAT MOST OF US HAVE TO CONFRONT IN OUR DAILY WORK WITH PATIENTS AND ALWAYS IN THE LIGHT OF CONCEPTUAL ASPECTS OF THE GAINING OF NEW KNOWLEDGE AND THE SYSTEMATIZING OF SUCH DATA WHICH MOST OF US CALL RESEARCH.

THIS QUESTION IS REFLECTED BY INFERENCE IN THE TITLE OF THIS PAPER THAT I HAVE BEEN ASKED TO CONSIDER WITH YOU, I.E. MUCH THOUGHT AND AN ATTEMPT AT PROPHECY AT WHICH I AM NOT GOOD! I HAVE CHOSEN STRAIGHT AWAY TO TELL YOU THAT INHALATION AGENTS ARE HERE TO STAY - AND WILL, IN MY VIEW, OCCUPY A CENTRAL POSITION IN THE FUTURE AS THEY HAVE

IN THE PAST. I HAVE WATCHED ANESTHETISTS WITH GREATER IMAGINATION AND MORE DISTINCTION THAN I HAVE, WRESTLE WITH THE ATTEMPT TO DEFINE "THE IDEAL" ANESTHETIC AGENT. THIS APPROACH HAS ALWAYS, EVEN IN MY REMOTE PAST DAYS, SEEMED TO BE A TOUR DE FORCE, NOT UNLIKE THE SEARCH OF OTHERS IN OTHER CLIMATES OF SPIRITUAL THOUGHT FOR THE HOLY GRAIL. THE SEARCH ITSELF FOR NEW IDEAS IS AN OUTSTANDING STIMULUS TO INNOVATION. THE ACHIEVEMENT OF THE IDEAL WILL ALWAYS BE LIKE MUCH OF THE REST OF THE REAL WORLD, NOT ONLY NOT ACHIEVABLE BUT A STIMULUS TO FURTHER AND RENEWED EFFORT. THE TROUBLE LOOMS WHEN THE FRUITS OF THE SEARCH PROCESS BECOME DOGMA AND ARE BELIEVED BY ALL TO BE ETERNALLY TRUE. THIS NOTION HAS ALWAYS MADE ME WONDER WHY, IN THIS RESPECT AS IN SOME OTHERS, ANESTHESIA SHOULD BE CONSIDERED SO DIFFERENT BY ITS OWN PRACTITIONERS FROM OTHER FIELDS OF MEDICINE. DOES ANYONE SEARCH FOR THE IDEAL AND PERFECT DRUG IN ALL OF CARDIOLOGY? DOES ANYONE DESIGN THE ONLY IDEAL SURGICAL OPERATION FOR A GIVEN DISEASE? DOES ANYONE ATTEMPT TO DESIGN A SINGLE CURE FOR CANCER, DIABETES AND HEART DISEASE? THE ANSWER OF COURSE IS THOSE SCIENTISTS AND PRACTITIONERS TRY TO BE BETTER BUT CAN NOT BE PERFECT. SOMEHOW THE CONCEPT THAT KNOWLEDGE AND CREATIVE APPLICATION OF THAT KNOWLEDGE TO CLINICAL PROBLEMS REQUIRES VARIATION, FLEXIBILITY AND THE TREMENDOUS ABILITY WHICH SO FEW OF US POSSESS PERFECTLY, I.E. LEARNING HOW TO CHANGE WITH THE EXPERIENCES OF APPLYING SCIENTIFIC KNOWLEDGE TO CLINICAL CIRCUMSTANCES AND BEING ABLE TO LEARN FROM CLINICAL EXPERIENCE. WHY ARE THESE IMPERFECTIONS AND APPROACHES SO ACCEPTABLE TO MUCH OF MEDICINE AND SURGERY AND TO ALL OF

SCIENCE AND NOT SO READILY TO ANESTHESIOLOGY?

FOR STARTERS, IT HAS ALWAYS SEEMED TO ME CONCEPTUALLY IRRATIONAL, AS IT HAS TO OTHERS, TO ANESTHETIZE THE ENTIRE BRAIN IN ORDER TO MAKE IT POSSIBLE FOR SOMEONE TO DISSECT ANOTHER PART OF THE BODY OR EVEN THE BRAIN ITSELF. THE REPEATED RESURGENCE OF REGIONAL ANESTHESIA, I THINK, REFLECTS SIMILAR THOUGHTS IN THE MINDS OF OTHERS. WHEN ONE GETS INTO THE ACTUAL EXPERIENCE OF TRYING TO PROVIDE THIS KIND OF CARE FOR PATIENTS WHO REQUIRE SURGICAL PROCEDURES, IT BECOMES APPARENT TO ALL SERIOUS OBSERVERS, BUT CERTAINLY WITH GOOD AND SUFFICIENT REASON, THAT THE SIMPLE PROVISION OF PAIN RELIEF FOR SURGICAL DISSECTION IS NOT WHAT ANESTHESIA IS ALL ABOUT. THERE IS NO DOUBT THAT ANALGESIA IS AN IMPORTANT FACET BUT, IT NOW IS ABUNDANTLY CLEAR AND ACCEPTED WIDELY, THAT IT IS THE TOTAL AND SAFE MANAGEMENT OF A PATIENT UNDERGOING A SURGICAL EXPERIENCE OF WHICH WE ARE TALKING. ACCORDINGLY, THE MANAGEMENT OF LIVING FUNCTIONS, INCLUDING, OF COURSE, RESPIRATION AND CIRCULATION, HEPATIC AND RENAL ACTIVITY, MUST BE TAKEN INTO ACCOUNT WHENEVER ANESTHESIA IS USED FOR ANY PURPOSE.

THE CONTINUED DISCUSSION AND ARGUMENT OF THE MERITS OF INHALATIONAL ANESTHESIA, VERSUS, WHAT IS CALLED BALANCED ANESTHESIA, SEEM TO ME TO IGNORE THE FUNDAMENTALS OF ANESTHETIC CARE FOR PATIENTS UNDERGOING SURGICAL PROCEDURES. THERE IS NO METHOD, NO MATTER WHAT ITS NAME CARRIES, THAT DOES NOT INCLUDE THE PRESENCE OF

A PROTECTED AIRWAY USUALLY WITH A TRACHEAL TUBE, THE MANAGEMENT OF EFFICIENT RESPIRATION, THE ADMINISTRATION OF OXYGEN IN VARYING APPROPRIATE CONCENTRATIONS AND IN THE CASE OF THE BALANCED METHODS, THE ALMOST UNIFORM USE AT PRESENT OF NITROUS OXIDE WITH OXYGEN, EXCEPT UNDER SPECIAL CONDITIONS THROUGH THIS ARTIFICIAL AIRWAY. OTHER AGENTS CAN BE VIEWED AS FUTURE CANDIDATE REPLACEMENTS FOR NITROUS OXIDE INCLUDING "GOD'S OWN AIR" OR OTHER ADMIXTURES OF OXYGEN.

HAVING OVERCOME TO SOME EXTENT, THE INTELLECTUAL HURDLE OF THE FACT THAT AIRWAY MANAGEMENT IS A UNIFORM CONCOMITANT OF ALL GENERAL ANESTHESIA, THE QUERY THEN ARISES AS TO WHAT KIND OF AGENTS SHOULD BE USED THROUGH OR IN THE PRESENCE OF THE OMNIPRESENT AIRWAY, THE CONTROL OF BREATHING AND THE PRESERVATION OF VISCERAL FUNCTION.

## II. THE POSITION OF INHALATION ANESTHETIC AGENTS AS THE MAINSTAY OF GENERAL ANESTHESIA DEFINED IN THIS WAY

IN THE PAST, THE CRITERIA FOR THE IDEAL ANESTHETIC AGENT WERE RELATIVELY SIMPLE. IT SHOULD NOT BE FLAMMABLE, IT SHOULD BE ACCEPTABLE TO PATIENTS, IT SHOULD HAVE NO INFLUENCE UPON VISCERAL FUNCTION, INCLUDING PULMONARY FUNCTION, AND IT SHOULD BE INERT. THESE WERE RALPH WATERS' CRITERIA. MAYBE WE CAN DO A BIT BETTER TODAY. SIMPLY TO MENTION THESE QUALITITES REVEALS A PROGRESSIVE

AWARENESS OF OUR COLLECTIVE IGNORANCE AND THE SOLUTIONS WHICH ARE DEVELOPED FOR THE PROBLEMS ENGENDERED BY THIS IGNORANCE.

FLAMMABILITY OF THE ETHER AND CYCLOPROPANE DAYS GAVE WAY TO HALOGENATION TO SUPPRESS THIS PARTICULAR HAZARD. UNTIL THE OUTSTANDING WORK OF VANDYKE AND HIS ASSOCIATES, FOLLOWED BY THAT OF OTHERS, THE DOGMA WAS BELIEVED THROUGHOUT THE ANESTHESIA WORLD THAT INHALED COMPOUNDS WERE INERT AND EXCRETED UNCHANGED VIA THE LUNGS AND IN SOME POORLY UNDERSTOOD WAY, MOSTLY BY PHYSICAL CHEMICAL ACTION AT CELL SURFACES, APPEARED TO PRODUCE THE ANESTHETIC EFFECTS THAT WERE CLINICALLY DESIRED. WHEN THE ANESTHETIC AGENTS WERE FOUND TO BE LIKE OTHER POTENT DRUGS, CERTAIN ASPECTS OF PHARMACOKINETICS AND BIODEGRADABLE SUSCEPTIBILITIES WERE AVAILABLE FOR VERIFICATION OR DENIAL. A BETTER PERSPECTIVE WAS OBTAINED FOR MANY OF US, IN THAT, WE WERE REQUIRED TO DEFINE OUR CLINICAL GOALS MUCH MORE CLEARLY AND SHARPLY AND TO DESIGN INHALANT, AND FOR THAT MATTER OTHER DRUGS, THAT WOULD SUBSERVE THE BEST INTEREST OF THE PATIENT, ASSUMING THAT THE DRUGS WERE WELL ADMINISTERED AND WELL MANAGED. A NUCLEAR EXPLOSION CAN STILL TAKE PLACE, NO MATTER HOW SKILLFULLY A

WEAPON MAY BE PUT TOGETHER, IF SOME IDIOT PRESSES THE TRIGGER  
BUTTON. THERE IS, THEREFORE, NO SUBSTITUTE FOR SKILLFUL USE OF THE  
MOST POWERFUL DRUGS AVAILABLE IN ANY CLINICAL PRACTICE, I.E.  
ANESTHESIOLOGY.

HAVING MADE THAT FAIRLY OBVIOUS STATEMENT, ONE CAN THEN  
ATTEMPT TO ADDRESS THE QUESTIONS AS TO WHAT CHARACTERISTICS IN THE  
STATE OF OUR PRESENT KNOWLEDGE AND ALSO, OUR PRESENT IGNORANCE ONE  
MIGHT WISH TO SEE INHALATION AGENTS HAVE AS ONE LOOKS TOWARD THE  
FUTURE.

THIS IS NOT TO SAY WE ARE NOT QUITE WELL OFF. WE ARE, BUT, WE  
CAN DO BETTER. WE MUST CONTINUE TO STRIVE TO DEVELOP INHALANT  
AGENTS THAT HAVE A BETTER SAFETY THERAPEUTIC RATIO. IN THE  
MEANWHILE, WE MUST EDUCATE OUR YOUNGER COLLEAGUES TO MINIMIZE THE  
DISADVANTAGES OF THOSE AGENTS WE HAVE TODAY.

WE MUST LEARN WITH VERY GREAT PRECISION, THE FACT THAT APART  
FROM PHARMACOKINETICS, THESE FOREIGN CHEMICALS CALLED INHALATION  
AGENTS HAVE EFFECTS WHICH ARE CLINICALLY UNDESIRABLE AND WE MUST, OF

COURSE, LEARN HOW TO USE THE PRESENT ONES WITH MAXIMUM SKILL AND TO DEVELOP OTHERS THAT WILL HAVE A LESSER DEGREE OF PHARMACOLOGICAL SIDE EFFECTS ON IMPORTANT VISCERAL FUNCTIONS.

IN THE AREA OF PHARMACOLOGICAL DYNAMICS, WE HAVE LEARNED MUCH ABOUT THE SPEED OF INDUCTION AND RECOVERY IN ITS RELATIONSHIP TO THE SOLUBILITY OF THESE AGENTS IN THE BLOOD AND THEIR SUBSEQUENT REDISTRIBUTION AND METABOLISM THROUGHOUT THE REST OF THE BODY. WE HAVE LEARNED ABOUT THEIR EXCRETION. THESE QUALITIES AND CHARACTERISTICS MUST BE STUDIED INTENSIVELY SO THAT OUR EXCELLENT AGENTS OF HALOTHANE, ENFLURANE AND ISOFLURANCE ARE USED WITH MORE INTELLIGENCE AND THAT OUR COLLEAGUES WITH THE APPROPRIATE SKILLS WILL FURTHER REFINE AND DEVELOP NEW COMPOUNDS WHICH MAKE IT EASIER TO BE SAFER WITH OUR PATIENTS. THESE AGENTS, AT LEAST ENFLURANE, APPEAR TO HAVE A LOWER BIODEGRADATION SUSCEPTABILITY THAN OTHERS AND AGENTS MUST BE SOUGHT, IF AT ALL POSSIBLE, THAT HAVE THE CHARACTERISTIC ACTIONS THAT WE WISH, I.E. EITHER NOT BIODEGRADABLE OR SUCH MINIMAL DEGRADATION THAT IT BECOMES A MINOR CLINICAL PROBLEM OR, IN A BURST OF OPTIMISM, METABOLIC PRODUCTS THAT ARE CLINICALLY

GOOD!

ONE MIGHT QUESTION WHETHER THE PRECEPTS THAT HAVE LED TO THE EXQUISITE DEVELOPMENTS IN INHALATION ANESTHESIA ARE STILL VALID. THEY ARE VALID, IN MY VIEW, UNTIL NEWER KNOWLEDGE COMES THAT SAYS THEY ARE NOW INVALID. CHANGE IS INHERENT IN THIS HABIT OF THOUGHT. IT IS OUR JOB TO ENCOURAGE AND ACCEPT CHANGE THAT IS USEFUL AND REJECT CHANGE THAT IS FRIVOLOUS.

THERE ARE THOSE WHO ARE CONCERNED WITH THE POLLUTION OF ANESTHETIC APPARATUS AND OF THE ATMOSPHERE IN WHICH PEOPLE IN SURGICAL THEATRES MUST WORK. THAT PROBLEM HAS TO BE ADDRESSED, IF AT ALL POSSIBLE, IN MAKING THE SUBSTANCES INNOCUOUS EVEN THOUGH AT PRESENT WE ARE DOING VERY MANY THINGS TO ATTEMPT TO REMOVE THEM FROM THE ATMOSPHERE THAT ALL OF US BREATHE IN THE SURGICAL THEATRE. PROBABLY THIS HAZARD IS OVERSTRESSED.

IT IS POSSIBLE TO ENVISAGE FURTHER DEVELOPMENT OF INHALATIONAL AGENTS, WHICH WILL EXCEED THE ADVANTAGES OF THE BALANCED ANESTHETIC APPROACH. THERE IS A "STIFF CHEST" IN SOME PATIENTS WITH BALANCED

ANESTHESIA AND MANY OF THEM EXHIBIT POSTOPERATIVE RESPIRATORY DEPRESSION WHICH MAY BE RECURRENT. THERE ARE PROBLEMS IN BALANCED ANESTHESIA DUE TO LARGE NARCOTIC AND/OR RELAXANT USAGE. THESE CAN BE IMPROVED WITH BETTER INHALATIONAL AGENTS. EGER BELIEVES THAT INSOFLURANE MAY BE THE BEST OF OUR ANESTHETIC AGENTS THUS FAR DEVELOPED. THERE IS NO REASON CONCEPTUALLY, WHY THOSE SUBSTANCES THAT WE PRESENTLY USE INTRAVENOUSLY, E.G. NARCOTICS, MUSCLE RELAXANTS AND HYPNOTICS AND SEDATIVES COULD NOT SERVE AN OVERALL CONCEPT BUILT AROUND THE AIRWAY AND THE MANAGEMENT OF VENTILATION WHICH, BY THE WAY, INCLUDES THE LUNG, AS A DELAY ORGAN FOR THE UPTAKE AND DISTRIBUTION OF ALL OF THESE SUBSTANCES, OXYGEN INCLUDED. THERE WILL BE AN ENHANCEMENT OF FLEXIBILITY IN PROVIDING SUPERB PATIENT CARE.

MANY YEARS AGO, SOME OF MY COLLEAGUES AND I MADE AN IMMATURE APPROACH TO THIS PROBLEM BY ATTEMPTING TO NEBULIZE THIOPENTAL AS PART OF AN ALL-INHALATION SYSTEM. WE NEVER DID GET TO THE QUESTION OF MUSCLE RELAXANTS FOR REASONS WHICH WILL BECOME OBVIOUS IN A MOMENT. IT WAS POSSIBLE, WITH CONSIDERABLE DERRING-DO TO INHALE

THIOPENTAL THROUGH AN ALL-INHALATIONAL SYSTEM IN SOMEWHAT SMALL AMOUNTS. THE pH AND OTHER CHARACTERISTICS OF THIS SUBSTANCE WERE NOT SUFFICIENTLY UNDERSTOOD TO BE MODULATED CORRECTLY AND THE END RESULT WAS SEVERE TRACHEO-BRONCHITIS IN A FEW OF THE SUBJECTS IN THESE EXPERIMENTS, MYSELF INCLUDED. CONCEPTUALLY, THEREFORE, THE NOTION THAT ANY PORTAL OF ENTRY FOR ANESTHETIC DRUGS ANYWHERE OBTAINABLE IN THE BODY IS NOT UNREASONABLE, WAS STRENGTHENED, BUT, IN MY VIEW, IT WOULD BE SO CONVENIENT IF EVERYTHING COULD BE GIVEN BY INHALATION, AT LEAST TO THE MAXIMUM DEGREE POSSIBLE - A GOAL NOT ALTOGETHER REALISTIC. I AM SORRY TO SAY, THIS IS THE FATE OF ALL PERFECT NOTIONS CONCEIVED BY IMPERFECT PEOPLE!

III. WHAT ARE THE GOALS, WHETHER OR NOT THEY ARE ATTAINABLE, THAT WE SHOULD SEEK?

A LIST OF DESIRABLE QUALITIES HAS BEEN DEVELOPED BY OTHERS AS BOTH INTELLECTUAL AND PRACTICAL EXERCISES. AT LEAST TWO OF THE INHALANT DRUGS KNOWN TODAY, I.E. ENFLURANE AND ISOFLURANE APPEAR TO HAVE GAINED WIDESPREAD ACCEPTANCE IF WELL ADMINISTERED - BUT THEY ARE NOT PERFECT - AS IN MY VIEW, NO DRUG CAN BE.

THE OTHER KNOWN AGENTS ALSO HAVE GREAT VALUE - AND SOME DISADVANTAGES.

WE SHOULD ATTEMPT TO DEVELOP, IN THE LIGHT OF OUR PRESENT KNOWLEDGE SEVERAL OF THE FOLLOWING CHARACTERISTICS, IN ADDITION TO THOSE THAT ALL OF US TAKE FOR GRANTED:

- (1) PHYSICAL CHARACTERISTICS - THE AGENT INHALED SHOULD HAVE AN EXTRAORDINARILY LOW SOLUBILITY IN THE BLOOD WHICH WILL PERMIT A RAPID INDUCTION AND RECOVERY BUT, IT MUST HAVE SOLUBILITY ENOUGH TO HAVE AN EFFECT OF CLINICAL IMPORTANCE.
- (2) IT MUST HAVE A HIGH POTENCY WHERE A LOW DOSE CAN PRODUCE THE CLINICAL EFFECTS DESIRED WITH A LOW POLLUTION POSSIBILITY. IT MUST BE FLEXIBLE AND RESPONSIVE TO DOSAGE CHANGE.
- (3) THE INHALANT AGENT SHOULD, PREFERABLY, NOT BE METABOLIZED IN THE BODY OR, IF SUCH IS BIOLOGICALLY IMPOSSIBLE, IT MUST BE CLOSE TO ZERO AS IT CAN BE. IF IT MUST BE METABOLIZED, THE METABOLIC PRODUCTS SHOULD BE SAFE AND MAYBE EVEN BENEFICIAL. SUCH EVENTS ARE KNOWN IN OTHER FIELDS OF PHARMACOLOGY.
- (4) PHARMACOLOGICAL SIDE EFFECTS, I.E. THOSE THAT WE DO NOT DESIRE FOR CLINICAL PURPOSES, MUST BE REDUCED TO A

CONTROLLABLE DEGREE AND PRODUCE BETTER ANALGESIA AT THE  
SAME TIME.

WHAT ARE WE REALLY SAYING?

MY BELIEF IS THAT THE CHARACTERISTICS OF GENERAL AND BALANCED  
ANESTHESIA INDICATE THE NEED FOR A PROTECTED AIRWAY VIA A TRACHEAL  
TUBE, THE MANAGEMENT OF INHALATION AND, THEREFORE, RESPIRATION. NO  
MATTER HOW DRUGS ARE ADMINISTERED, THESE ARE THE BACKBONE FOR MAKING  
INHALATION ANESTHESIA A NECESSARY AND PROBABLY THE MOST IMPORTANT  
METHOD OF PROVIDING SURGICAL ANESTHESIA FOR NOW AND FOR THE FUTURE.

#### IV. CONCLUSION - A VIEW TOWARDS THE FUTURE

IN MY VIEW, WE STILL MUST CONSIDER THE DEVELOPMENT OF  
INHALATION ANESTHETIC AGENTS AS ONE OF TRANSITION - EVEN THOUGH  
IT IS MANY DECADES IN DURATION - SINCE WE DO NOT AS YET HAVE  
SUFFICIENT KNOWLEDGE OF THE PRECISE MECHANISM OF ANESTHESIA AND ARE,  
THEREFORE, UNABLE TO THINK OF A SUITABLE SYSTEM THAT PROVIDES THOSE  
REQUIREMENTS FOR SURGICAL PATIENTS AND FOR THOSE PATIENTS IN OUR  
OTHER AREAS OF INTEREST, E.G. PATIENTS WITH PAIN PROBLEMS AND THOSE  
IN INTENSIVE CARE. THE BASIC SCIENCE SEARCH FOR A BETTER

UNDERSTANDING OF THE MECHANISM OF ANESTHESIA IS AN ABSOLUTE PREREQUISITE FOR THE DESIGN OF ULTIMATE WAYS IN WHICH WE WILL ANESTHETIZE AND TAKE BETTER CARE OF OUR PATIENTS. IT MAY VERY WELL BE, HOWEVER, THAT WE SHALL HAVE A THIRD FAMILY OR A FOURTH OR EVEN A FIFTH FAMILY OF ANESTHETIC AGENTS BEYOND THE GENUS "FLAMMABELLORIUS", THE GENUS "NONFLAMMABELLORIUS" AND ULTIMATELY, HOPEFULLY, THE GENUS "RATIONALABUS"!

AS A GROUP OF SPECIALISTS, WE HAVE INSUFFICIENTLY ACQUIRED THE SCIENTIFIC HABIT OF THOUGHT THAT SAYS THAT WE ARE USING DRUGS, CHEMICALS AND OTHER MATERIALS AS VEHICLES TO TAKE CARE OF PATIENTS. THE EMPHASIS HAS TOO OFTEN BEEN ON THE DRUG DESIGN ITSELF WHICH I VIEW AS A LIMITING FACTOR RATHER THAN AS A FACILITATORY FACTOR IN THE CARE OF PATIENTS. IF THAT POSITION IS REASONABLE, IT IS NEXT NECESSARY AFTER THE RESEARCH FOR UNDERSTANDING THE MECHANISM OF ANESTHESIA TO DEAL WITH THOSE FACTORS WHICH MAKE ANESTHETIC CARE BETTER AND SAFER. THE FIRST AMONG THESE, IN MY JUDGEMENT, IS INDIVIDUALLY TAILORED AND HIGHLY INTELLIGENT EDUCATION OF OUR YOUNG PEOPLE TO USE THE SCIENTIFIC INFORMATION AND CLINICAL EXPERIENCE

MUCH BETTER FOR THEIR CARE OF PATIENTS.

RESEARCH IN THE AREAS OF PHARMACOLOGY, PHYSIOLOGY, BIOCHEMISTRY, BIOMEDICAL ENGINEERING AND MANY OTHER FIELDS IS CRUCIAL TO MAKE IT POSSIBLE FOR US TO DO OUR JOB BETTER, MORE EFFECTIVELY AND MORE COMFORTABLY FOR THE SICK.

IT IS ALSO ESSENTIAL THAT ALL OF OUR TOOLS DESIGNED FOR PATIENT CARE BE MADE MORE RATIONAL, SIMPLER, SO THAT THE CLEAR AND BRILLIANT INTELLIGENCE OF THE PHYSICIAN WHO USES THEM WILL BE THE IMPORTANT ATTRIBUTE AND NOT THE LIMITATION OF THE EQUIPMENT ITSELF.

IN MY OPINION, EQUIPMENT DESIGN AND EQUIPMENT USAGE IS NOW ROUGHLY EQUIVALENT TO THE TIME WHEN AIRCRAFT DESIGN WAS SAFE - BUT PROPELLER DRIVEN PRIOR TO THE JET AGE. EQUIPMENT MUST BE REDESIGNED TO ENABLE SAFER AND BETTER CARE - TO REDUCE THE HAZARD OF EQUIPMENT FAILURE AND, ESPECIALLY, TO REDUCE THOSE MECHANICAL ACCIDENTS DUE TO POOR DESIGN AND HUMAN ERROR WHICH HAVE BEEN SHOWN TO BE IMPORTANT TO PREVENT MISHAPS THAT OCCUR TO PATIENTS. WE MUST, IN SHORT, MAKE IT EASIER TO ADMINISTER ANESTHETIC AGENTS AND TO AVOID ANY MECHANICAL MISCHIEF AND

THUS, ALSO, TO MINIMIZE HUMAN ERROR.

I HAVE BEEN MOST IMPRESSED WITH THE SOPHISTICATION OF MONITORING FUNCTIONS AND THE APPARATUS USED FOR THESE PURPOSES.

I HAVE BEEN SINGULARLY UNIMPRESSED WITH THE FULSOME USE THAT ANESTHESIOLOGISTS MAKE OF THE INFORMATION THAT IS PROVIDED BY THESE DEVICES. A TWIN EFFORT OF BETTER EDUCATION IN THEIR USE AND BETTER DESIGN IS REQUIRED SO THAT THE PHYSICIAN WHO ADMINISTERS ANESTHESIA AND THE SURGEON WHO OPERATES ON PATIENTS ARE AIDED AND NOT IMPEDED BY A HOST OF MACHINES WHICH MAY BE DIVERSIONARY RATHER THAN, AS THEY CAN BE, AIDS TO BETTER CARE.

THE EXTREME URGENCY OF THE SEARCH FOR MORE RATIONALLY BASED ANESTHETIC DRUGS, MACHINES AND OTHER AIDS TO US MUST GO ON SO THAT THEIR FUNCTIONS ENHANCE WHAT WE WISH TO DO IN THE SAME SPIRIT THAT ANTIBIOTICS, FOR INSTANCE, ARE USED TO CONTROL INFECTION. IT WOULD BE A BETTER WORLD IF WE WERE FREE OF INFECTION BUT, IT IS UNREALISTIC TO EXPECT. HENCE, ANTIBIOTICS WILL BE ALWAYS USEFUL. I HAVE SOMETHING OF THE SAME VIEW ABOUT ANESTHETIC AGENTS. IT WOULD BE NICE IF WE COULD INDUCE THOSE REQUIREMENTS FOR ANESTHESIA WITHOUT

THE DRUGS, MACHINES AND APPARATUS THAT HAVE THE POTENTIALITY FOR PROBLEM PRODUCTION, AS WELL AS, FOR EFFECTIVE CLINICAL USE. THAT TOO IS NOT THE REAL WORLD AND WE MUST GO ON WITH WHAT WE CAN.

ESPECIALLY FOR THE YOUNGER PEOPLE TO WHOM I AM PRIVILEGED TO TALK TODAY - THE OPPORTUNITY OF DEVELOPING NEW KNOWLEDGE THAT WILL BE CONSTRUCTIVE IN OUR CARE OF PATIENTS, IS ENORMOUS. IT DOES REQUIRE HARD WORK, CREATIVITY AND AN EMPATHETIC VIEW OF OUR SCIENTIFIC COLLEAGUES' WORK AS WELL AS OUR OWN. IMPROVEMENT IS ALWAYS POSSIBLE. PERFECTION, I THINK, WILL NOT OCCUR IN OUR LIFETIME OR, PERHAPS, ANYBODY ELSE'S LIFETIME BUT, THAT MAKES IT ALL THE MORE FUN TO TRY TO GET AS CLOSE AS WE CAN TO THAT STATE OF PERFECTION AS OUR MINDS, OUR WORK AND OUR CARING PERMIT. YOU ARE FORTUNATE THAT YOU LIVE IN A WORLD WHERE SO MUCH OPPORTUNITY TO MAKE THINGS BETTER EXISTS.

ONE OF YOUR LEADERS IN THAT FAMOUS PLACE CALLED "ELSEWHERE" WAS OF THE OPINION THAT OUR MISSIONS IN ANESTHESIOLOGY HAVE BEEN LARGELY ACCOMPLISHED. I BELIEVE THEY HAVE ONLY BEGUN.