THE OPPORTUNITY AND CHALLENGE OF MOLECULAR AND CELLULAR BIOLOGY FOR ANESTHESIOLOGY

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THIS AUDIENCE HAS BEEN PRIVILEGED TO LISTEN TO A GROUP OF PAPERS ON THE MECHANISM OF ANESTHESIA THAT WERE EXCITING, INTERESTING AND UP TO THE STATE OF THE ART OF OUR FIELD. IT WOULD SEEM TO BE PRESUMPTUOUS FOR A MORE SENIOR PERSON IN OUR SPECIALITY - AS AMERICANS MIGHT TERM IT - A SENIOR CITIZEN - TO COMMENT ON THIS MOST ADVANCED ASPECT OF OUR SPECIALTY AS AN EXPERT. THIS QUALIFICATION I DO NOT POSSESS.

IT IS MY INTENTION TO EXAMINE IN A FUNDAMENTAL AND AS SOME MIGHT THINK OF IT, A PHILOSOPHICAL WAY, THE VARIOUS REASONS WHY WE HAVE BOTH PROBLEMS AND OPPORTUNITIES IN THIS PARTICULAR FIELD DESIGNED TO ELUCIDATE THE MECHANISM OF ANESTHESIA.

IT IS REALLY QUITE STARTLING WHEN ONE THINKS OF IT, THAT FOR APPROXIMATELY 140 YEARS OR SO, THE MAJOR DISCOVERY OF ANESTHESIA HAS BEEN EXPLOITED AND DEVELOPED IN THE MOST SOPHISTICATED OF WAYS TO PROVIDE PAIN RELIEF FOR PATIENTS AND EXCELLENT OPERATING CONDITIONS FOR SURGEONS AND YET THE PROCESS MUST STILL BE CONSIDERED IN THE FINAL ANALYSIS, EMPIRICAL.

THE MANY THEORIES WHICH HAVE BEEN PROPOSED TO EXPLAIN THE MECHANISM OF ANESTHESIA IN PAST YEARS CONSIST IN UNDERSTANDING LARGELY THE EITHER PHYSICAL OR CHEMICAL CHARACTERISTICS OF THOSE SUBSTANCES WHICH ARE KNOWN TO PRODUCE THE NET EFFECT WHICH WE CALL THE ANESTHETIC STATE AND TO ATTEMPT TO REASON BACKWARDS, SOMETIMES SIDEWARDS, BECAUSE OF THESE COMMON PROPERTIES

AS TO WHAT REALLY MIGHT BE HAPPENING TO CAUSE THE PHENOMENON OF ANESTHESIA. WE HAVE LOOKED MORE AT OUR AGENTS, TO TRY TO UNDERSTAND THESE MECHANISMS AND LESS AT THE MECHANISMS OF THE DISRUPTION OF CELLULAR COMMUNICATION UNTIL RECENT YEARS FOR EXPLANATIONS.

WITH THE MOST RECENT APPLICATIONS OF A FIELD KNOWN AS MOLECULAR OR CELLULAR BIOLOGY TO MANY OF US, THERE APPEARS TO BE A VAST PROMISE FOR THE FIRST TIME OF ELUCIDATING WHAT HAPPENS.

I WOULD STRONGLY SUGGEST, HOWEVER, THAT WE LOOK AT AS MANY VIEWS OF THIS POSSIBILITY AND QUESTION AS WE CAN. IT IS CONCEIVABLE, ALTHOUGH FAR FROM CERTAIN, THAT WHAT WE SHOULD BE STUDYING IS THE PROCESS BY WHICH THE COMMUNICATION BETWEEN CELLS IN THE CENTRAL NERVOUS SYSTEM IS EITHER DISRUPTED OR ALTERED IN SUCH A WAY AS TO PRODUCE THE STATE WE COMMONLY APPRECIATE TO BE ANESTHETIC.

I SHALL NOT ATTEMPT TO REVIEW THE VARIOUS THESES OF THE PAST NOR OF THE CUTTING EDGE OF THE WORK GOING ON AT THE PRESENT AS EXAMPLES OF HOW OPTIMISTIC WE MAY HAVE A RIGHT TO BE. I SHALL ATTEMPT RATHER TO BE OBSERVANT IN AS DETACHED A WAY AS POSSIBLE AND OPTIMISTIC BECAUSE I BELIEVE NATURE IS GRUDINGLY AND RELUCTANTLY, BUT NONETHELESS, STEADILY ALLOWING US TO UNDERSTAND MORE OF HER SECRETS. IT IS ENTIRELY BELIEVABLE TO ME THAT THE WAY IN WHICH CELLULAR COMMUNICATION IS CHANGED BY THOSE SUBSTANCES THAT PRODUCE ANESTHESIA MAY COME INTO UNDERSTANDING IN THE NOT TOO DISTANT FUTURE.

LIKE ALL AGES OF SCIENCE, INCLUDING WHAT LEWIS THOMAS CALLS THE YOUNGEST SCIENCE, I.E., MEDICINE, WE ARE NOT SHORT IN SUPPLY OF INDIVIDUALS

COMPETENT TO MAKE THESE DISCOVERIES. IN FACT, IN MY JUDGMENT, GREAT ABILITIES ARE COMMON, BUT GREAT ACHIEVEMENTS ARE RARE. IT IS A REMARKABLE THING TO CONTEMPLATE THAT, IN ALL OF OUR AGES THERE HAVE ALWAYS BEEN MINDS THAT ARE EXTRAORDINARY AND SOMEHOW THERE HAS TO BE SOMETHING IN THE ENVIRONMENT THAT MAKES THE GREAT MIND ABLE TO COPE WITH AND TO MAKE THE GREAT DISCOVERY. I BELIEVE THAT WE ARE IN SUCH A PERIOD AT PRESENT AND THIS IS PARTIALLY THE REASON FOR MY OPTIMISM. THERE IS UNDOUBTEDLY AN EINSTEIN, A SHAKESPEARE, AND A MICHELANGELO ALIVE TODAY AND POSSIBLY ONE OF THESE WILL BE INTERESTED IN SOLVING THE MOLECULAR ASPECT OF THE PROBLEM IN ANESTHESIA. HE MAY BE IN THIS ROOM.

PERHAPS THE FIRST COMMENTARY ABOUT MOLECULAR BIOLOGY IS WHAT IS IT AND WHY DOES IT OFFER SUCH HOPE AS MANY BELIEVE. ONE COULD, OF COURSE, TAKE THE POSITION THAT THE DISTINGUISHED SCIENTIST IN THE STUDY OF LIFE, PROFESSOR ERWIN CHARGAFF, HAS STATED "MOLECULAR BIOLOGY IS THE PRACTICE OF BIOCHEMISTRY WITHOUT A LICENSE." THIS IS A SOMEWHAT, PERHAPS TOO CYNICAL, VIEW OF IT, BUT IT DOES MAKE THE SUGGESTION THAT THIS FIELD THAT WE BELIEVE TO BE SO NEW REALLY IS AN EXTENSION OF BIOCHEMISTRY WHICH IN ITS ULTIMATE ASPECT, ALSO INCLUDES THAT INTERESTING JUNCTURE WHERE CHEMISTRY AND PHYSICS ARE INDISTINGUISHABLE AND THAT ALSO APPLIES TO THE STUDY OF CELL FUNCTION.

WITHOUT NECESSARILY PARTICIPATING IN THE JUDGMENT AS TO THE VALIDITY OF THIS PARTICULAR NOTION, THERE IS A CONCEPTUAL IMPORTANCE THAT MAY BE OF VALUE TO US IN PENETRATING THE NOTION OF THE CHALLENGE AND THE OPPORTUNITY FOR MOLECULAR BIOLOGY IN ANESTHESIA.

WE SHOULD CONSIDER THE CONCEPT OF ENTROPY IN THIS REGARD. I AM NOT

ASHAMED TO SAY THAT I DID NOT HAVE ANY IDEA OF THE POTENTIAL IMPORTANCE OF THIS CONCEPT TO THE SUBJECT WE ARE NOW DISCUSSING UNTIL RECENTLY. ENTROPY IS THAT STATE IN WHICH THERE IS A DIMINISHED CAPACITY FOR SPONTANEOUS CHANGE. IT IS IN THE MINDS OF PHYSICISTS, ALSO, THE MEASURE OF THAT PART OF THE HEAT OR ENERGY OF A SYSTEM WHICH IS NOT AVAILABLE TO PERFORM WORK. ENTROPY INCREASES IN ALL NATURAL (SPONTANEOUS AND IRREVERSIBLE) PROCESSES. IN A SENSE, THIS IS A DOWNHILL RUN OF ENERGY AND IT MAY VERY WELL BE THAT PEOPLE WHO STUDY MOLECULAR BIOLOGY AND CELL FUNCTION WILL FIND SOME USE IN THIS IDEA BECAUSE THE STUDENTS OF INFORMATION THEORY ARE ATTRACTED BY LOOKING AT THE CONCEPTS OF ENTROPY IN CONNECTION WITH CELLULAR COMMUNICATION. FOR INSTANCE, RECENTLY AT LOS ALAMOS NATIONAL LABORATORY IN NEW MEXICO, THE IDEA WAS PROPOSED THAT A CHANGE IN THE COMMUNICATION OF NERVE CELLS WITH EACH OTHER AT THE SYNAPSES COULD OCCUR IN A SOMEWHAT DIFFERENT WAY. LAYNE AND SCOTT PROPOSED THAT BARBITURATES DISRUPT THE FLOW OF ENERGY ALONG PROTEIN MOLECULES. THEY SUGGEST THAT WEAK HYDROGEN BONDS ARE FORMED BETWEEN A BARBITURATE MOLECULE AND AN ADJACENT PROTEIN STRAND. THEY ALSO FURTHER SUGGEST THAT THIS PARTICULAR WEAK BONDING DISTURBS THE PROPAGATION OF SINGLE ISOLATED WAVES CALLED SOLITONS ALONG THE PROTEIN'S BACKBONE.

THAT FOR ME WAS DIFFICULT TO UNDERSTAND. MORE KNOWLEDGEABLE PEOPLE AMONG YOU MAY HAVE LESS TROUBLE. THE MAIN NOTION, AT PRESENT, THAT WE NEED TO UNDERSTAND IS THAT THE PROPAGATION OF SINGLE ISOLATED WAVES, WHICH IS WHAT SOLITONS ARE, APPEAR NORMALLY TO TRAVEL AS CONCENTRATED VIBRATIONAL ENERGY PULSES ALONG THE HYDROGEN BONDAGE SITES OF ALPHA-HELICAL PROTEINS.

WHEN AN ANESTHETIC MOLECULE THAT CONTAINS THE APPROPRIATE CONFIGURATION APPROACHES THIS PROTEIN, NEW HYDROGEN BONDS FORM THAT SHIFT A SECTION OF THE PROTEIN'S SPINE AND IMPEDE THE ABILITY OF A PROTEIN TO CONDUCT SOLITONS. THIS INTERACTION REDUCES ENERGY TRANSFER ALONG THE PROTEIN MOLECULE IN THE SAME WAY THAT A LEAK REDUCES FLOW IN A PLUMBING SYSTEM. THIS IS APPARENTLY A SPECIALIZED FORM OF THE RUNNING DOWN OF ENERGY OR ENTROPY.

THE INTRIGUING PART ABOUT THESE KINDS OF ALPHA-HELICAL PROTEINS IS THEY APPEAR TO PLAY AN IMPORTANT ROLE IN COMMUNICATION BETWEEN A NERVE CELL'S INTERIOR AND ITS EXTERNAL ENVIRONMENT. THEY, IN ADDITION, FORM PARTS OF BUNDLES OF FILAMENT-LIKE PROTEINS WHICH EXPAND THE MEMBRANES AND CLOSE IN THE CELLS. THE MEMBRANE IMBEDDED STRUCTURES DO PROTRUDE FROM CELL WALLS AND APPARENTLY CAN BE INFLUENCED BY CHEMICALS OUTSIDE THE CELL. VARIOUS SUBSTANCES LIKE HORMONES AND POSSIBLY OTHER MATERIALS STIMULATE THESE PROTEINS AND SIGNAL THEIR PRESENCE TO THE CELL'S INTERIOR ALWAYS BY THE WAY OF SOLITONS THAT CARRY ENERGY INTO OR OUT OF THE CELLS. IN THIS CONCEPT, ANESTHETICS CAN ALTER THE SIGNALING PROCESS AND THEREFORE DO IT BY INTERFERING WITH SOLITON PROPAGATION. IT IS ALSO POSSIBLE, ACCORDING TO LAYNE AND SCOTT, THAT SOLITONS CAN BE A MEANS FOR TRANSFERING ELECTRONS FROM AN ELECTRON DONOR TO AN ACCEPTOR OVER LONG DISTANCES. THESE ELECTRON CARRYING SOLITONS MAY INFLUENCE THE WAY MEMBRANES PUMP CHARGES TO MAINTAIN A GRADIENT OF ELECTRICITY ACROSS THE MEMBRANE. TO QUOTE THEM, THEY STATE THAT "WITH THIS VIEW, ANESTHESIA CAN BE UNDERSTOOD IN TERMS OF A LOSS OF BOTH VIBRATIONAL AND GRADIENT ENERGIES" - AN ASPECT APPLIED TO ANESTHESIA

OF THE NOTION OF ENTROPY.

THERE IS, OF COURSE, WITH MANY ENCHANTING IDEAS A GREAT DIFFICULTY. NO ONE HAS ACTUALLY OBSERVED A SOLITON IN CHEMICAL SYSTEMS. IT IS THEORETICALLY POSSIBLE THAT WITH ENOUGH ENERGY PROVIDED, ALPHA-HELICAL PROTEINS CAN MAINTAIN THE SOLITON, BUT THEY HAVE NOT BEEN SEEN. THE QUESTION THAT LAYNE IS ADDRESSING IS WHETHER A NORMAL AMOUNT OF BIOLOGICAL ENERGY IS SUFFICIENT TO FORM A SOLITON. THE NEXT PHASE IN THIS KIND OF WORK IS TO FIND OUT WHETHER THERE ARE SOLITONS IN BIOLOGICAL SYSTEMS.

ONE COULD TAKE A CYNICAL VIEW OF THESE TREMENDOUS EFFORTS AND AGREE WITH GEORGE BERNARD SHAW WHEN HE SAID THAT "SCIENCE IS ALWAYS WRONG. IT SOLVES PROBLEMS ONLY TO REPLACE THEM BY OTHERS." OF COURSE, THE NATURE OF SUPERB SCIENCE IS TO DO EXACTLY WHAT SHAW WAS CRITICAL ABOUT. THE MORE WE KNOW, THE MORE WE REALIZE THERE STILL IS LEFT TO LEARN FROM NATURE.

ONE OF THE PROBLEMS WE ARE UNDERGOING IS THE DEFINITE URGE ON THE PART OF COMPETENT SCIENTISTS IN THIS FIELD TO DO WHAT THEY HAVE ALWAYS DONE IN OTHER FIELDS AND THAT LEADS TO A DIFFICULTY.

THE PROPOSAL TO ELUCIDATE THE METHOD OF CELLULAR COMMUNICATION AS ONE OF THE EXPLANATIONS AND PERHAPS THE ONLY ONE OF THE ANESTHETIC PROCESS CAN BE FRAUGHT WITH DIFFICULTY. IN FACT, SIR FRANCIS BACON RECOGNIZED THAT MANY EXPERIMENTS SHOULD NOT BE EXPECTED TO LEAD TO PRACTICAL RESULTS. INDEED HE SAYS, "SCIENTISTS SHOULD BE WILLING TO CARRY OUT A VARIETY OF EXPERIMENTS WHICH ARE OF NO USE IN THEMSELVES, BUT SIMPLY SERVE TO DISCOVER CAUSES AND AXIOMS; WHICH I CALL EXPERIMENTA LUCIFERA, EXPERIMENTS OF LIGHT TO DISTINGUISH THEM FROM THOSE WHICH I CALL FRUCTIFERA, EXPERIMENTS OF

FRUIT."

"NOW EXPERIMENTS OF THIS KIND," HE CONTINUES, "HAVE ONE ADMIRABLE PROPERTY AND CONDITION: THEY NEVER MISS OR FAIL FOR SINCE THEY ARE APPLIED, NOT FOR THE PURPOSE OF PRODUCING ANY PARTICULAR EFFECT, BUT ONLY OF DISCOVERING THE NATURAL CAUSES OF SOME EFFECT, THEY ANSWER THE END EQUALLY WELL WHICHEVER WAY THEY TURN OUT, FOR THEY SETTLE THE QUESTION."

ONE MIGHT SERIOUSLY QUESTION WHY SOMEONE LIKE ME WITHOUT CREDENTIALS IN THIS FIELD WOULD BE ADVISING, SUGGESTING AND PERHAPS ADMONISHING THE EXPERTS ABOUT VARIOUS ASPECTS OF THE CHALLENGES AND OPPORTUNITIES OF MOLECULAR BIOLOGY. I CAN ONLY SUGGEST IN THE WORDS OF SIR FRANCIS BACON AGAIN, THAT THERE HAS TO BE SOMEBODY WHO "RANG THE BELLS WHICH CALLED THE WITS TOGETHER." I HOPE THIS WILL BE VIEWED IN THAT SPIRIT.

ONE CAN AGREE WITH THE DISTINGUISHED RENAL PHYSIOLOGIST, HOMER SMITH, MY GREAT TEACHER WHEN I WAS VERY MUCH YOUNGER, WHO STATED OPTIMISTICALLY "I WOULD DEFINE MECHANISM, AS WE USE THE WORD TODAY, AS DESIGNATING THE BELIEF THAT ALL THE ACTIVITIES OF THE LIVING ORGANISM ARE ULTIMATELY TO BE EXPLAINED IN TERMS OF ITS COMPONENT MOLECULAR PARTS. THIS WAS DESCARTES' GREATEST CONTRIBUTION TO PHILOSOPHY. ABANDON CARTESIAN MECHANISM AND YOU WILL CLOSE UP EVERY SCIENTIFIC BIOLOGICAL LABORATORY IN THE WORLD AT ONCE, YOU WILL TURN BACK THE CLOCK BY THREE FULL CENTURIES."

THEREFORE, WE CONTINUE TO STRUGGLE WITH THESE IDEAS HOPING TO FIND THE MECHANISM THAT IS TRUE FOR ALL FUNCTION AND IN SMITH'S VIEW IT WAS APPROPRIATE TO EXAMINE INANIMATE AS WELL AS ANIMATE OBJECTS FOR

ENLIGHTENMENT. TO VIEW IT IN ITS MORE OPTIMISTIC SENSE IN THE "LIVES OF A CELL," THE DISTINGUISHED SCIENTIST/WRITER LEWIS THOMAS STATES "THERE ARE PIECES OF EVIDENCE THAT WE HAVE HAD IT THE WRONG WAY ROUND. MOST OF THE ASSOCIATIONS BETWEEN THE LIVING THINGS WE KNOW ABOUT ARE ESSENTIALLY COOPERATIVE ONES, SYMBIOTIC IN ONE DEGREE OR ANOTHER; WHEN THEY HAVE THE LOOK OF ADVERSARIES, IT IS USUALLY A STANDOFF RELATION, WITH ONE PARTY ISSUING SIGNALS, WARNINGS, FLAGGING THE OTHER OFF." THE EXTENSION OF THIS NOTION, ALTHOUGH THOMAS CLEARLY COULD NOT HAVE IT IN MIND IS THERE MAY BE SOME ACCOMMODATION THAT IS TAKING PLACE BETWEEN THE EXTERNAL IATROGENIC ADMINISTRATIONS OF APPARENTLY FOREIGN SUBSTANCES WHICH WE CALL ANESTHETIC AGENTS TO INDUCE A BIOLOGICAL CHANGE FOR THE WELFARE OF THE PATIENT. THIS IS, OF COURSE, ANOTHER KIND OF SYMBIOSIS IN WHICH THE CHANGES IN CELLULAR COMMUNICATION MUST BE VIEWED AS AN ACCOMMODATION THAT IS TEMPORARY, TRANSIENT AND FOR THE GOOD OF THE PATENT EVEN THOUGH IT WAS NOT DESIGNED BY NATURE TO FUNCTION THIS WAY. THOMAS GOES ON TO SAY IN ANOTHER SECTION OF THIS DELIGHTFUL BOOK, THE OPTIMISTIC VIEW THAT ALL IS RUGGED IN NATURE AND THAT A GOOD CASE CAN BE MADE FOR STRENGTH FOR SURVIVAL. I EXTEND THIS NOTION TODAY TO YOU TO SUGGEST THAT IT IS APPROPRIATE AS WELL TO PURSUE OUR ATTEMPTS TO UNDERSTAND AND MODIFY MOLECULAR ACTION IN THE CENTRAL NERVOUS SYSTEM BY EXTERNAL AND FOREIGN SUBSTANCES KNOWN AS ANESTHETIC AGENTS.

THERE IS AN AREA WITHIN OUR OWN CELLS, THE GROUP OF ORGANELLES KNOWN AS MITOCHONDRIA WHICH ILLUSTRATE THIS HABIT OF THOUGHT FURTHER.

THE MITOCHONDRIA ARE IN THE INTERIOR OF THE CELLS. THEY DRIVE THEM. THEY PROVIDE THE ENERGY THAT SENDS OUT MESSAGES FOR OUR BENEFIT. BUT AS

THOMAS SAYS IN A STRICT SENSE, THEY ARE NOT OURS. "THEY TURN OUT TO BE SEPARATE CREATURES, THE COLONIAL POSTERITY OF MIGRANT PROKARYOCYTES, PROBABLY PRIMITIVE BACTERIA THAT SWAM INTO ANCESTRAL PRECURSORS OF OUR EUKARYOTIC CELLS AND STAY THERE. EVER SINCE, THEY HAVE MAINTAINED THEMSELVES AND THEIR WAYS REPROCATING IN THEIR OWN FASHION, PRIVATELY, WITH THEIR OWN DNA AND RNA QUITE DIFFERENT FROM OURS. THERE ARE AS MUCH SYMBIONTS AS THE RHIZOBIAL BACTERIA IN THE ROOTS OF BEINGS. WITHOUT THEM WE COULD NOT MOVE A MUSCLE, DRUM A FINGER, THINK A THOUGHT."

THIS IS ONE OF THE DIRECTIONS THAT WE SHOULD THINK MORE ABOUT. SINCE THE MITOCHONDRIA HAVE FIGURED A WAY OF BECOMING PERMANENT INHABITANTS IN OUR CELLS, AND IT TURNS OUT FOR OUR OWN GOOD, COULD WE, AND SHOULD WE LOOK MORE CLOSELY TO THE INFLUENCES OF WHAT WE ACCOMPLISHED FOR THE GOOD OF OUR PATIENTS BY ATTEMPTING TO HAVE THESE SMALL CREATURES, ALREADY DESIGNED BY NATURE, TO BE BENEFICIAL TO US TO CONTINUE TO DO SO WHEN MODIFIED ARTIFICIALLY UNDER OUR CAREFUL, GENTLE AND SUPPORTIVE ADMINISTRATIONS.

THERE IS A CONCEPT THAT WE SOMEHOW OR ANOTHER MUST ADDRESS. THERE IS IN THE MOST RECENT YEARS, IN FACT, JUST THE LAST DECADE OR SO A HUGE MASS OF INCREDIBLE AND IMPORTANT INFORMATION IN WHAT WE ARE CALLING MOLECULAR BIOLOGY. THERE ARE POWERFUL PIECES OF INFORMATION TO EXPLAIN IN GREAT DETAIL, THE PROCESS OF LIFE ITSELF AND HOW IT IS PRESERVED AND ADVANCED. UNFORTUNATELY, THIS VAST AND EXPANSIVE KNOWLEDGE AND TECHNOLOGY HAS NOT, AS MANY OF US SEE IT, BEEN ACCOMPANIED BY SIMILAR ADVANCES IN THE APPLICATION OF THIS KNOWLEDGE. WE KNOW SO MUCH MORE ABOUT MOLECULAR BIOLOGY AND SO RELATIVELY LITTLE MORE ABOUT HOW TO APPLY THIS KNOWLEDGE TO PATIENTS

WITH DISEASE OR IN THE CASE OF OUR SPECIALTY, TO ALTERING THE STATE OF MOLECULAR FUNCTION FOR THE BENEFIT OF SICK PEOPLE.

WHEN ONE DESPAIRS, IT IS NECESSARY TO REMIND OURSELVES, AS WELL AS OUR PUBLIC, THAT TO BE OPTIMISTIC ABOUT THE SITUATION, WE MUST RECALL THAT WITHOUT FUNDAMENTAL KNOWLEDGE NOTHING WILL TAKE PLACE. WITH THE FUNDAMENTAL KNOWLEDGE, WHICH NOW EXISTS, SOMETHING MAY TAKE PLACE WHEN THERE ARE THE CONNECTIONS MADE BETWEEN THIS KNOWLEDGE AND THE INTERRUPTION OF FUNCTION DELIBERATELY ORGANIZED AS IN OUR CASE OR IN THE CASE OF OTHERS, DISRUPTED BY EVENTS OF NATURE LIKE INFECTION.

IT REQUIRES US ONCE AGAIN TO EXAMINE REALLY THE DIFFERENCE BETWEEN SCIENCE THAT IS APPLIED AND BASIC. MANY OF US, AND I HAVE BEEN AMONG THEM, BELIEVED FOR A LONG TIME THERE IS ONLY THE DIFFERENCE BETWEEN GOOD AND BAD SCIENCE.

I HAVE COME TO REALIZE THAT THIS IS AN EXTRAORDINARILY NAIVE AND IMMATURE VIEW.

THE BASIC DIFFERENCE BETWEEN THESE TWO CONCEPTS IS THE WAY IN WHICH CONCEPTUALLY THE RESEARCH IS ORGANIZED. IF ONE WISHES TO DO SOMETHING IMPORTANT IN THE AREA OF APPLIED SCIENCE, IT REQUIRES A HIGH DEGREE OF KNOWLEDGE THAT IS VERIFIABLE AT THE OUTSET. THE PROTOCOLS FOR RESEARCH MUST BE CLEAR, LACED WITH HARD FACTS AND WITH DISTINCT AND CLEAR MEANING. THE WORK AND THE WORKERS MUST BE ORGANIZED UNDER A CENTRAL AUTHORITY WITH DETAILED TIME SCHEDULES AND AN APPROPRIATE REWARD SYSTEM. HOWEVER, MOST IMPORTANT OF ALL, THE BASIC FACTS MUST BE KNOWN TO BEGIN WITH AND THEY COME FROM BASIC RESEARCH. IN THE AREA OF BASIC RESEARCH, SURPRISE IS AN IMPORTANT ELEMENT. EVERYTHING IS

QUITE DIFFERENT FROM THAT OF APPLIED RESEARCH. AT THE OUTSET, A HIGH DEGREE OF UNCERTAINTY IS PRESENT, OTHERWISE, IT ISN'T LIKELY AS THOMAS POINTS OUT TO BE AN IMPORTANT PROBLEM. THERE IS AN INCOMPLETE LIST OF FACTS, THERE IS AMBIGUITY. THE PROBLEM CONSISTS FREQUENTLY OF DISCOVERING CONNECTIONS WHERE POSSIBLE BETWEEN BITS OF INFORMATION THAT APPEAR TO BE UNRELATED. EXPERIMENTS MUST BE PLANNED ON THE BASIS OF POSSIBILITY OR PROBABILITY AND CERTAINLY NOT FOR CERTAINTY. IF AN EXPERIMENT TURNS OUT THE WAY ONE PREDICTS IT, IT IS NICE, BUT IT IS REALLY A GREAT EVENT ONLY IF A SURPRISE EMERGES. THOMAS BELIEVES, AND I SHARE THIS VIEW, THAT ONE CAN MEASURE THE QUALITY OF THE WORK BY THE INTENSITY OF ASTONISHMENT. NO MATTER HOW IT TURNS OUT, THE SCIENTIST WINS, AND PROGRESS IS MADE.

WE ARE NOW IN THE POSITION OF HAVING THIS VAST ARRAY OF EXCITING, IMPORTANT INFORMATION ABOUT HOW CELLS INFORM EACH OTHER ABOUT FUNCTION. OUR TASK, IT SEEMS TO ME, IS TO BE ABLE SOMEHOW TO PENETRATE THAT VAST ARRAY OF ACCOMPLISHMENT WITH APPROPRIATE QUESTIONS THAT CAN TELL US HOW THESE POWERFUL AND IMPORTANT DRUGS WE USE WORK TO IMPACT ON THE NORMAL FUNCTION OF THESE CELLULAR SYSTEMS. THAT, IT SEEMS TO ME, IS THE TASK FOR THOSE WHO ARE INTELLECTUALLY, PHYSICALLY AND EMOTIONALLY QUALIFIED TO ADDRESS THE SUBJECT.

AT SOME POINT, I BELIEVE WITH GREAT OPTIMISM, AN INTELLECTUAL GIANT - UNDOUBTEDLY NOT A COMMITTEE OF GIANTS - WILL SEE THE CONNECTIONS THAT ARE SO ELUSIVE AT THE MOMENT. WHEN THE MECHANISM OF ANESTHESIA OR THE WAY IN WHICH CELLS INFORM EACH OTHER IS BETTER UNDERSTOOD, THE NEXT ASPECT OF PROGRESS IS POTENTIALLY IN OUR HANDS - ESPECIALLY IF WE USE ANESTHETIC

ACTIVITY AS A TOOL IN THE STUDY OF LIFE - AND TRY TO COMPREHEND THE INFORMATION THAT NATURE WILL GRADUALLY REVEAL.