AAAS Talk
February 1976 ✓

BIOLOGISTS HAVE ACHIEVED SO MUCH IN THE LAST CENTURY, AND PARTICULARLY IN THE LAST TWENTY-FIVE YEARS, THAT YOU MAY WONDER WHY I CHOSE TO TALK ~~TODAY~~ ABOUT THE FUTURE RATHER THAN CONCENTRATE ON THE PRESENT. ESPECIALLY AT MY AGE, AT THE THRESHOLD OF RETIREMENT, IT WOULD SEEM MORE APPROPRIATE TO SUM UP THE ACHIEVEMENTS THAT I HAVE BEEN LUCKY ENOUGH TO WITNESS RATHER THAN TRYING TO FORECAST WHAT OTHERS WILL BE DOING AFTER MY TIME.

MY REASONS FOR CONCENTRATING ON THE FUTURE RATHER THAN THE PAST ARE TWO. THE FIRST ~~AND~~ IS A GENERAL ONE, WHICH I CAN BEST EXPRESS IN THE WORDS OF BERTRAND RUSSELL: "IT IS IMPORTANT TO CARE IMMENSELY ABOUT THINGS THAT ARE GOING TO HAPPEN AFTER ONE IS DEAD." WHAT RUSSELL MEANT, OF COURSE, IS THAT THE TEST OF ONE'S HUMANITY IS TO IDENTIFY, NOT WITH ONE TIME OR ONE GROUP OR ONE JOB, BUT WITH THE CONTINUITY OF THE ~~INTELLECTUAL~~ ENTERPRISE OF MANKIND. SUCH BELIEF WAS SURELY PART OF THE SECRET OF LONG LIFE THAT MADE RUSSELL LIVE TO BE A STURDY 98!

MY SECOND REASON FOR LOOKING AT THE FUTURE IS THAT THERE HAS RECENTLY BEEN A CERTAIN GLOOM IN THE WORLD OF BIOLOGY. IT MAY JUST BE THE GLOOM THAT FOLLOWS EVERY SURFEIT OF SUCCESS, BUT IT MUST BE TAKEN SERIOUSLY BECAUSE IT MAY BE ~~IS~~ AN EVE OF AN UNHEALTHY SITUATION.

ON THE ONE HAND, THERE ARE THE PROPHETS OF DOOM, WHO TELL US THAT ALL THAT WAS EXCITING TO SOLVE IN BIOLOGY HAS BEEN SOLVED: THAT, ALAS, NO NEW COSMIC LAWS HAVE BEEN DISCOVERED; AND THAT ALL THAT REMAINS TO BE DONE IS TO MOP UP -- EXCEPT PERHAPS FOR EXPLAINING THE HUMAN BRAIN. A SMALL ORDER INDEED; LIKE SAYING THAT, HAVING LEARNED TO CLIMB BEACON HILL, ALL THAT REMAINS IS TO CLIMB ANNAPURNA! THIS TREND IS, OF COURSE, PURE WELTSCHMERZ OR SNOBBERY, AND I SEE LITTLE DANGER OF ITS SPREADING FAR AMONG THE NEW GENERATION OF BIOLOGISTS.

THE SECOND SOURCE OF QUESTIONING, ON THE OTHER HAND, IS MORE SERIOUS AND MORE DANGEROUS. IT IS THE "SO-WHAT" TYPE OF QUESTIONING. IT IS THE SOURCE OF A REAL CRISIS, OR RATHER PSEUDO-CRISIS, WHICH TAKES THE FORM OF ANTI-REDUCTIONISM: OF AN ATTACK ON SCIENTIFIC REDUCTIONISM, AN ATTACK CARRIED OUT IN THE NAME OF WHAT IS VARIOUSLY CALLED WHOLISM OR INTEGRATIONISM. THE ARGUMENT(ATION) OF THE ANTI-REDUCTIONISTS IS SIMPLE: THE MORE ~~THE~~ MOLECULAR BIOLOGISTS (FIND) ~~FIND~~ OUT ABOUT THE MOLECULAR STRUCTURE OF ORGANISMS, AND THE RELATION OF THAT STRUCTURE TO ORGANIC FUNCTIONS, THE MORE THE INTEGRATIONISTS COMPLAIN THAT <u>WHATEVER</u> THE REDUCTIONISTS FIND ~~OUT~~ IS <u>NOT</u> THE IMPORTANT PART OF BIOLOGY. WE ARE TOLD THAT THE ORGANISM, AND THE HERD, AND THE SPECIES, AND THE ECOLOGICAL NICHE ARE WHAT MATTERS. IT ALL SOUNDS AS IF THESE MOST COMPLEX LEVELS OF ORGANIZATION DERIVED THEIR REALITY, NOT FROM THEIR

COMPONENT ELEMENTS, WITH THEIR SPECIFIC MOLECULAR STRUCTURES AND FUNCTIONS, BUT FROM SOME ALMOST MYSTICAL ELEMENT OF "WHOLENESS" COMING SOMEHOW FROM SOMEWHERE ELSE -- IN OTHER WORDS, THE MYTH OF "EMERGENCE." TO CITE ONE EXAMPLE, AN EMINENT WHOLISTIC BIOLOGIST WHO READ THE MANUSCRIPT OF A BOOK OF MINE, WROTE ME A SERIOUS AND URGENT PLEA TO INTRODUCE ~~SOMEWHERE~~ AT LEAST THE IDEA THAT "SOMETHING SPECIAL," SOMETHING OUTSIDE CURRENT EVOLUTIONARY THEORY, MAY HAVE ENTERED THE PICTURE TO MAKE POSSIBLE THE EMERGENCE OF MAN. SINCE I AM AGAINST DISCRIMINATION OF ANY SORT, I WONDERED: WHY SHOULDN'T THE HONEY BEES, OR THE BIRDS OF PARADISE, OR THE WHALES FEEL ENTITLED TO THE SAME EXCEPTIONALITY WITHIN EVOLUTION, JUST BECAUSE THEY DON'T HAVE A CHANCE TO REVIEW MANUSCRIPTS PRIOR TO PUBLICATION?

THE EMPHASIS ON THE COMPLEX AND THE HARD-TO-EXPLAIN AS BEING THE ONLY VALID CENTERS OF INTEREST IMPLIES A MYSTICAL ATTITUDE, ALMOST A HOPE THAT BRIDGES WILL NOT BE FOUND BETWEEN THE COMPLEX, INTEGRATIVE LEVELS AND THE SIMPLER LEVELS OF INTERPRETATION. I USED TO ATTRIBUTE, CYNICALLY, THE ANTI-REDUCTIONIST ATTITUDE OF ORGANISMIC BIOLOGISTS TO AN UNWILLINGNESS TO LEARN BIOCHEMISTRY. BUT ANTI-REDUCTIONISM IS NOT JUST AN ODDITY AMONG BIOLOGISTS. IT IS AN ATTITUDE THAT BIOLOGISTS BORROW, UNCONSCIOUSLY, FROM THE SOCIAL SCIENCES, WHERE A NONREDUCTIONIST, PHENOMENOLOGICAL APPROACH IS NECESSARY AND JUSTIFIED. LET ME ILLUSTRATE WHAT I MEAN WITH AN EXAMPLE.

I RECENTLY HAD THE EXPERIENCE OF DINING WITH A GROUP OF DISTINGUISHED SOCIAL PSYCHOLOGISTS. DURING DINNER, I BROUGHT UP CONVERSATIONALLY SOME FACTS OF NEUROPHYSIOLOGY THAT I HAD LEARNED A FEW DAYS EARLIER AND I HAD FOUND EXCITING, AND I THOUGHT WOULD INTEREST MY COMPANIONS. Suddenly THERE WAS AN EMBARRASSED SILENCE, AS IF I HAD MENTIONED DEATH AT A WAKE; OR AS IF I HAD ~~MENTIONED~~ spoken of THE DEVIL IN THE HOME OF A METHODIST MINISTER. LATER THAT EVENING, ONE OF THE PSYCHOLOGISTS ASKED ME, WITH SOMETHING LIKE COMPASSIONATE UNDERSTANDING, "YOU ARE A REDUCTIONIST, AREN'T YOU?" IN THE TONE AN ENLIGHTENED LIBERAL MIGHT USE TO ASK, "ARE YOU A COMMUNIST?" OR "ARE YOU A HOMOSEXUAL?"

UPON REFLECTION, IT SEEMS TO ME THAT ANTIREDUCTIONISM IS AN UNDERSTANDABLE AND PROPER ATTITUDE IN THE SOCIAL SCIENCES. AFTER ALL, BETWEEN BIOLOGY (INCLUDING PHYSIOLOGICAL PSYCHOLOGY) AND THE SOCIAL SCIENCES (STARTING WITH SOCIAL PSYCHOLOGY) THERE EXISTS A TRUE GAP OF SUBJECT MATTER. THE GAP REFLECTS OUR CURRENT IGNORANCE OF THE PHYSICAL AND BIOLOGICAL BASIS OF HUMAN COGNITION. PHILIP MORRISON, WHO ~~WAS~~ IS ONE OF ~~THIS MORNING'S~~ Today's SPEAKERS, ONCE DEFINED CHEMISTRY AS "WHAT TO DO WHILE YOU WAIT FOR THE SCHROEDINGER EQUATION." ~~BUT~~ In fact THE GAP BETWEEN PHYSICS AND CHEMISTRY IS ONLY A TECHNICAL GAP. ~~THE~~ But the GAP BETWEEN NATURAL AND SOCIAL SCIENCE IS WIDER, BECAUSE AN ENTIRE LEVEL OF COMPLEXITY, THAT OF THE HUMAN MIND, REMAINS TO BE EXPLORED. SOCIAL SCIENCES DEAL WITH THE STRUCTURE OF HUMAN SOCIETY, THAT IS, WITH MEN AND WOMEN AS SOCIAL ANIMALS.

HUMAN BEHAVIOR IS CONDITIONED BY SOCIETY AS WELL AS BY THE HUMAN BRAIN. BUT HOW THE HUMAN BRAIN WORKS STILL ESCAPES US. PHYSIOLOGICAL PSYCHOLOGISTS, WHO ARE REALLY BIOLOGISTS, ARE HARD AT WORK ON THIS, BUT PROGRESS IS SLOW. AS A RESULT, THE SOCIAL SCIENTISTS HAVE TO OPERATE STRICTLY AT THEIR OWN LEVEL OF PHENOMENOLOGY. IF ~~SOCIAL SCIENTISTS HAD TO~~ THEY WORRIED THEMSELVES ALL THE TIME ABOUT THE POSSIBLE BIOLOGICAL SUBSTRATE OF THEIR SUBJECT MATTER, THEIR WORK WOULD BE BADLY HAMPERED. IN FACT, I BELIEVE THAT SOCIAL SCIENCE IS ACTUALLY ENDANGERED BY MISGUIDED EFFORTS TO BIOLOGIZE HUMAN BEHAVIOR, AS I SHALL MENTION LATER IN THIS LECTURE.

WITHIN BIOLOGY THE ANTI-REDUCTIONIST ATTITUDE HAS NO VALID JUSTIFICATION. IN THIS LECTURE I INTEND TO SET FORTH A ~~PURE~~ REDUCTIONIST CREED: NOT A NEGATIVE CREED, THAT DENIES THE VALUE OF DEALING WITH PHENOMENA AT THE LEVEL OF OBSERVABLE PATTERNS, BUT A POSITIVE REDUCTIONIST CREED.

A POSITIVE REDUCTIONISM IS FOUNDED ON THREE PRINCIPLES, FIRST, THAT ANY INTERPRETATION OF PHENOMENA AT ANY LEVEL MUST BE CONGRUENT WITH THE LAWS OF PHYSICS AS GENERAL LAWS OF NATURE; SECOND, THAT THE INTERPRETATION MUST POTENTIALLY BE REDUCIBLE TO THE PROPERTIES OF STRUCTURES FULLY INTERPRETABLE

IN TERMS OF ~~THE~~ PHYSICAL LAWS, AND THIRD, THAT IT IS THE PROPER TASK OF THE SCIENTIST TO FOSTER THE ACHIEVEMENT OF SUCH REDUCTION.

REDUCTIONISM SHOULD OF COURSE BE HISTORICAL RATHER THAN MECHANICAL. TO SAY THAT CHEMISTRY OR GEOLOGY OR BIOLOGY MUST BE INTERPRETABLE IN TERMS OF PHYSICAL LAWS DOES NOT MEAN THAT THE STARS, THE PLANETS, THE SPECIES THAT EXIST ARE THE ONLY ONES THAT ~~MIGHT~~ COULD HAVE ~~BEEN~~ EXISTED; AND THAT IF WE KNEW THE ENTIRE HISTORY OF THE UNIVERSE WE COULD CALCULATE THE ABUNDANCE OF CHEMICAL ELEMENTS ON JUPITER OR THE GENE FREQUENCIES AMONG PYGMIES IN CENTRAL AFRICA. WHAT REDUCTIONISM MEANS IS THE CONFIDENCE THAT THE DECISIVE ELEMENTS IN BIOLOGICAL EVOLUTION, FROM THE EARLIEST TEMPLATE MOLECULES TO THE MOST COMPLEX INTERACTIONS BETWEEN SPECIES AND POPULATIONS HAVE INVOLVED PHYSICAL PROCESSES ONLY; THAT THESE PROCESSES HAVE NOT BEEN DIFFERENT IN ANY RESPECT FROM THOSE OBSERVED IN PHYSICAL PHENOMENA; AND THAT ALL BIOLOGICAL PHENOMENA CAN ULTIMATELY BE INTERPRETED IN TERMS OF THE BEHAVIOR OF ATOMIC AND MOLECULAR STRUCTURES.

THE MOLECULAR BIOLOGY OF THE GENE, TO USE THE FELICITOUS TITLE OF WATSON'S TEXTBOOK, HAS BROUGHT TO BIOLOGY A UNIFYING CENTER, COMPARABLE TO THAT PROVIDED TO PHYSICS BY ~~THE ATOMIC~~ Quantum THEORY. JUST AS THE ACHIEVEMENTS OF PHYSICS INTERPRET THE BROAD LINES OF CHEMISTRY WITHOUT AS YET MAKING THE EXPLANATION FULLY EXPLICIT, THE MODERN THEORY OF THE GENE EXPLAINS BIOLOGY WITHOUT AS YET MAKING ALL OF IT EXPLICIT. WHERE DO WE GO FROM HERE?

AN ORGANISM OPERATES, NOT WITH GENES BUT WITH GENE PRODUCTS, THAT IS, WITH PROTEINS. PROTEINS ARE THE LOVE OF PROTEIN CHEMISTS, BUT TO THE MOLECULAR BIOLOGIST THEY ARE A NIGHTMARE. WHEREAS GENES ARE ALL (OR ALMOST ALL) DNA, WITH A UNIFORM TAPE-LIKE STRUCTURE AND A CODED SET OF SPECIFICATIONS AND SIGNALS, PROTEINS START WITH SPAGHETTI-LIKE FILAMENTS AND FUNCTION ONLY WHEN THE FILAMENTS HAVE BALLED UP IN THEIR OWN SPECIFIC SHAPES, THOUSANDS OF DIFFERENT SHAPES. DESPITE SOME HELPFUL PRINCIPLES, IT STILL TAKES YEARS OF WORK TO UNRAVEL THE SHAPE OF ONE PROTEIN AND THE RELATION TO ITS FUNCTION. AT THE MOMENT WE CAN NO MORE PREDICT THE PROPERTIES OF A PROTEIN FROM THE SEQUENCES OF ITS AMINO ACIDS THAN A CHEMIST CAN WRITE THE WAVE EQUATION FOR A NEW COMPLEX ORGANIC COMPOUND. THE FRONTIER OF PROTEIN CHEMISTRY WILL CONTINUE TO BE EXPLORED FOR DECADES, BUT MEANWHILE THE MOLECULAR BIOLOGIST MUST SEEK OTHER AND GREENER PASTURES.

THE FIRST FIELD I WISH TO TAKE UP IS THAT OF ONTOGENY, THAT IS, EMBRYOLOGY: THE MAKING OF A COMPLEX ORGANISM OUT OF CELLS WITH IDENTICAL GENES. IN A COMPLEX ORGANISM DIFFERENT GENES FUNCTION DIFFERENTIALLY IN DIFFERENT CELLS. IN A UNICELLULAR ORGANISM LIKE A BACTERIUM, DIFFERENTIAL GENE FUNCTION IS ELICITED DIRECTLY BY THE ENVIRONMENT: SPECIFIC SUBSTANCES CAUSE THE ACTIVATION OR INHIBITION OF THE FUNCTION OF SPECIFIC GENES. WE KNOW HOW THIS IS DONE IN BACTERIA, BUT WE ALSO KNOW THAT IN THE CELLS OF HIGHER ORGANISMS IT MUST BE DONE DIFFERENTLY. WE DO NOT YET KNOW HOW, BUT WE ARE CONFIDENT THAT WE SHALL SOON FIND OUT.

BUT WHEN A HUMAN EMBRYO, CONTAINING ONLY A FEW THOUSANDS CELLS, BEGINS TO TURN SOME OF THESE CELLS INTO PRECURSORS OF THE BRAIN, OTHERS INTO THE ANCESTORS OF THE GUT, AND OTHERS STILL INTO THE SOURCES OF MUSCLES AND BONES, THE SIGNALS CANNOT COME FROM THE OUTSIDE: THEY MUST COME FROM WITHIN, FROM THE GENES THEMSELVES. THE SIGNALS MUST BE PROGRAMMED IN TIME AS WELL AS IN SEQUENCE OF EVENTS. WHAT IS THE MOLECULAR BASIS OF THIS PROCESS? SURPRISINGLY, THE BEST ANALOGY TO DATE COMES FROM CERTAIN VIRUSES. WHEN VIRUSES ENTER A SUITABLE CELL THEY UNFOLD A SEQUENTIAL PATTERN OF EVENTS THAT IS FULLY PROGRAMMED WITHIN THE VIRAL GENES. THIS PROGRAM, WHICH IS REGULATED BY A SERIES OF FEED-BACK AND FEED-AHEAD COMPONENTS, HAS BEEN ALMOST COMPLETELY UNRAVELED FOR ONE OR TWO VIRUSES. IT SUGGESTS AT LEAST THE KINDS OF MECHANISMS THAT COULD BE INVOLVED IN EMBRYOGENESIS: TURNING-ON MECHANISMS SPECIFIC FOR ACTIVATING A GROUP OF GENES, WHOSE PRODUCTS CAN ~~IN TURN~~ THEN TURN ON OR OFF OTHER GENE SETS, and so on.

IN EMBRYOLOGY, HOWEVER, THERE IS THE ADDED PROBLEM OF DIFFERENTIATION. THE PROGRAM PRESCRIBES, NOT ONLY WHEN AND IN WHICH SEQUENCE THE CHANGES OCCUR, BUT WHERE: THAT IS, WHICH CELLS OR GROUPS OF CELLS WILL GO IN WHICH DIRECTION. AND THE CHANGES ARE OFTEN IRREVERSIBLE. IT IS EVIDENT THAT WE ARE DEALING HERE WITH SOMETHING OF A DIFFERENT ORDER OF COMPLEXITY FROM WHAT MOLECULAR BIOLOGISTS HAVE ENCOUNTERED IN BACTERIA ~~OR VIRUSES~~. THE SITUATIONS THAT ARE RELEVANT TO DIFFERENTIATION ARE NOT LIKE THOSE IN WHICH

ONE GENE IS TURNED ON OR OFF ACCORDING TO HOW MUCH OF ITS PRODUCT IS NEEDED IN A GIVEN ENVIRONMENT. THE ESSENCE OF DIFFERENTIATION IS STABILITY AND OFTEN IRREVERSIBILITY. SUPERFICIALLY AT LEAST, THE BACTERIAL SITUATION DIFFERS FROM DIFFERENTIATION IN HIGHER ORGANISMS AS A TELEPHONE CALL DIFFERS FROM A WEDDING. AT THE MOLECULAR LEVEL, IN OTHER WORDS, WE KNOW HOW SWITCHES ARE TURNED ON AND OFF BUT WE DO NOT YET KNOW HOW CELLS MAKE COMMITMENTS THAT LAST TILL DEATH THEM PART. FOR THAT REASON, EMBRYOLOGY HAS REMAINED PHENOMENOLOGICAL, NONREDUCTIONIST FOR A VERY LONG TIME. NOW, HOWEVER, THIS CITADEL BEGINS TO YIELD TO THE STRATEGIES OF MOLECULAR BIOLOGY, THAT IS, TO THE CONCERTED APPLICATION OF GENETIC AND BIOCHEMICAL ANALYSES.

ESSENTIALLY, WHAT IS BEING DONE IS TO BREAK DOWN THE COMPLEX SITUATION INTO MANY, POTENTIALLY LESS COMPLEX ELEMENTS. IF THE PROBLEM OF HOW GENES ARE REGULATED IN THE CELLS OF HIGHER ORGANISMS STILL BAFFLES US, WE TURN FIRST TO THE MOLECULAR ORGANIZATION OF CHROMOSOMES, WHERE THE GENES ARE LOCATED. ONE BEGINS BY HOMOLOGIZING SPECIFIC STRUCTURES WITHIN CHROMOSOMES WITH THE LOCATION AND SIZE OF THE GENES. ONE IDENTIFIES THE PROTEINS OF THE CHROMOSOMES, HOPING TO UNDERSTAND WHICH OF THEM ARE INVOLVED IN REGULATION OF GENE ACTIVITY. ONE CAN ISOLATE THE PRIMARY MESSAGES THAT CODE FOR PROTEINS MADE BY SPECIFIC DIFFERENTIATED CELLS. THIS TELLS US THAT THE MESSAGES ARE IN FACT SPECIFICALLY

MADE and kept IN THOSE CELLS, RATHER THAN MADE IN ALL CELLS AND SPECIFICALLY USED ONLY IN SOME CELLS.

THE METHODS OF GENETIC ENGINEERING CURRENTLY UNDER DEVELOPMENT, ATTACHING PIECES OF DNA FROM CELLULAR CHROMOSOMES TO DNA DERIVED FROM BACTERIA, ~~PROMISE TO~~ MAY LEAD ~~US~~ FURTHER TOWARD THE ISOLATION OF THE PIECES OF CHROMOSOME THAT CONTAIN SPECIFIC GENES.

BESIDES PURSUING THE GENES IN ACTION BY WAY OF CHROMOSOME STRUCTURE, THE MOLECULAR BIOLOGIST IS AFTER THE SECRETS OF DIFFERENTIATION BY STUDYING THE SIGNALS THAT CAUSE DIFFERENT CELLS TO ACT IN SPECIFIC WAYS AND TO BECOME COMMITTED TO DIFFERENT DESTINIES. THE PROBLEM IS STILL BEWILDERING, NOT FOR LACK OF CLUES, BUT BECAUSE OF THEIR ABUNDANCE AND VARIETY. PROTEIN FACTORS, PEPTIDES, AND STEROID HORMONES ELICIT IN DIFFERENT CELLS OF THE ADULT ORGANISM OR OF THE EMBRYO SUCH A VARIETY OF SPECIFIC RESPONSES THAT MAY AT FIRST SEEM TO PROMISE NOTHING BUT CHAOS. BUT THE CHAOS ~~BEGINS~~ HAS BEGUN TO YIELD TO BIOCHEMICAL DISSECTION. SOME OF THE MYSTERY DISAPPEARS AS THE PROCESS THAT ~~STARTS WITH~~ goes from THE ENCOUNTER OF A CELL WITH AN EXTERNAL FACTOR TO THE RESPONSE of the cell IS BROKEN DOWN INTO A SERIES OF STEPS. FOR EXAMPLE, A STEROID HORMONE MUST ENTER A CELL AND COMPLEX WITH A CYTOPLASMIC PROTEIN. THE COMPLEX -- NOT EITHER OF THE TWO COMPONENTS SEPARATELY -- THEN MOVES TO THE CELL NUCLEUS AND ACTIVATES SPECIFIC GENES. THE

DIFFERENT RESPONSES OF DIFFERENT CELLS MAY REFLECT DIFFERENCES IN ENTRY OF THE HORMONE, OR IN ITS COMBINATION WITH CARRIER PROTEIN, OR IN THE AFFINITY FOR VARIOUS CHROMOSOMAL SITES, OR IN THE RESPONSE OF INDIVIDUAL GENES. THE LAST POSSIBILITY SEEMS TO BE THE IMPORTANT ONE: IN THOSE CELLS THAT RESPOND TO THE HORMONE, THE HORMONE-CARRIER COMPLEX BINDS TO HUNDREDS OF CHROMOSOMAL SITES, BUT ONLY ONE OR A FEW GENES RESPOND. EVIDENTLY, THE GENE SET IS PROGRAMMED TO RESPOND SPECIFICALLY TO A RELATIVELY UNSPECIFIC STIMULUS. HOW? WE HOPE THE ANSWER WILL COME SOON.

THE THIRD AND MOST POWERFUL REDUCTIONIST APPROACH TO EMBRYOLOGY IS BY GOING FROM ORGANISMS OR ORGANS TO CULTURES OF CELLS. APART FROM THE RANGE OF EXPERIMENTATION THAT CELL CULTURES MAKE POSSIBLE ON THE PROBLEMS I HAVE ALREADY MENTIONED -- CHROMOSOME-GENE RELATION AND GENE-SIGNAL INTERACTION -- CELL CULTURES MAKE IT POSSIBLE TO ANALYZE A KEY ASPECT OF DEVELOPMENT, THE CONTROL OF CELL PROLIFERATION. FOR IN THE COURSE OF DEVELOPMENT, DIFFERENTIATION IS INTIMATELY TIED UP WITH CONTROLLED PROLIFERATION. AT ONE EXTREME, CELLS LIKE NEURONS OR MUSCLE FIBERS DO NOT DIVIDE ANY MORE IN THE ADULT BODY. EVEN WHEN THEY STILL PROLIFERATE, DURING EMBRYOGENESIS, THEY PROLIFERATE IN A CONTROLLED WAY, WHICH GENERATES THE SPECIFIC SIZES AND SHAPES OF THE ORGANS. AT THE OTHER EXTREME ARE STEM CELLS, WHICH CONTINUE TO PROLIFERATE THROUGHOUT LIFE, BUT ONLY IN A LINEAR FASHION:

FOR EXAMPLE, WHEN A STEM CELL OF THE SKIN DIVIDES, IT GENERATES ONE STEM CELL AND ONE CELL COMMITTED TO DIFFERENTIATION. THIS COMMITTED CELL WILL NO MORE DIVIDE, BUT WILL CHANGE INTO A HORNY SKIN CELL AND THEN DIE. DIFFERENTIATION, THEREFORE, IS CLOSELY TIED TO CONTROL OF CELL PROLIFERATION. THE CANCER PROBLEM, INCIDENTALLY, IS A VARIATION ON THIS THEME.

CULTURED CELLS ARE AN INEXHAUSTIBLE SOURCE OF INFORMATION IN THIS RESPECT. THEY MAKE IT POSSIBLE TO CLARIFY THE CONNECTION BETWEEN THE CELL CYCLE FROM ONE DIVISION TO THE NEXT AND THE PROCESS OF GENE DUPLICATION. THEY HAVE REVEALED THE ROLE OF HORMONES AND OTHER SUBSTANCES ON THE TRIGGERING AND INHIBITING OF THE CYCLE. THEY HAVE REVEALED THE UNSUSPECTEDLY CENTRAL ROLE THAT THE OUTER MEMBRANE OF THE CELL PLAYS IN ACTIVATING VARIOUS PHASES OF CELL PROLIFERATION. THE MOLECULAR BIOLOGY OF THE CELL MEMBRANE HAS BECOME A CENTRAL ASPECT OF THE STUDY OF DIFFERENTIATION. FOR EXAMPLE, THE SPECIFIC DIFFERENTIATION OF BONE MARROW STEM CELLS INTO RED BLOOD CELL PRECURSORS IS TRIGGERED, IN CELL CULTURE AS WELL AS IN THE INTACT ORGANISM, BY A PROTEIN CALLED ERYTHROPOIETIN, WHICH NEVER ENTERS THE CELL BUT COMBINES WITH A SPECIFIC MEMBRANE SITE. THE SAME CELL, IN RESPONSE TO A DIFFERENT STIMULUS, WOULD HAVE GENERATED WHITE BLOOD CELLS. EVIDENTLY, THE MEMBRANE OF THE UNDIFFERENTIATED BONE MARROW CELL HAS A MULTIPLICITY OF RECOGNITION SITES, WITH SPECIFIC AFFINITIES

FOR DIFFERENT SIGNAL MOLECULES, EACH OF WHICH TRIGGERS A DIFFERENT RESPONSE -- THAT IS, ACTIVATES A DIFFERENT SET OF GENES.

AT THIS POINT THE MOLECULAR BIOLOGIST FEELS EXCITED. HE HAS NOT YET BROKEN THE CODE OF DIFFERENTIATION, AS HE HAD SUCCESSFULLY BROKEN THE GENETIC CODE AND THE SIGNAL CODE OF BACTERIAL GENE FUNCTION. BUT THE FORTRESS IS BEGINNING TO CRUMBLE. WHAT IS NEEDED NEXT, AND IS ALREADY ~~BEGINNING TO~~ BECOMING AVAILABLE, IS A SET OF SYSTEMS SIMPLIFIED ONE STEP FURTHER: SYSTEMS IN WHICH A PIECE OF CHROMOSOME, PLACED IN A TEST TUBE WITH THE APPROPRIATE ENZYMES AND FACTORS, WILL GENERATE ITS OWN MESSAGE AND ITS PROTEIN PRODUCT. THEN THE ROLE OF THE STIMULANTS OR INHIBITORS THAT ACT DURING DEVELOPMENT AND IN VARIOUS ADULT ORGANS WILL BECOME TESTABLE. I PREDICT THE FIRST OUTPUTS OF THIS PROGRAM ARE LESS THAN FIVE YEARS AWAY AND THE MOLECULAR UNDERSTANDING OF THE CONTROLS OF CELL PROLIFERATION LESS THAN TEN.

IF UNDERSTANDING EMBRYOLOGY, THAT IS, UNRAVELING THE PROGRAM THAT MAKES ALL OF US WHAT WE ARE IN OUR GROWTH, HEALTH, ILLNESSES, AND DEATH SEEMS A STAGGERING TASK, THE OTHER TASK THAT I PROPOSE FOR MOLECULAR BIOLOGISTS IS POSSIBLY MORE DIFFICULT. I REFER TO THE MOLECULAR INTERPRETATION OF EVOLUTION.

EVOLUTION, OF COURSE, TAKES TIME. IT TOOK FOUR BILLION YEARS OF EARTH HISTORY TO PRODUCE ANIMALS; IT TOOK 200 MILLION YEARS TO GENERATE MAMMALS FROM THEIR REPTILE ANCESTORS; IT MAY HAVE TAKEN TWENTY MILLION YEARS TO GENERATE MAN FROM OUR COMMON ANCESTORS WITH TODAY'S LIVING APES.

SUPERFICIALLY, THERE WOULD SEEM TO BE NO GREAT HURRY TO FIND OUT HOW ALL THIS HAPPENED. IT IS NOT LIKELY TO START HAPPENING MUCH FASTER, NOR IS THERE MUCH WE CAN DO ABOUT IT EXCEPT BEING SENSIBLE ABOUT ATOM BOMBS AND POLLUTION. BUT THIS IS NOT THE WHOLE STORY. WE DO HAVE A STAKE IN UNDERSTANDING THE MECHANISMS OF EVOLUTION, AND UNDERSTANDING THEM SOON, BECAUSE THE CONSEQUENCES OF EVOLUTION ARE PRESSINGLY UPON US, MATERIALLY, MORALLY, AND INTELLECTUALLY, ALL THE TIME.

SINCE DARWIN'S TIME WE UNDERSTAND THE GRAND LINES OF EVOLUTION: VARIATION PROVIDES THE MATERIAL UPON WHICH NATURAL SELECTION PLAYS. BUT THIS AWARENESS OF THE MAIN FORCES IS ABOUT AS ILLUMINATING TO AN EVOLUTIONIST AS QUANTUM MECHANICS IS TO A CHEMIST. WHICH VARIATIONS CONTRIBUTE TO THE EMERGENCE OF NEW SPECIES? BY WHAT COMBINATION OF EVENTS DO SOME LINES OF DESCENT PETER OUT, OTHERS BECOME IMMOBILIZED, OTHERS STILL BLOSSOM INTO THOUSANDS OF DIRECTIONS? A PRESSING QUESTION IS THAT OF THE TIME SCALE OF EVOLUTION. IS THAT SCALE CONGRUENT WITH THE TIME

(PARAMETERS)

PARAMETERS OF VARIATION AND SELECTION AS WE MEASURE THEM? AND ARE VARIATION AND SELECTION INDEPENDENT FORCES, THE LATTER JUST ACTING ON THE OUTPUT OF THE FORMER, OR ARE THEY TIED TOGETHER INTO AN INTERACTING SYSTEM BY STRUCTURAL FEEDBACKS?

FOR MANY YEARS BIOCHEMISTS HAVE COMPARED A FEW HOMOLOGOUS PROTEINS, THAT IS, PROTEINS WITH SIMILAR FUNCTION IN ORGANISMS RANGING ALL THE WAY FROM YEASTS TO HUMANS. THIS IS LIKE STUDYING THE HISTORY OF SPECIFIC GENES. THROUGH THIS KIND OF MOLECULAR EVOLUTIONARY HISTORY THE AMOUNT OF VARIATION PER UNIT OF GEOLOGICAL TIME CAN BE ESTIMATED. I WILL NOT GO HERE INTO THE QUESTIONS OF CALCULATING THE RATE OF EVOLUTION FROM THESE DATA, EXCEPT TO SAY THAT THE RESULTS NOT ONLY FIT QUITE WELL THE CLASSIFICATION PROPOSED BY TAXONOMISTS, BUT ALSO THE TIME SCALE OF PALEONTOLOGISTS. THE HARD PROBLEMS COME UP, HOWEVER, WHEN WE COME TO THE BIG QUESTIONS: THE ORIGIN OF NEW GENES, THE 100-FOLD DIFFERENCE IN AMOUNT OF DNA AND OF GENES per cell FROM YEAST TO MAMMALS, AND, MORE DRAMATIC, THE RAPID EVOLUTION OF CERTAIN LINES OF DESCENT AT SPECIFIC TIMES.

NOT SURPRISINGLY, NAIVE CALCULATIONS BASED ON DATA AVAILABLE AS RECENTLY AS 10 YEARS AGO LAND US INTO TROUBLE. THE MUTATIONS THAT THE GENETICIST KNOWS BEST -- CHANGES OF INDIVIDUAL DIGITS OF THE GENETIC SCRIPT OR REARRANGEMENTS OF PIECES OF CHROMOSOME -- SEEM TO BE NEITHER FREQUENT ENOUGH NOR VARIED ENOUGH TO REASSURE THE EVOLUTIONIST THAT

THEY KNOW ~~ARE~~ THE WHOLE STORY OF GENETIC VARIATION. HENCE, HYPOTHESES OF UNKNOWN FORCES, OR OF LIFE HAVING BEEN IMPORTED FROM OUTER SPACE TO COLONIZE THE EARTH, HAVE BEEN SERIOUSLY ENTERTAINED.

FORTUNATELY, THE SITUATION HAS IMPROVED IN TWO IMPORTANT WAYS. FIRST, MOLECULAR BIOLOGISTS HAVE UNCOVERED THE EXISTENCE OF NEW ~~VARIOUS~~ KINDS OF GENETIC VARIATION THAT MAY SERVE TO SPEED UP EVOLUTION BY GENERATING A GREATER VARIETY OF CHANGES. AMONG THEM ARE, TO NAME A FEW, MUTATOR GENES THAT CAUSE THE FREQUENCY OF MUTATION TO INCREASE BY A FACTOR OF 10 OR 100; GENETIC CONTROL OF CROSSING OVER, WHICH MAY ALTER THE FREQUENCY OF RECOMBINATION; INSERTION SEQUENCES, WHICH PERMIT THE INSERTION OF FRAGMENTS OF GENETIC MATERIAL INTO CHROMOSOMES AND BRING ABOUT NEW GENE COMBINATIONS; AND CONTROLLING ELEMENTS, WHICH CAN TURN ON OR OFF GROUPS OF GENES MORE OR LESS PERMANENTLY IN DIFFERENT LINES OF DESCENT. THESE AND OTHER PROCESSES THAT MAY STILL AWAIT DISCOVERY ~~CAN~~ PROVIDE A GREATER RANGE OF GENOTYPES FOR NATURAL SELECTION TO ACT UPON.

BUT THE PROBLEM OF THE SPURTS OF FAST EVOLUTION STILL REMAINS. THESE ARE INSTANCES IN WHICH EVOLUTION SEEMS TO HAVE PERSISTENTLY CONCENTRATED ON IMPROVING SOME SPECIFIC DEVICE, IGNORING EVERYTHING ELSE, LIKE A GAMBLER WHO BETS ALL ON ONE HORSE OVER AND OVER AGAIN. IN THIS WAY EVOLUTION BRINGS ABOUT ASTONISHING CHANGES. AN ELECTRIC

FISH, WHICH GENERATES AND MONITORS AN ELECTRIC FIELD FOR ITS OWN NOURISHMENT AND PROTECTION, HAS IN ITS BRAIN AN ENORMOUS LOBE WHICH IS ENTIRELY DEVOTED TO DECODING AND EMITTING ELECTRIC SIGNALS, AND WHICH IS MISSING IN ITS NON-ELECTRIC RELATIVES. MORE IMPORTANT STILL, THE HUMAN BRAIN SEEMS TO HAVE GROWN IN LESS THAN ONE MILLION YEARS TO ALMOST DOUBLE ITS SIZE, CONCOMITANT WITH THE DEVELOPMENT OF HUMAN MENTAL FACULTIES, ESPECIALLY LANGUAGE.

THE PROBLEM OF SUCH EVOLUTIONARY SPURTS IS UNRESOLVED BECAUSE THE MECHANISMS ARE NOT YET KNOWN. BUT IT IS NOT INSOLUBLE. WE REALIZE NOW THAT WHAT IS NEEDED IS SOME ADDITIONAL FEEDBACK, SUCH AS COULD BE PROVIDED BY A TIE-UP BETWEEN RATES OF VARIATION AND OF SELECTION. IF, AT SPECIFIC TIMES AND IN SPECIFIC ENVIRONMENTS, SELECTION WERE FAVORING A CERTAIN CLASS OF GENOTYPES (FOR EXAMPLE, MORE COMPLEX CEREBRAL FUNCTIONS) AND IF THE SELECTIVE VALUE OF THOSE GENOTYPES WERE ENHANCED BY INCREASED RATES OF GENETIC VARIATION OR RECOMBINATION, THEN SELECTION WOULD FAVOR ENHANCED VARIABILITY AND ACCELERATE THE RATE OF EVOLUTION IN A NON-LINEAR WAY. SUCH A COUPLED SELECTIVE PRESSURE, ON GENETIC VARIABILITY AND ON A SPECIFIC CLASS OF GENOTYPES, MAY HAVE CONTRIBUTED TO THE RAPID EVOLUTION OF HOMINIDS, AND MAY ALSO EXPLAIN THE HIGH DEGREE OF POLYMORPHISM OF THE HUMAN SPECIES COMPARED TO OTHER PRIMATES. (A CONVINCING ANALYSIS OF THE CONCEPT OF SELECTION FOR VARIABILITY HAS RECENTLY BEEN PRESENTED BY PROFESSOR LAYZER).

AN UNDERSTANDING OF THESE PHENOMENA, MORE PARTICULARLY A CLARIFICATION OF FEEDBACKS BETWEEN VARIATION AND SELECTION, IS IMPORTANT FOR SEVERAL REASONS. ONE OF THEM IS THE NEED TO DISPEL CONFUSIONS THAT ARISE WHEN PEOPLE DEAL WITH HUMAN FACULTIES IN A BIOLOGICAL WAY. IF ONE IGNORES THE HIGH RATES OF EVOLUTION THAT BRING ABOUT A DOMINANT SPECIES LIKE MAN, THERE CREEPS INTO BIOLOGY A TENDENCY TO HOMOLOGIZE TRAITS AND BEHAVIORS BETWEEEN DIFFERENT SPECIES, ORDERS, OR PHYLA, AS THOUGH EVOLUTION HAD STAYED PUT IN SOME WAYS WHILE MOVING RAPIDLY IN OTHER WAYS. THUS SOME ETHOLOGISTS HAVE JUMPED FROM OBSERVATIONS OF INSTINCTUAL AGGRESSIVITY IN INSECTS OR FISHES, TO INTERPRETING VIOLENCE AMONG HUMANS AS RESULTING FROM COMPARABLE MECHANISMS. SOCIOBIOLOGISTS MAY JUMP FROM DESCRIPTIONS OF RELATIONS BETWEEN MEMBERS OF ONE SPECIES TO SIMPLISTIC INTERPRETATIONS OF THE BEHAVIOR OF OTHER SPECIES. THIS IS UNJUSTIFIED AND, AT TIMES, IRRESPONSIBLE. // THE ~~SEMANTIC~~ IMPLICATIONS OF ~~THE~~ SEMANTIC CONFUSIONS BETWEEN BIOLOGY AND HUMAN AFFAIRS CAN BE OMINOUS. LOOSE TALK OF GENES FOR AGGRESSION IN A STICKLEBACK FISH MAY BE RIGHT OR WRONG, BUT IS CERTAINLY INNOCUOUS. TO SUGGEST, HOWEVER, THAT THERE ARE GENES OR CHROMOSOME FOR VIOLENT BEHAVIOR IN HUMANS IS NOT A BIOLOGICAL STATEMENT; IT IS A SOCIOPOLITICAL ACTION. IT IS AN INCURSION INTO THE FIELD OF VALUES, AN INCURSION THAT MAY INFLUENCE THE TREATMENT OF INDIVIDUALS AND THE PASSAGE OF LEGISLATION ON SOCIAL PROBLEMS. SUFFICE IT TO RECALL HOW FIFTY YEARS AGO THE INSISTENCE OF SOME BIOLOGISTS TO IDENTIFY PELLAGRA AS A

GENETIC DISEASE OF THE LOWER CLASSES AND TO IGNORE THE EVIDENCE THAT PELLAGRA WAS A VITAMIN DEFICIENCY, MAY HAVE DELAYED FOR DECADES THE PROPER SOCIAL INTERVENTION AT THE NUTRITIONAL LEVEL.

CHRISTOPHER LASCH: PSYCHIATRIC PARADIGM for social action.

AS WE BIOLOGISTS APPROACH THE STUDY OF EVOLUTION OF OUR OWN SPECIES WE OUGHT TO BE MINDFUL OF WHAT DR. LEON EISENBERG HAS CALLED "THE HUMAN NATURE OF HUMAN NATURE" -- OF THE FACT THAT, IN BRINGING ABOUT LANGUAGE AND MIND, EVOLUTION HAS CREATED A COMPLETELY NOVEL AND UNIQUE SET OF FORCES -- CULTURE, AND TRADITION, AND VERBALIZABLE IMAGINATION. THESE FORCES HAVE NOT ISOLATED MAN KIND FROM ITS BIOLOGICAL NATURE, BUT HAVE SUPERIMPOSED UPON IT A NEW LEVEL, THAT OF COGNITION, ~~THAT~~ WHICH CONDITIONS AND FILTERS ALL HUMAN ACTIVITIES. ANY ATTEMPT TO SINGLE OUT BEHAVIORS FOR BIOLOGICAL INTERPRETATIONS MUST, NOT ONLY ~~CORRECT FOR~~ EVALUATE SOCIAL AND CULTURAL INFLUENCES, BUT TAKE ACTIVELY INTO ACCOUNT THE INTERPLAY BETWEEN BIOLOGICAL AND CULTURAL FACTORS. JUST AS IN THE BIOLOGY OF DOMESTIC ANIMALS OR PLANTS WE CANNOT IGNORE THE ROLE THAT MAN KIND HAS PLAYED, SO IN ATTEMPTING TO BIOLOGIZE HUMAN BEHAVIOR WE MUST BE AWARE THAT IN MAN EVEN BIOLOGY IS SUBJECT TO CULTURE AND UNDERSTANDING.

IN CLOSING, LET ME SINGLE OUT ONE FRONTIER THAT TODAY MAY SEEM AS UNREACHABLE AS MOUNT EVEREST SEEMED TO BE 50 YEARS AGO. AND YET, IT IS EXCITING ENOUGH TO WARRANT SERIOUS ATTENTION. I REFER TO WHAT I MAY CALL BIOLINGUISTICS,

OR THE BIOLOGY OF HUMAN LANGUAGE. THE REASON FOR SINGLING OUT THIS FIELD IS TWO-FOLD. FIRST, HUMAN LANGUAGE IS THE SPECIAL FACULTY THROUGH WHICH ALL CONSCIOUS HUMAN ACTIVITY IS FILTERED; A FACULTY WHOSE DEVELOPMENT MAY WELL HAVE PLAYED THE DRIVING ROLE IN THE ALMOST CATASTROPHIC EVOLUTION FROM APE-KIND TO HUMANKIND. AND SECOND, LANGUAGE ALONE, AMONG THE UNIQUELY HUMAN ~~BRAIN~~ FACULTIES, ~~OFFERS TO THE~~ OF THE HUMAN BRAIN OFFERS TO THE SCIENTIST A SYSTEMATIC THEORY, THE STRUCTURAL LINGUISTICS DEVELOPED BY ~~MODERN LINGUISTS~~ CHOMSKY AND HIS FOLLOWERS, WHICH MAY BE AMENABLE TO CONFRONTATION WITH BIOLOGICAL DATA. WHAT I MEAN IS THAT FORMAL LANGUAGE STRUCTURE, PLUS SOME FACTS ALREADY KNOWN ABOUT LANGUAGE AND BRAIN STRUCTURE, PLUS THE ADVANCING KNOWLEDGE OF BRAIN ORGANIZATION PROVIDED BY PHYSIOLOGISTS, ~~I~~ HOLD SOME PROMISE THAT BETWEEN LINGUISTICS AND NEUROBIOLOGY A KIND OF CONVERGENCE MAY SOON BE POSSIBLE, ~~LIKE THE CONVERGENCE WHICH FORTY YEARS AGO BROUGHT FORMAL GENETICS TOGETHER WITH BIOCHEMISTRY TO CREATE MOLECULAR BIOLOGY. AND THE~~ THAT MAY PROVIDE A WEDGE INTO THE BIOLOGICAL EXPLORATION OF THE HUMAN MIND.

AT THIS POINT, YOU MAY FEEL THAT I HAVE ~~I FEEL IN THE AUDIENCE A MOVEMENT OF IMPATIENCE, AS IF I HAD~~ PUSHED SPECULATION TOO FAR, PROJECTING BIOLOGY MUCH TOO FAR INTO THE FUTURE. BUT, AS I MENTIONED AT THE START, I AM TOO OLD TO LOOK ANYWHERE BUT AHEAD.

OR THE BIOLOGY OF HUMAN LANGUAGE. THE REASON FOR SINGLING OUT THIS FIELD IS TWO-FOLD. FIRST, HUMAN LANGUAGE IS THE SPECIAL FACULTY THROUGH WHICH ALL CONSCIOUS HUMAN ACTIVITY IS FILTERED; A FACULTY WHOSE DEVELOPMENT MAY WELL HAVE PLAYED THE DRIVING ROLE IN THE ALMOST CATASTROPHIC EVOLUTION FROM APE-KIND TO HUMANKIND. AND SECOND, LANGUAGE ALONE, AMONG THE UNIQUELY HUMAN FACULTIES OF THE HUMAN BRAIN, OFFERS TO THE SCIENTIST A SYSTEMATIC THEORY, THE STRUCTURAL LINGUISTICS DEVELOPED BY CHOMSKY AND HIS COLLEAGUES, WHICH MAY BE AMENABLE TO CONFRONTATION WITH BIOLOGICAL DATA. WHAT I MEAN IS THAT FORMAL LANGUAGE STRUCTURE, PLUS SOME FACTS ALREADY KNOWN ABOUT LANGUAGE AND BRAIN STRUCTURE, PLUS THE ADVANCING KNOWLEDGE OF BRAIN ORGANIZATION PROVIDED BY PHYSIOLOGISTS, HOLD SOME PROMISE THAT BETWEEN LINGUISTICS AND NEUROBIOLOGY A KIND OF CONVERGENCE MAY SOON BE POSSIBLE, LIKE THE CONVERGENCE WHICH FORTY YEARS AGO BROUGHT FORMAL GENETICS TOGETHER WITH BIOCHEMISTRY TO CREATE MOLECULAR BIOLOGY.

I FEEL IN THE AUDIENCE A MOVEMENT OF IMPATIENCE, AS IF I HAD PUSHED SPECULATION TOO FAR, PROJECTING BIOLOGY INTO A TOO DISTANT FUTURE. AS I MENTIONED AT THE START, I AM TOO OLD TO LOOK ANYWHERE BUT AHEAD.