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SOURCE MATERIALS FOR GENERAL AND HUMAN BIOLOGY. FINAL REPORT.

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DEVELOPED AND SUBJECTIVELY EVALUATED ARE INSTRUCTIONAL MATERIALS FOR USE IN AN INTRODUCTORY COLLEGE LEVEL GENERAL EDUCATION BIOLOGY COURSE, WHICH EMPHASIZES THE DYNAMIC AND INVESTIGATIVE ASPECTS OF SCIENCE. THE MATERIALS, WHICH USE A CASE HISTORY APPROACH, WERE DEVELOPED BY EDITING EXCERPTS FROM CLASSICAL SCIENTIFIC PAPERS WITH ADEQUATE EDITORIAL ADDENDA TO SUPPLY BACKGROUND AND CONTINUITY. THE MATERIALS WERE USED IN THREE YEARS BY A TOTAL OF 300 SOPHOMORE STUDENTS ATTENDING WASHINGTON UNIVERSITY. THE COURSE PROCEDURE WAS FOR THE STUDENTS TO INDIVIDUALLY CRITIQUE THE MATERIAL AND TO DISCUSS EACH PAPER EXHAUSTIVELY IN GROUPS OF 15-20 STUDENTS WHILE ALSO PARTICIPATING IN "PROCESS-ORIENTED" LECTURES AND PROBLEM-BASED LABORATORIES. SUBJECTIVELY, BASED ON AN EXTENSIVE INDIVIDUAL CONVERSATION SURVEY, IT IS CONCLUDED THAT THE PAPERS TEND TO ENGAGE THE INTEREST AS WELL AS THE CRITICAL AND INTELLECTUAL FACULTIES OF STUDENTS. THE COMPLETE SET OF MATERIALS CONSISTING OF 12 PAPERS IS INCLUDED. (DS)

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FINAL REPORT
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May 27, 1968

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE

Office of Education
Bureau of Research

Final Report

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SOURCE MATERIALS FOR GENERAL AND HUMAN BIOLOGY

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May 27, 1968

The research reported herein was performed pursuant to a contract with the Office of Education, U.S. Department of Health, Education, and Welfare. Contractors undertaking such projects under Government sponsorship are encouraged to express freely their professional judgment in the conduct of the project. Points of view or opinions stated do not, therefore, necessarily represent official Office of Education position or policy.

U.S. Department of
Health, Education, and Welfare

Office of Education
Bureau of Research

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SUMMARY

This grant covered the use of experimental reading materials in an introductory biology course for persons presumably not continuing in biology. The materials were intended to bring the students into direct contact with science as an open-ended enterprise through the use of edited excerpts from history-making scientific papers. The papers were used for three years, by a total of 300 students. They were made subjects of intensive discussion in small discussion groups all taught by the principal investigator. Subjective estimates indicate considerable acceptance and success.

Introduction

The principal part of this report will be a copy of the materials which the subject contract permitted us to prepare and test in use (see Part B). Part A will contain brief statements on purposes, procedures, and results.

PART A

Purposes. One hears a great deal of lip-service to the goal of teaching science not as a compilation of facts and constructs but as an "open ended," "ongoing," adventure. The effort to do that has seemed worthwhile - for example, to the various national commissions on science education of which the writer was a member of several and chairman of one - for both practical and esthetic reasons. Practically, the hope is, by somehow inducing the student to behave like a scientist, to enlarge his mind in the direction of scientific competences and habits (tentativeness, skepticism, deductive precision, etc.). Esthetically, the assumption is that problem-solving, properly presented, is more intriguing than technical mastery and memorization.

But how accomplish these goals? Several ways have been suggested - the "problem lab," "thought problem" exercises oral or written, involvement of the student in reliving the "stories" of discovery and bioscientific progress. It is the last of these three to which this project was dedicated. The means used were not entirely new. They had an antecedent in the Harvard experiment with case histories in science as a part of general education. But our planned use of the case history method was very different from Harvard's. The Harvard "Cases" were legitimately designed to illustrate what Conant has called the "strategy" of science, the ambiance of ideas, needs, technical developments which have permitted - or enforced - the continuous revision of scientific ideas. Our "Cases" were designed to focus, rather, on the scientific mind. Given a scientific problem, what, and how much, was considered to be already established as fact? what seemed to need of further explanation? what data were fed into the interpretive machinery? what axioms operated to orient the analytical process? In general, if you were a scientist confronted with a constellation of givens, what explanatory hypotheses would you venture and how would you validate them? Our purpose was to involve our students in such questions as these.

Procedures. Some twelve "papers" (case histories, but not in Conant's sense) were developed, each showing how one scientist or several scientists one after another "wrapped their minds around" a particular "stubborn" problem - of inheritance, nutrition, respiration, etc. The papers were assigned, about one every other week, to four annual classes of about seventy-five students each - divided, however, into discussion sections with an average attendance of fifteen to twenty. The student was asked not to come to class until and unless he had "read" - really read - the paper, that is, had asked himself certain questions about it. *What is the paper about*? (A remarkable number of college sophomores can "read" something through without gathering what its subject is.) *What is the author's purpose*? (The purpose in scientific papers is almost uniformly argumentative - i.e. to convince the reader that the author's thesis is correct.) *What is the author's thesis*? *How is the paper "architected" conceptually (what are its parts and how arranged and why)*? *Does the author convince you*? *Why, or why not*? These questions tend to put the student, we find, "inside" the mind of the scientist. We cannot prove that this happens, but we strongly intuit that it does so.

Results. It was never the intention in this project to test the outcome in other than a subjective way, since objectivity through matched samples and single-variable differences was never possible. A systematic program has been pursued, over the years, of asking students whether they liked the course, how it compared in interest, difficulty, and apparent usefulness with other courses taken and what part of this course they found most rewarding.

The results of this intensive but subjective survey have been interesting. Earlier, the course tended to be rated as one of the most difficult but also one of the most interesting and useful of the (average of seven) courses which the students, sophomores, had studied in university. There was about equal enthusiasm - for (a) the lectures and (b) the discussions of the papers. In earlier experiments at Washington University with historical papers, these papers had been ranked by students as the most valuable part of the course. Unexpectedly, during the three-year course of the present experiment, the laboratory end of the course (usually considered, by nonbiologically-oriented students as unrewarding) got a very high rating. (This has to do, we think, with the method used of canceling all course-work except labs for a period of two weeks during which the students came at four times of their own choosing and worked through the lab materials at their own pace [but not auto-instructionally, plenty of supervision was provided]).

Another drift was noticeable during the three-year experiment. A confrontation is occurring in American higher education, part of which is the demand of students that they feel the relevant urgency of the subjects they study. This was reflected in our course. During this last year, especially, the instructor found it less easy than before to "entrap" the student in a real involvement with the subject. It is too early to know how serious or lasting this "revolution" is to be or what adjustments should be made in recognition of it. Will the effort to show biology as a quest prove easier or more difficult?

One adaptation we plan is the introduction of as much <u>tutorial experience</u> for the student as economics will allow. In another course, this year, students were assigned to write papers in topics linking biology to some subject of their own special interest - politics, history, conservation, philosophy, logic, even literature and art. By and large - and again on subjective evidence - we believe that this produced a motivational feedback and made the students more interested in biology itself. But how can you be sure? The question which faces us, in planning further revision, is whether the adaptation to individual motivations is sound, and how it relates to the goal - central to this project - of presenting the "story line" of biology itself.

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IDENTIFIERS

ABSTRACT

It is pretty generally agreed that introductory science courses, especially for nonscience students, should emphasize the dynamic and investigative aspect of science as much as or even more than its factual aspect. This project was designed to test the hypothesis that the indicated goal could be approached successfully by inducing students to "act like scientists" specifically through reliving some of the great investigative stories of biology. To this end, support was sought for the development of special reading materials which the students read carefully and discussed exhaustively in small discussion sections while simultaneously attending "process oriented" lectures and problem-based labs.

(continued on next page)

The materials were carefully edited excerpts of classic scientific papers with adequate editorial addenda to supply background and continuity. By "test the hypothesis" it is not meant that the project tried to conduct a scientifically significant experiment with matched samples, single variables, etc. Subjectively, and basing our opinion on an intensive individual conversational survey, we found the papers tended to engage the interest and critical and creative intellectual faculties of students. The titles of the papers are given below.

"Life and Air"
"Ideas of Evolution"
"The Search for the Unit of Life"
"Historic Studies on Nerves"
"Investigation of Enzyme Action"
"Discovery and Demonstration of the Circulation of the Blood"
"Life Existing Independently in an 'Internal Environment'"
"The Story of Diabetes"
THE ORIGIN OF SPECIES
"Classic Studies in Immunology"
"The Search for an Explanation of Heredity"
"Spontaneous Generation"

PART B

Set of Special Reading Materials

My understanding is that textual materials prepared under contracts from the Office of Education imply the automatic entrance of those materials to the public domain. Therefore, I see no objection to the release of the documents. However, it should be clearly understood that, in some cases, the quoted materials are copyright and that copyright permissions granted for use at Washington University do not automatically extend to further reproduction in connection with which, therefore, the investigator assumes no risk.

Thomas S. Hall

Life and Air

[1]Life in its familiar manifestations depends on the availability of air. This was plain to people even before there was any science as such. In Greek, the word for breathe had the same root (psych-) as the word for life. In the Bible, when the Shunammite's son died, the prophet Elisha - assuming that the boy needed air - successfully applied artificial respiration.

[2]Life-air relations became a scientific problem when people began to ask why air is needed. This question was asked as soon as there began to be any formal science, namely in Greek Asia Minor in the sixth century B.C. Beginning then, Greek science lasted for about seven hundred years and produced a whole series of answers to the question why is life dependent on air?

[3]Some thinkers believed that air itself was alive; when we breathe in air, we simultaneously breathe in life. This conception seems surprising, at first, in its implication that the world and the air within and above it are themselves alive. This is precisely what many Greek thinkers did believe, viz., that the whole cosmos is a kind of great animate being. Some early theorists thought of air as a kind of "cement" - it not only occupies the space between things, but holds them together in a specific spatial relation. The most fruitful ideas, however, were those that linked air with heat. Aristotle - the great scientific and philosophical genius of the fourth century B.C. - supposed that a certain "inborn heat" was responsible for all vital processes and that air was necessary to cool the body and keep the inborn heat from becoming too intense.

[4]By far the most pregnant Greek inquiry into respiration was that of Galen, a highly creative and influential physician, surgeon, physiologist, and anatomist of the second century A.D. Galen supposed that life needs air for the same reason that a fire does. He observed that in a lamp air does three things: it fans the flame, it moderates the heat, and it carries off the sooty vapors that burning produces. Galen supposed that a subdued but potentially dangerous fire burns in the human heart. Air coming to the heart from the lungs fans and moderates this fire and carries off vaporous excesses. Galen accepted another idea about air, not original with him, namely that when it enters the blood it is changed into a rarer substance termed "vital spirits." When these reach the brain, they undergo a further change into "animal spirits" which the brain sends through the nerves to control muscular action.

[5]What we may term the modern investigation of respiration begins in the seventeenth century A.D. when vast and revolutionary advances occur in most branches of natural science. Around 1650 three views were current on the subject. First, air contains some substance that is necessary to, and actually used up by, the organism. Second, air is not used up: it is, rather, an absorptive substance that can take up excess vapors given off by the blood. Third, air is not fundamental to the respiratory process; all that is necessary is for the animal to breathe; breathing helps the circulation (e.g., by pushing blood into the heart). The last of these hypotheses was investigated by the ingenious technician and microscopist Robert Hooke in 1662 just a few years before he announced his famous discovery of cells. Hooke says that

> ". . . because some eminent physicians had affirmed that the motion of the lungs was necessary to life upon the account of promoting the circulation of the blood, and that it was conceived the animal would immediately be suffocated as soon as the lungs should cease to be moved, I did (the better to fortify my own hypothesis of this matter, and to be the better able to judge of several others) make the following additional experiment . . .."

[6]Hooke reminds his colleagues in the Royal Society that

> "I did heretofore give this illustrious Society an account of an experiment I formerly tried of keeping a dog alive after his thorax was all displayed by the cutting away of the ribs and diaphragm; and after the pericardium of the heart was also taken off . . . the dog being kept alive by the reciprocal blowing up of his lungs with bellows . . . for the space of an hour or more." (In this experiment, the trachea is) "cut off just below the epiglottis and bound upon the nose of the bellows."

[7]The foregoing experiment now suggests to Hooke a way of finding out whether breathing normally functions (a) to promote the circulation or (b) to supply air.

> [8]"The dog having been kept alive, (as I have now mentioned) for above an hour, in which time the trial had been often repeated, in suffering the dog to fall into convulsive motions by ceasing to blow the bellows, and permitting the lungs to subside and lie still, and of suddenly reviving him again by renewing the blast, and consequently the motion of the lungs: This, I say, having been done, and the judicious spectators fully satisfied of the reality of the former experiment; I caused another pair of bellows to be immediately joined to the first, by a contrivance, I had prepared, and pricking all the outer

coat of the lungs with the slender point of a very sharp penknife, this second pair of bellows was moved very quick, whereby the first pair was always kept full and always blowing into the lungs; by which the lungs were also always kept very full, and without any motion; there being a continued blast of air forced into the lungs by the first pair of bellows, supplying it as fast, as it could find its way quite through the coat of the lungs, by the small holes pricked in it, as was said before. This being continued for a pretty while, the dog, as I expected, lay still, as before, his eyes being all the time very quick, and his heart beating very regularly: But, upon ceasing this blast, and suffering the lungs to fall and lie still, the dog would immediately fall into dying convulsive fits; but be as soon revived again by the renewing the fullness of his lungs, with the constant blast of fresh air.

9"Towards the latter end of this experiment a piece of the lungs was cut quite off; where it was observable, that the blood did freely circulate, and pass through the lungs, not only when the lungs were kept thus constantly extended, but also when they were suffered to subside and lie still. Which seem to be arguments, that as the bare motion of the lungs without fresh air contributes nothing to the life of the animal, he being found to survive as well when they were not moved as when they were; so it was not the subsiding or movelessness of the lungs, that was the immediate cause of death, or the stopping the circulation of the blood through the lungs, but the want of a sufficient supply of fresh air.

10"I shall shortly further try, whether the suffering the blood to circulate through a vessel, so as it may be openly exposed to the fresh air, will not suffice for the life of an animal; and make some other experiments, which, I hope, will thoroughly discover the genuine use of respiration; and afterwards consider of what benefit this may be to mankind."

11The question whether air is merely an absorbent of waste vapor or supplies something that is used up in respiration is considered by Robert Boyle. He places a great variety of living things under a bell jar attached to a vacuum pump and pumps out the air. He does the same thing to burning objects. Boyle is not famous for the clarity of his presentation, but a careful reading of what follows will show what his results suggested to him.

12He says that there is an "Opinion . . . touching respiration which makes the genuine use of it to be ventilation not of the heart but of the blood in its passage through the lungs; in which passage it is disburdened of those excrementitious steams proceeding, for the most part, from the superfluous serosities of the blood . . .. And this opinion . . . may be explicated in two ways: . . . first . . . that as a flame cannot long burn in a narrow and close place because the fuliginous steams it incessantly throws out cannot long be received into the ambient body . . . so the vital fire in the heart requires an ambient body of a yielding nature to receive into it the superfluous serosities and other recrements of the blood whose seasonable expulsion is requisite to depurate the mass of the blood and make it fit both to circulate and to maintain the vital heat residing in the heart."

13 Note Boyle's point that the ambient air should be "yielding", as this turns out later to be crucial to his argument. Meanwhile, however, we hear that "The other way of explicating the above-mentioned hypothesis is . . . that the air does not only as a receptacle admit into its pores the excrementitious vapors of the blood when they are expelled through the windpipe but . . . also associates itself (in the lung) with the exhalations of the circulating blood and when it is exploded, carries them away with itself . . .."

14 This idea that air associates itself explosively with something leaving the blood is connected with the great interest at the time in gunpowder. A gunpowder detonation - and, interestingly, thunder in the sky - were supposed to be due to an explosive union of sulphur with "nitre" a substance present both in the earth and in the air.

15 On the basis of hundreds of experiments showing that animals die sooner and flames are extinguished sooner in a vacuum than in air, Boyle arrives at the following conclusion.

16 "Now of these two ways of explicating the use of respiration, our engine affords us this objection against the first; that upon the exsuction of the air, the animals die a great deal sooner than if it were left in the vessel; though by that exsuction the ambient space is left much more free to receive the steams that are either breathed out of the lungs of the animal, or discharged by insensible transpiration through the pores of his skin."

17 Elsewhere he gives tentative support to the alternate "explication": he suggests - without pretense of proof - that air supplies a nitrous substance that unites explosively in the lung with an exhalation leaving the blood.

18 The late seventeenth century produced a number of variants of the idea put forward by Boyle and Hooke. Other physiologists and physicians associated with Boyle and Hooke at Oxford and/or London expressed variously the idea that respiration and combustion use up a nitrous substance obtained from the air. But this promising line

of thought was then side-tracked and not followed-up for nearly a century. One of the prime causes of the delay was a new and temporarily very influential theory of combustion advanced by a German chemist and physician named Stahl. Stahl insisted that burning does not take up anything from the air but rather gives off something to it. This something, given off in burning, Stahl called "fixed-fire" or phlogiston. The phlogiston-theory largely dominated chemical thought on this subject for three quarters of a century until it was rather suddenly overthrown, and a new (and, as far as it went, a much more correct) idea of combustion and respiration was introduced. The crucial discovery was made by an English chemist and clergyman, Joseph Priestley. We shall see, however, that Priestley radically misinterpreted his results which were repeated - and more correctly interpreted - by his French contemporary, Lavoisier. These events were revolutionizing in their impact and began a new, great era in the history of chemistry.

[19]Priestley approaches the problem from a broad, ecological viewpoint, extrapolating from events that occur in a closed container to events occurring in the atmosphere at large.

> [20]"It is well known," he says, "that flame cannot subsist long without change of air, so that the common air is necessary to it, except in the case of substances, into the composition of which nitre enters; for these will burn in vacuo, in fixed air, and even under water, as is evident in some rockets, which are made for this purpose. The quantity of air which even a small flame requires to keep it burning is prodigious. It is generally said, that an ordinary candle consumes, as it is called, about a gallon in a minute. Considering this amazing consumption of air, by fires of all kinds, volcanoes, etc. it becomes a great object of philosophical inquiry, to ascertain what change is made in the constitution of the air by flame, and to discover what provision there is in nature for remedying the injury which the atmosphere receives by this means . . .."

> [21]He then reports that "I have been so happy, as by accident to have hit upon a method of restoring air, which has been injured by the burning of candles, and to have discovered at least one of the restoratives which nature employs for this purpose. It is vegetation."

[22]If Priestley can demonstrate to us that vegetation, in fact, purifies air, we shall expect him to tell us how it does so. For an explanation, he falls back on the phlogiston theory.

> [23]"This restoration of vitiated air, I conjecture, is effected by plants imbibing the phlogistic matter with

which it is overloaded by the burning of inflammable bodies. But whether there be any foundation for this conjecture or not, the fact is, I think, indisputable. I shall introduce the account of my experiments on this subject, by reciting some of the observations which I made on the growing of plants in confined air, which led to this discovery.

24"One might have imagined that, since common air is necessary to vegetable, as well as to animal life, both plants and animals had affected it in the same manner; and I own I had that expectation, when I first put a sprig of mint into a glass-jar, standing inverted in a vessel of water; but when it had continued growing there for some months, I found that the air would neither extinguish a candle, nor was it at all inconvenient to a mouse, which I put into it.

25"The plant was not affected any otherwise than was the necessary consequence of its confined situation; for plants growing in several other kinds of air, were all affected in the very same manner . . ..

26"Finding that candles burn very well in air in which plants had grown a long time, and having had some reason to think, that there was something attending vegetation, which restored air that had been injured by respiration, I thought it was possible that the same process might also restore the air that had been injured by the burning candles.

27"Accordingly, on the 17th of August 1771, I put a sprig of mint into a quantity of air, in which a wax candle had burned out, and found that, on the 27th of the same month, another candle burned perfectly well in it. This experiment I repeated, without the least variation in the event, not less than eight or ten times in the remainder of the summer . . ..

28"This remarkable effect does not depend upon any thing peculiar to mint, which was the plant that I always made use of till July 1772; for on the 16th of that month, I found a quantity of this kind of air to be perfectly restored by sprigs of balm, which had grown in it from the 7th of the same month."

29A few years later, Priestley made another crucial discovery in the course of trial-and-error experiments in which using a large magnifying glass he focused the sun's rays on various materials. Among materials he used was a red powder obtained previously by heating mercury. ". . . I presently found," Priestley says, "that by means of this lens, air was expelled from it (the mercury powder) very readily. Having got about three or four times as much (air) as the bulk of my materials, I admitted water to it, and found that . . . (the air) was not imbibed by

. . . (the water). But what surprised me more than I can well express, was, that a candle burned in this air with a remarkably vigorous flame . . .; I was utterly at a loss to account for it."

30 Despite the extraordinary brilliance with which the candle burned in the air so obtained, Priestley at first supposed it to be ordinary atmospheric ("common") air. But then "I procured a mouse," he says, "and put it into a glass vessel, containing two ounce-measures of air from . . . (his mercuric powder). Had it been common air, a full-grown mouse, as this was, would have lived in it about a quarter of an hour. In this air, however, my mouse lived a full half hour." In this and other ways, Priestley convinced himself that his air was "four or five times as good" as common air. He interprets his results as follows.

31 Air may contain varying amounts of phlogiston. Animals breathe in common, moderately phlogisticated air, add phlogiston to it, and breathe it out in a more phlogisticated condition. In a closed container, an animal may so load the air with phlogiston that the animal dies (similarly a candle goes out). Plants absorb air that has been phlogisticated by animals. They take part of the phlogiston out of this air and add it to their tissues. They return the air to the atmosphere in a less phlogisticated condition. Animals get phlogiston by eating plant tissues. Were air to be totally deprived of its phlogiston it could be properly termed "dephlogisticated" and Priestley applies this term to the sort of air that he gets by heating his mercury powder. In 1774 he visits Paris and, at a dinner party, reports all these results orally and informally to his host, the French chemist Lavoisier.

32 During the ensuing months, Lavoisier repeats Priestley's experiments, gets the same results, and publishes them (without mentioning Priestley in his paper). Lavoisier pursues his experiments much farther. He heats mercury in air for twelve days. The mercury turns to powder, gaining weight in the process. The air loses as much weight as the mercury gains. The leftover air won't support life or combustion. Lavoisier heats his powder. It gives off a gas, losing weight as it does so. Lavoisier adds this gas to the leftover air and thus turns it back into ordinary air. His conclusions: ordinary air contains two gases, azote (our nitrogen) and oxygen. In burning, oxygen combines with, and adds to the weight of, the burning substance.

[33]Lavoisier also shows that carbon can combine with oxygen to form what he calls "fixed air" (our carbon dioxide). Meanwhile the English physicist Cavendish shows that hydrogen burns in (combines with) oxygen to form water. Lavoisier and his co-workers mistakenly surmise that the blood secretes into the lung cavities a fluid whose molecules are made of hydrogen and carbon. The hydrogen and carbon unite there to form water and fixed air (carbon dioxide). Another fifty years must pass before biologists become completely convinced that the oxidation occurs throughout the body as a whole, and that its adaptive value is its use in the production of energy.

[34]Perhaps because of the great prestige of Lavoisier and his co-worker Séguin the idea of combustion in the lungs held sway for a time. But there were also opponents of this idea who insisted that oxygen is absorbed by the blood and argued that combustion occurred in the blood itself. In 1837 the German chemist, Gustav Magnus, showed convincingly that arteries contain more oxygen than veins, veins more carbon dioxide than arteries. He concluded that physiological combustion occurs in blood as it passes through the capillary system. Only slowly and tentatively did the idea gain ground that oxidation occurs in the tissues. The physicist and physiologist van Helmholtz proved that isolated muscle produces heat in contracting and he, along with others, showed at about the same time that under proper conditions heat can be converted to work. Only in about 1850 was it fairly generally seen that respiration has as its central use the generation of energy for physiological processes in general.

[35]Around the middle of the nineteenth century a debate was in progress concerning the meaning of the presence of micro-organisms in fluids undergoing fermentation. The chief antagonists were the German founder of physiological chemistry, Justus Liebig, and the French biochemist (and, later, microbiologist) Louis Pasteur. The two agreed that fermentation involves a conversion of sugar into alcohol and carbon dioxide. They disagreed as to the nature and role of the yeast.

[36]According to Liebig ". . . yeast is nothing but vegetable fibrine, albumen, or caseine in a state of decomposition . . ." He supposed that these decomposing plant proteins somehow communicate their disintegrative activity to the sugar. He ascribes this to ". . . the ability which a chemical substance possesses, when in the

process of decomposition or combination, to cause or enable another substance which is touching it, to undergo this same change which it itself is undergoing."

[37]Pasteur espoused an idea put forth originally by Theodore Schwann (author of the cell theory). Schwann (1837) had seen yeasts as living plants. He said that ". . . alcoholic fermentation must be considered to be that decomposition which occurs when the sugar fungus (yeast) utilizes sugar and nitrogen containing substances for its growth, in the process of which the elements of these substances which do not go into the plant are preferentially converted into alcohol."

[38]In a series of controlled experiments, Pasteur is able to show that sugar in an initially sterile solution will be converted to alcohol if and only if the solution is inoculated with yeast. In the course of these experiments he notes that yeast cells live and multiply in the absence of air. This discovery of what Pasteur calls "life without air" initiates a century-long effort to discover the chemical nature of "anerobic respiration." This will ultimately turn out to be a complicated step-by-step series of molecular transformations in which the sugar molecule is gradually converted into carbon dioxide and alcohol. The initial transformations experienced by the sugar molecule are the same for cells respiring anaerobically (in the absence of air) and aerobically (in the presence of air). But later steps differ in the two cases. Where oxygen is present the eventual end products are carbon dioxide and water. Where oxygen is absent, the end products are carbon dioxide and alcohol. Pasteur's victory over Liebig's view, namely his demonstration that living microorganisms cause fermentation is one of the most fateful developments of modern science. Pasteur will presently demonstrate that microorganisms also cause decay and that they are agents of many diseases.

[39]Pasteur is first struck by the possibility of life-without-air in 1861 while studying the capacity of a certain large motile bacillus (he mistook it for a single-celled animal) to convert sugar and certain other substances into lactic acid. He says that

> [40]"The very existence of fermentation-producing infusoria (single-celled animals) is noteworthy enough. But one should note another curious phenomenon. That is that these infusorial animals live and divide indefinitely in the complete absence of air or free oxygen."

41He goes further and reports that "Not only are these infusoria able to live without air; air is in fact fatal to them. If a flow of CO_2 is passed through the medium in which they are developing their vitality and multiplication are not affected. But if under otherwise similar conditions one replaces CO_2 with a flow of air, all die within an hour or two, and the butyric fermentation which can only continue while they live - now comes to a stop."

42Pasteur now makes a careful experimental comparison of life with and without air as manifested by an organism that can live both ways. His first results are summarized in the following abstract of a paper delivered to the Chemical Society of Paris in 1861.

"On Ferments" (Bulletin of the Chemical Society of Paris, of session of April 12, 1861. pp. 61-63 (Abstract)).

43"M. Pasteur reports on supposed changes of form occurring in yeast cells in response to the external conditions of their development. In a critique of the work of botanists on this subject, Pasteur points out the sources of error in their experiments. These errors are such that even though the conclusions the botanists draw are correct, it would be necessary, according to him, to give entirely new proofs.

44"So far M. Pasteur, who is still pursuing his studies, has not succeeded in producing slime mold out of yeast nor in transforming the spores of the slime mold into yeast.

45"M. Pasteur now further communicates to the Society some new observations on brewer's yeast and the relations that exist between its mode of growth and its (fermentative) properties, depending whether, at the beginning of its period of fermentative activity, it is placed in contact with [a] oxygen gas or [b] carbon dioxide gas.

46"Yeast sown in a saccharine and albuminous liquor entirely deprived of even the smallest quantities of air, multiplies, gains in weight, and causes sugar to ferment. Thus, yeast can live and provoke fermentation, even though the fluids in which it is sown contain not the least trace of free oxygen gas.

47"On the other hand, M. Pasteur acknowledges that given air in the fluids or at its surface, the yeast still multiplies - does so, indeed, even more than in the absence of air; that is to say that in the same time, other things being equal, a greater amount of yeast forms; but this yeast, during its development, acts only weakly as a ferment, although it acts on sugar energetically if one later places it in contact with sugar water in the absence of gaseous oxygen.

[48]"M. Pasteur had earlier succeeded in removing nine-tenths of the fermentative character of yeast; but what it is important to notice is that under these circumstances the individual yeast particles in M. Pasteur's experiments, take up oxygen from the air and give off carbon dioxide thus living in the manner of all other small plants.

[49]"M. Pasteur had already pointed out the analogy which exists between the mode of life of brewer's yeast and of the torulaceae (these are acid yeasts) and ordinary slime moulds, by showing that these different creatures could develop in liquors containing nothing but sugar, ammonia, and phosphates. But brewer's yeast always remains quite distinct from the lower plants by virtue of its double property of (a) being able to live without free oxygen gas and (b) acting as a ferment. The new facts just announced establish that brewer's yeast can live with the aid of free oxygen gas and under its influence multiplies with extraordinary activity. With respect to organic development there is no longer any difference - under these special conditions - between yeast and the lower plants. At the same time, the difference between them is effaced with respect to fermentative properties. The fermentative nature tends to disappear so as to give way to nutritive properties of the sort that take place in ordinary lower plants."

IDEAS OF EVOLUTION

A case-study in biology

1 The theory of evolution is commonly associated with the name of Charles Darwin, but it is not always clearly understood exactly what role Darwin played in the establishment of that theory. And first of all we must be sure to understand that he was not the first to propose that new species may arise by evolution (as opposed, for example, to special creation). During the eighteenth century a running argument occurred with respect to the extent-of-change that a species (or some of its members) might undergo and whether in this way an entirely new species might evolve.

2 One participant in that debate was Louis Leclerc, Count Buffon (ca. 1749), from whom we hear that

> a "Whenever man began to change his climate, and to migrate from one country to another, his nature was subject to various alterations." He goes on to hypothesize that ". . . after many ages had elapsed, after he had crossed whole continents and intermixed with races already degenerated by the influence of different climates; after he was habituated to the scorching heats of the south, and the frozen regions of the north; the changes he underwent became so great and so conspicuous, as to give room for suspecting, that the Negro, the Laplander, and the White, were really different species, if, on the one hand, we were not certain, that one man only was originally created, and, on the other, that the White, the Laplander, and the Negro, are capable of uniting, and of propagating the great and undivided family of the human kind. Hence those marks which distinguish men who inhabit different regions of the earth, are not original, but purely superficial. It is the same identical being who is varnished with black under the Torrid Zone, and tawned and contracted by extreme cold under the Polar Circle."

> 3 "This circumstance is alone sufficient to show, that the nature of man is endowed with greater strength, extension, and flexibility, than that of any other terrestrial being; for vegetables, and almost all the animals, are confined to particular soils and climates. This extention of our nature depends more on the qualities of the mind than on those of the body."

4 Perhaps the key point in the above statement is that, unless we had reasons for believing otherwise, there would be "room for suspecting that the White, the Laplander, and the Negro were really different species". It is very important to understand exactly what were Buffon's reasons (presented above) for believing that they are <u>not</u> separate species.

5 Having shown now what might be taken to be different species of man are not so in fact, Buffon now turns our attention to animals:

> a "In brute animals, these effects are greater and more suddenly accomplished; because they are more nearly allied to the earth than man; because their food, being more uniformly the same, and nowise prepared, its qualities are more decided, and its influence stronger; and because the animals, being unable to clothe themselves, or to use the element of fire, remain perpetually exposed to the action of the air, and all the inclemencies of the climate. For this reason, each of them, according to its nature, has chosen its zone and its country: for the same reason, they remain there, and, instead of dispersing themselves, like man, they generally continue in those places which are most friendly to their constitutions."

6 We should be sure that we understand why and how the response of animals to environmental change differs from the human response. This will help us understand the difference he draws between domestic and wild animals.

a Thus he says that when animals are

> " . . .forced by men, or by any revolution on the globe, to abandon their native soil, their nature undergoes changes so great, that, to recognise

> them, recourse must be had to accurate examination, and even to experiment and analogy. If to these natural causes of alteration in free animals, we add that of the empire of man over those which he has reduced to slavery, we shall be astonished at the degree to which tyranny can degrade and disfigure Nature; we shall perceive the marks of slavery, and the prints of her chains; and we shall find, that these wounds are deeper and more incurable, in proportion to their antiquity; and that, in the present condition of domestic animals, it is perhaps impossible to restore their primitive form, and those attributes of Nature which we have taken from them."

Buffon now turns his attention to wild animals:

> "The wild animals, not being under the immediate dominion of man, are not subject to such great changes as the domestic kinds. Their nature seems to vary with different climates; but it is no where degraded . . . ."

Yet wild animals do vary, he continues, though the cause of variation here is different:

> "As climate and food have little influence on wild animals, and the empire of man still less, the chief varieties amongst them proceed from another cause. They depend on the number of individuals of those which produce, as well as of those that are produced. In those species in which the male attaches himself to one female, as in that of the roebuck, the young demonstrate the fidelity of their parents by their entire resemblance to them. In those, on the contrary, the females of which often change the male, as in that of the stag, the varieties are numerous: and as, through the whole extent of Nature, there is not one individual perfectly similar to another, the varieties among animals are proportioned to the number and frequency of their produce. In species the females of which bring forth five or six young three or four times a year, the number of varieties must be much greater than in those which produce

> but a single young once a year. The small animals, accordingly, which produce oftener, and in greater numbers than the larger kinds, are subject to greater varieties."

9 In seeking a different cause of variation for wild animals, Buffon hits upon what is to become one of the key points in the later attempt of scientists to learn how species originate: namely, that even at birth animals in the same species, even in the same litter, already differ from each other, and from the parents which produced them - that is, new "varieties" of individuals arise somehow during the reproductive process. The big question - what causes this innate variability of living things - Buffon neglects to consider. Instead, he goes on to make in his characteristically casual way what was to be one of the most important forward strides in the history of biological thought.

10 To understand what he is about to say about animals, remember what he had to say above about man: what might seem to be different species are actually divergent derivatives from a common stock. He now extends this to <u>species of animals</u>. The dog, fox, jackal and wolf might seem to have been separately created species; but are they?

11 In the following paragraph, be alert to discover what it is that Buffon is trying to prove by his experiments.

> a "The dog, the wolf, the fox, the jackal, and the isatis, form another genus, the different species of which are so similar, particularly in their internal structure and the organs of generation, that it is difficult to conceive why they do not intermix. From the experiments I made with regard to the union of the dog with the wolf and fox, the repugnance to copulation seemed to proceed rather from the wolf than the dog, that is, from the wild, and not from the domestic animal; for the bitches which I put to the trial would have willingly permitted the fox and wolf; but the she-wolf and female fox would never suffer the approaches of the dog. The domestic state seems to render animals less faithful to their species. It likewise makes them more ardent and more fertile; the bitch generally produces twice in a year: but the she-wolf and the female fox produce only once in the same period: and it is probable, that the dogs who have become wild and have multiplied in the island of

Juan Fernandes, and in the mountains of St. Domingo, produce but once a year, like the fox and wolf. Were this fact ascertained, it would fully establish the unity of genus in these three animals, who resemble each other so much in structure, that their repugnance to intermixing must be solely ascribed to some external circumstances. ..."

"Beyond this brief glance which we have cast over these varieties, indicating to us the alterations peculiar to each species, a more important consideration presents itself, with a broader aspect, namely that of the alteration of the species themselves, this more ancient decline which seems to have occurred since time immemorial in each family, or, if one prefers, in each genus within which we can include related species. We have over the entire earth only a few isolated species which, as in man's case, constitute species and genus simultaneously; the elephant, the rhinoceros, the hippopotamus, the giraffe form genera or simple species propagating in a direct line only with no collateral branches. All the rest appear to form families in which we may recognize ordinarily a chief common stock from which there appear to have emerged different species in proportion to the smallness and size and the fertility of the individuals concerned."

12 Buffon is notorious for the clarity neither of his style nor the thought that underlies it. Exactly what he wanted to say is uncertain, beyond the fact that the several "species" that make up a single genus may have originated through divergent descent from a single stock. It is significant, too, that he had what he, at least, considered a way of validating this point experimentally.

13 His presentation raises a number of pregnant questions. How did the first species in each genus arise? Why are no two individuals alike? Why are they alike at all? Assuming food or climate does affect an individual, through what mechanism is the individual's responsive change transmitted? Why must we believe that such change is "degenerative"?

14 Some answers to these queries are supplied by the next major theorist on the subject of evolution, Jean Baptiste de Monet de Lamarck (ca. 1809). His thought arises in part out of the active taxonomic endeavors of his eighteenth century predecessors, many of whom liked to point to what they called the "great enchainment" or "great chain of being" - a scale on which one might arrange, in sequence,

inorganic molecules, organic molecules, plants, creatures intermediate between plants and animals, animals, and men. At least one biologist who took himself seriously even added angels to the upper end of the scale!

15 Lamarck's major contribution was his assertion that this chain is an evolutionary chain. Throughout time certain families within each species have become progressively more and more highly developed until they were converted into entirely new, better-developed species. All species are thus related through progressive evolution.

16 Lamarck is at pains to detail the way in which this occurs. He points out that

> a ". . . great alterations in the environment of animals lead to great alterations in their needs and these alterations in their needs necessarily lead to others in their activities. Now if the new needs become permanent, the animals then adopt new habits which last as long as the needs that evoked them. This is easy to demonstrate, and indeed requires no amplification.
>
> b "It is then obvious that a great and permanent alteration in the environment of any race of animals induces new habits in these animals.
>
> c "Now, if a new environment, which has become permanent for some race of animals, induces new habits in these animals, that is to say, leads them to new activities which become habitual, the result will be the use of some one part in preference to some other part, and in some cases the total disuse of some part no longer necessary.
>
> d "Nothing of all this can be considered as hypothesis or private opinion; on the contrary, they are truths which in order to be made clear, only require attention and the observation of facts."

17 Assuming that Lamarck adduces evidence for this concept, there is another critical point that requires an explanation: not only do highly-evolved forms have more highly perfected

organs than less-evolved forms, but they also have parts (organs) that the lower forms lack entirely. What has Lamarck to say about the initial appearance of an organ in the evolution of a species? Careful reading of the next paragraph will reveal a rather surprising answer to this question:

> "We shall shortly see by the citation of known facts in evidence, in the first place, that new needs which establish a necessity for some part really bring about the existence of that part, as a result of efforts; and that subsequently its continued use gradually strengthens, develops and finally greatly enlarges it; in the second place, we shall see that in some cases, when the new environment and the new needs have altogether destroyed the utility of some part, the total disuse of that part has resulted in its gradually ceasing to share in the development of the other parts of the animal; it shrinks and wastes little by little, and ultimately, when there has been total disuse for a long period, the part in question ends by disappearing. All this is positive; I propose to furnish the most convincing proofs of it. ..."

18 In the next part of the paper, Lamarck cites an impressive array of directly observable biological facts which he believes his hypothesis explains in a satisfactory manner. Only a few of these will be presented here. In reading these, we should be on the alert to discern what his object is in presenting them. Also important is the question whether any other hypothesis offers an equally satisfactory explanation.

> "Now I am going to prove that the permanent disuse of any organ first decreases its functional capacity, and then gradually reduces the organ and causes it to disappear or even become extinct, if this disuse lasts for a very long period throughout successive generations of animals of the same race . ...
>
> "Since such a proposition could only be accepted on proof, and not on mere authority, let us endeavour to make it clear by citing the chief known facts which substantiate it.

c "The vertebrates, whose plan of organisation is almost the same throughout, though with much variety in their parts, have their jaws armed with teeth; some of them, however, whose environment has induced the habit of swallowing the objects they feed on without any preliminary mastication, are so affected that their teeth do not develop. The teeth then remain hidden in the bony framework of the jaws, without being able to appear outside; or indeed they actually become extinct down to their last rudiments.

d "In the right-whale, which was supposed to be completely destitute of teeth, M. Geoffroy has nevertheless discovered teeth concealed in the jaws of the foetus of this animal. The professor has moreover discovered in birds the groove in which the teeth should be placed, though they are no longer to be found there.

e "Even in the class of mammals, comprising the most perfect animals, where the vertebrate plan of organisation is carried to its highest completion, not only is the right-whale devoid of teeth, but the anteater (Myrmecophaga) is also found to be in the same condition, since it has acquired a habit of carrying out no mastication, and has long preserved this habit in its race.

f "Eyes in the head are characteristic of a great number of different animals, and essentially constitute a part of the plan of organisation of the vertebrates.

g "Yet the mole, whose habits require a very small use of sight, has only minute and hardly visible eyes, because it uses that organ so little.

h "Oliver's Spalax (Voyage en Egypte et en Perse), which lives underground like the mole, and is apparently exposed to daylight even less than the mole, has altogether lost the use of sight: so that it shows nothing more than vestiges of this organ. Even these vestiges are entirely hidden under the skin and other parts, which cover them up and do not leave the slightest access to light.

"The Proteus, an aquatic reptile allied to the salamanders, and living in deep dark caves under the water, has only vestiges of the organ of sight, vestiges which are covered up and hidden in the same way.

"The following consideration is decisive on the question which I am now discussing.

"Light does not penetrate everywhere; consequently animals which habitually live in places where it does not penetrate, have no opportunity of exercising their organ of sight, if nature has endowed them with one. Now animals belonging to a plan of organisation of which eyes were a necessary part, must have originally had them. Since, however, there are found among them some which have lost the use of this organ and which show nothing more than hidden and covered up vestiges of them, it becomes clear that the shrinkage and even disappearance of the organ in question are the results of a permanent disuse of that organ.

"Lastly, it was part of the plan of organisation of the reptiles, as of other vertebrates, to have four legs in dependence on their skeleton. Snakes ought consequently to have four legs, especially since they are by no means the last order of the reptiles and are farther from the fishes than are the batrachians (frogs, salamanders, etc.).

"Snakes, however, have adopted the habit of crawling on the ground and hiding in the grass; so that their body, as a result of continually repeated efforts at elongation for the purpose of passing through narrow spaces, has acquired a considerable length, quite out of proportion to its size. Now, legs would have been quite useless to these animals and consequently unused. Long legs would have interfered with their need of crawling and very short legs would have been incapable of moving their body, since they could only have had four. The disuse of these parts thus became permanent in the various races of these animals, and resulted in the complete disappearance of these same parts, although legs really belong to the plan of organisation of the animals of this class. ...

"We have seen that the disuse of any organ modifies, reduces and finally extinguishes it. I shall now prove that the constant use of any organ, accompanied by efforts to get the most out of it, strengthens and enlarges that organ, or creates new ones to carry on functions that have become necessary.

"The bird which is drawn to the water by its need of finding there the prey on which it lives, separates the digits of its feet in trying to strike the water and move about on the surface. The skin which unites these digits at their base acquires the habit of being stretched by these continually repeated separations of the digits; thus in course of time there are formed large webs which unite the digits of ducks, geese, etc., as we actually find them. In the same way efforts to swim, that is to push against the water so as to move about in it, have stretched the membranes between the digits of frogs, sea-tortoises, the otter, beaver, etc.

"On the other hand, a bird which is accustomed to perch on trees and which springs from individuals all of whom had acquired this habit, necessarily has longer digits on its feet and differently shaped from those of the aquatic animals that I have just named. Its claws in time become lengthened, sharpened and curved into hooks to clasp the branches on which the animal so often rests . ...

"It seems from the study of this fact that we may adopt one or other of the two following conclusions, and that neither of them can be verified.

"<u>Conclusion adopted hitherto</u>: Nature (or her Author) in creating animals, foresaw all the possible kinds of environment in which they would have to live, and endowed each species with a fixed organisation and with a definite and invariable shape, which compel each species to live in the places and climates where we actually find them, and there to maintain the habits which we know in them.

"<u>My individual conclusion</u>: Nature has produced all the species of animals in succession, beginning with the most imperfect or simplest, and ending her work with the most perfect, so as to create a gradually increasing complexity in their organisation;

> these animals have spread at large throughout all the habitable regions of the globe, and every species has derived from its environment the habits that we find in it and the structural modifications which observation shows us. ...
>
> "Everything then combines to prove my statement, namely: that it is not the shape either of the body or its parts which gives rise to the habits of animals and their mode of life; but that it is, on the contrary, the habits, mode of life and all the other influences of the environment which have in course of time built up the shape of the body and of the parts of animals. With new shapes, new faculties have been acquired, and little by little nature has succeeded in fashioning animals such as we actually see them.
>
> "Can there be any more important conclusion in the range of natural history, or any to which more attention should be paid than that which I have just set forth?"

Note: The above excerpts are portions of a somewhat longer passage forming a chapter in a long work by Lamarck. The omitted sections of the chapter are largely additional citations of directly observable phenomena which the doctrine of Lamarck explains satisfactorily (though no more so than certain other doctrines).

Unlike Buffon, whose meaning is often difficult to perceive, Lamarck is admirably clear. Indeed he well illustrates the type of nineteenth-century theorist whom the philosopher Whitehead had in mind when he spoke of "those clear-headed thinkers who were so clearly wrong." We all know how time overturned Lamarck's assumption that environmentally-induced bodily change can be transmitted. Yet we should be sure to remember that this idea was not merely Lamarck's. Nearly everybody, from Aristotle (360 B.C.) onward believed in the transmission of somatically acquired characters. Even Darwin coming a half-century after Lamarck subscribed to this notion.

Lamarck performed a service in furnishing a possible explanation of the events that might have led to progressive change including change sufficiently radical to produce all new species beyond the first two - one plant, one animal - which originated, he supposed, through spontaneous generation.

22 Without discrediting Lamarck's main contention, Darwin adds to it another which he considers more important. He sees occurring everywhere a phenomenon which would lead inevitably, generation to generation, to higher and higher adaptedness. The thing we want to note here is that, as he frankly admits, this phenomenon was called to his attention by another. In the early 1820's Darwin, just home from a three-year round-the-world voyage, read Thomas Malthus' "Essay on Population" (1801). Darwin was seeking some insight into the cause of that evolutionary progress which his studies of life in many climates and on several continents had so dramatically demonstrated.

23 Malthus himself was not interested in evolution, as suggested by the statement that

> a "In an inquiry concerning the improvement of society, the mode of conducting the subject which naturally presents itself, is -
>
> b 1. To investigate the causes that have hitherto impeded the progress of mankind towards happiness; and,
>
> c 2. To examine the probability of the total or partial removal of these causes in future.
>
> d "To enter fully into this question, and to enumerate all the causes that have hitherto influenced human improvement, would be much beyond the power of an individual. The principal object of the present essay is to examine the effects of one great cause intimately united with the very nature of man; which, though it has been constantly and powerfully operating since the commencement of society, has been little noticed by the writers who have treated this subject. The facts which establish the existence of this cause have, indeed, been repeatedly stated and acknowledged; but its natural and necessary effects have been almost totally overlooked; though probably among these effects may be reckoned a very considerable portion of that vice and misery, and of that unequal distribution of the bounties of nature, which it has been the unceasing object of the enlightened philanthropist in all ages to correct.

e
"The cause to which I allude, is the constant tendency in all animated life to increase beyond the nourishment prepared for it.

f "It is observed by Dr. Franklin, that there is no bound to the prolific nature of plants or animals but what is made by their crowding and interfering with each other's means of subsistence. Were the face of the earth, he says, vacant of other plants, it might be gradually sowed and overspread with one kind only, as, for instance, with fennel: and were it empty of other inhabitants, it might in a few ages be replenished from one nation only, as, for instance, with Englishmen.

g "This is incontrovertibly true. Throughout the animal and vegetable kingdoms Nature has scattered the seeds of life abroad with the most profuse and liberal hand; but has been comparatively sparing in the room and the nourishment necessary to rear them. The germs of existence contained in this earth, if they could freely develop themselves, would fill millions of worlds in the course of a few thousand years. Necessity, that imperious, all pervading law of nature, restrains them within the prescribed bounds. The race of plants and the race of animals shrink under this great restrictive law; and man cannot by any efforts of reason escape from it.

h
"In plants and irrational animals, the view of the subject is simple. They are all impelled by a powerful instinct to the increase of their species, and this instinct is interrupted by no doubts about providing for their offspring. Wherever, therefore, there is liberty, the power of increase is exerted, and the superabundant effects are repressed afterwards by want of room and nourishment.

i
"The effects of this check on man are more complicated. Impelled to the increase of his species by an equally powerful instinct, reason interrupts his career, and asks him whether he may not bring beings into the world for whom he cannot provide the means of support. If he attend to this natural suggestion, the restriction too frequently produces vice. If he hear it not, the human race will be

> be constantly endeavouring to increase beyond the means of subsistence. But as, by that law of our nature which makes food necessary to the life of man, population can never actually increase beyond the lowest nourishment capable of supporting it, a strong check on population, from the difficulty of acquiring food, must be constantly in operation. This difficulty must fall somewhere, and must necessarily be severely felt in some or other of the various forms of misery, or the fear of misery, by a large portion of mankind.

24 It should be noted that Malthus asserts not that population in fact increases but that it tends to do so. His special interest is in factors that prevent this tendency from materializing. He distinguishes (a) ultimate from immediate and (b) positive from preventive checks.

> a "The ultimate check to population appears then to be a want of food, arising necessarily from the different ratios according to which population and food increase. But this ultimate check is never the immediate check, except in cases of actual famine.
>
> b "The immediate check may be stated to consist in all those customs, and all those diseases, which seem to be generated by a scarcity of the means of subsistence; and all those causes, independent of this scarcity, whether of a moral or physical nature, which tend prematurely to weaken and destroy the human frame.
>
> c "These checks to population, which are constantly operating with more or less force in every society, and keep down the number to the level of the means of subsistence, may be classed under two general heads - the preventive and the positive checks.
>
> d "The preventive check, as far as it is voluntary, is peculiar to man, and arises from that distinctive superiority in his reasoning faculties which enables him to calculate distant consequences. The checks to the indefinite increase of plants and irrational animals are all either positive or, if preventive, involuntary. But man cannot

look around him, and see the distress which frequently presses upon those who have large families; he cannot contemplate his present possessions or earnings which he now nearly consumes himself, and calculate the amount of each share, when with very little addition they must be divided, perhaps, among seven or eight, without feeling a doubt whether, if he follow the bent of his inclinations, he may be able to support the offspring which he will probably bring into the world. In a state of equality, if such can exist, this would be the simple question. In the present state of society other considerations occur. Will he not lower his rank in life, and be obliged to give up in great measure his former habits? Does any mode of employment present itself by which he may reasonably hope to maintain a family? Will he not at any rate subject himself to greater difficulties, and more severe labour than in his single state? Will he not be unable to transmit to his children the same advantages of education and improvement that he had himself possessed? Does he even feel secure that, should he have a large family, his utmost exertions can save them from rags and squalid poverty, and their consequent degradation in the community? And may he not be reduced to the grating necessity of forfeiting his independence and of being obliged to the sparing hand of charity for support?

e

"These considerations are calculated to prevent, and certainly do prevent, a great number of persons in all civilised nations from pursuing the dictate of nature in an early attachment to one woman. ...

f "The positive checks to population are extremely various, and include every cause, whether arising from vice or misery, which in any degree contribute to shorten the natural duration of human life. Under this head, therefore, may be enumerated all unwholesome occupations, severe labour and exposure to the seasons, extreme poverty, bad nursing of children, large towns, excesses of all kinds, the whole train of common diseases and epidemics, wars, plague, and famine.

g "On examining these obstacles to the increase of population which are classed under the heads of preventive and positive checks, it will appear that they are all resolvable into moral restraint, vice, and misery.

h "Of the preventive checks, the restraint from marriage which is not followed by irregular gratifications may properly be termed moral restraint.

i "Promiscuous intercourse, unnatural passions, violations of the marriage bed, and improper arts to conceal the consequences of irregular connections are preventive checks that clearly come under the head of vice.

j "Of the positive checks, those which appear to arise unavoidably from the laws of nature, may be called exclusively misery; and those which we obviously bring upon ourselves, such as wars, excesses, and many others which it would be in our power to avoid, are of a mixed nature. They are brought upon us by vice, and their consequences are misery.

25 Darwin's discovery of Malthus' theory of "positive checks" is one of the most decisive events in the history of human thought. Notoriously he adds to Malthus' speculation, the further question: given the operation of "positive check" which organisms will perish, and which will survive? In answering this question he arrives at his famous conclusion that competition is one of the primary causes of progress.

The Search for the Unit of Life

[1]In the fifth century B.C. two Greek scientific thinkers, Leucippus and Democritus, developed the theory that the entire cosmos consists of just two components, namely (a) indivisible, impenetrable atoms of many different shapes and sizes and (b) empty space in which these atoms are moving. Democritus postulated, further, that the smallest, roundest, fastest-moving atoms were alive. He had the idea, which seems curious enough to us, that when these atoms occur in pure aggregation they constitute fire, whereas, when they possess just the right sort of interspersed distribution among certain other sorts of atoms, the resulting combination can move about, nourish itself, reproduce, in a word, live. We might say, then, that the small round rapidly-moving atoms were in a sense, for this particular early thinker, living units.

[2]A number of later Greek and Latin thinkers agreed with Democritus, but most did not accept his idea. After an episodic career, with some support and some opposition, the idea of living particles reappeared in the eighteenth century in a new formulation. A major French naturalist, Count Buffon, theorized (in 1749) that all living systems are built of certain quite large (but still subvisible) living particles which he called "organic molecules." At about the same time, energetic efforts were being made to interpret the visible microstructure of living bodies. Cells had been seen and described in the seventeenth century first by Robert Hooke (and then by such other microscopists as Leeuwenhoek, Malpighi, and Grew). But in 1750 the idea had not yet been put forward - that the whole organism is built out of cells. The microscopes then in use were not of the best, and the biologists of the day, especially the Dutch medical teacher and theorist Boerhaave and the Swiss physiologist von Haller, interpreted what they saw through their lenses as a complex meshwork of fibers. They saw what today we know to be cells but thought these were merely the open spaces in the three-dimensional fibrous mesh. Boerhaave and Haller did not think of the fibers as living, but certain other thinkers of the period held that view. One of these was the physician Theophile Bordeu; another was the philosopher and man of letters Denis Diderot. Diderot thought very cleverly and critically about biology but did not personally engage in biological research. Bordeu and Diderot supposed that the constitutive fibers of the body are individually alive. Diderot suggested that after the death of the organism as a whole certain individual fibers can continue to live (he probably got this idea from the microscopic worms that are sometimes to be found in decaying flesh). These two thinkers also thought that the elongated male sex cells, clearly visible through the microscope, were individual living fibers.

[3]Diderot developed the idea that in an animal <u>living particles</u> (like those stipulated by Buffon) compose <u>living fibers</u> (he got this idea from Bordeu) which compose <u>living organs</u> (this, too, is Bordeu's idea) which, finally, compose the animal as a whole.

[4]At the end of the century (1798-1801) a brilliant young anatomist takes issue with the idea of Diderot and Bordeu, and in doing so ushers in a major reform in biological thought. Let us see what this young Frenchman, whose name is Xavier Bichat, has to say about the units of life.

> [5]"All animals are an assemblage of different organs, which executing each a function, concur in their own manner, to the preservation of the whole. It is several separate machines in a general one, that constitutes the individual. Now these separate machines are themselves formed by many textures of a very different nature, and which really compose the elements of these organs. Chemistry has its simple bodies, which form, by the combinations of which they are susceptible, the compound bodies; such are caloric, light, hydrogen, oxygen, carbon, azote, phosphorus, &c. In the same way anatomy has its simple textures, which, by their combinations four with four, six with six, eight with eight, &c. make the organs. These textures are (he here lists 21 sorts of "textures" which we would call "tissues")
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> [6]"These are the true organized elements of our bodies. Their nature is constantly the same, wherever they are met with. As in chemistry, the simple bodies do not alter, notwithstanding the different compound ones they form. The organized elements of man form the particular object of this work.
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> [7]"The idea of thus considering abstractedly the different simple textures of our bodies, is not the work of the imagination; it rests upon the most substantial foundation, and I think it will have a powerful influence upon physiology as well as practical medicine. Under whatever point of view we examine them, it will be found that they do not resemble each other; it is nature and not science that has drawn the line of distinction between them."

[8]Bichat supposed that tissue was endowed with one or more of four unexplicable "vital properties" which enable it to behave in a special way. He classifies these properties as follows:

	Organic	Animal
Sensibility	common to all tissue	common to all tissue; predominant in none
Contractility	a. invisible; in all tissue b. visible; in involuntary or smooth muscle	voluntary skeletal muscle

[9]"Shall I speak of the vital properties? See the animal sensibility predominant in the nerves, contractility of the same kind particularly marked in the voluntary muscles, sensible organic contractility, forming the peculiar property of the involuntary, insensible contractility and sensibility of the same nature, which is not separated from it more than from the preceding, characterizing especially the glands, the skin, the serous surfaces, &c. &c. See each of these simple textures combining, in different degrees, more or less of these properties, and consequently living with more or less energy . . ..

[10]"Much has been said since the time of Bordeu, of the peculiar life of each organ, which is nothing else than that particular character which distinguishes the combination of the vital properties of one organ, from those of another. Before these properties had been analyzed with exactness and precision, it was clearly impossible to form a correct idea of this peculiar life. From the account I have just given of it, it is evident that the greatest part of the organs being composed of very different simple textures, the idea of a peculiar life can only apply to these simple textures, and not to the organs themselves . . ..

[11]"When we study a function, it is necessary carefully to consider in a general manner, the compound organ that performs it; but when you wish to know the properties and life of this organ, it is absolutely necessary to decompose it. In the same way, if you would have only general notions of anatomy, you can study each organ as a whole; but it is essential to separate the textures, if you have a desire to analyze with accuracy its intimate structure."

[12]Bichat's designation of tissues as living units leaves unanswered the question why one tissue's properties differ from another's. He considered the problem insoluble. But as we shall see students of cells were to provide a partial answer. During the second half of the eighteenth and first decades of the nineteenth century, it became gradually apparent that, as far as plants are concerned, they consist entirely - or almost entirely - of cells, though cells were not thought of, at first, as living units. Microscopists paid attention mostly to the cell <u>wall</u> and were only secondarily interested in the <u>contents</u>.

[13]The cell nucleus was first seen in the seventeenth century, but only in 1835 did the English botanist Robert Brown portray it accurately. A few years thereafter, namely in 1838, another botanist Matthias Schleiden concluded from extensive studies that not only do all cells have a nucleus at least temporarily but further that when cells are formed, a nucleus is formed first and then the cell develops around the nucleus. He did not have any picture of cell-division.

He thought the nucleus arose through molecular aggregation in a homogeneous extracellular matter in the neighborhood of other living cells. Schleiden also picked up another idea (expressed somewhat similarly ten years before by another German botanist Jan Meyen) namely that the young cell is the unit of life; it is in a sense an organism all in itself, and the whole plant is a sort of superorganism. Each cell, Schleiden said, leads a double life: its own life and its life as a member of an aggregate - somewhat as each human lives both as an individual and as a member of an organized society.

14 Schleiden communicated all these thoughts orally to his friend and associate Schwann, who immediately began to search in animals, especially animal embryos, to see whether there, too, no new cell can be formed without the prior formation of a nucleus. A year later he published a book (Microscopical Researches into the Accordance . . . of Animals and Plants) that was to change the course of biology. From this book, the following excerpts - giving Schwann's main conclusions - have been taken.

> 15 "The formative process of the cells of plants was clearly explained by the researches of Schleiden, and appeared to be the same in all vegetable cells. So that when plants were regarded as something special, as quite distinct from the animal kingdom, one universal principle of development was observed in all the elementary particles of the vegetable organism, and physiological deductions might be drawn from it with regard to the independent vitality of the individual cells of plants, &c. But when the elementary particles of animals and plants were considered from a common point, the vegetable cells seemed to be merely a separate species, co-ordinate with the different species of animal cells, just as the entire class of cells was co-ordinate with the fibres, &c., and the uniform principle of development in vegetable cells might be explained by the slight physiological difference of their elementary particles.
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> 16 "The object, then, of the present investigation was to show, that the mode in which the molecules composing the elementary particles of organisms are combined does not vary according to the phsyiological signification of those particles, but that they are everywhere arranged according to the same laws; so that whether a muscular fibre, a nerve-tube, an ovum, or a blood-corpuscle is to be formed, a corpuscle of a certain form, subject only to some modifications, a cell-nucleus, is universally generated in the first instance; around this corpuscle a cell is developed, and it is the changes which one or more of these cells undergo that determine the subsequent forms of the elementary particles; in short, that there is one common principle of development for all the elementary particles of organisms.

17"In order to establish this point it was necessary to trace the progress of development in two given elementary parts, physiologically dissimilar, and to compare them with one another. If these not only completely agreed in growth, but in their mode of generation also, the principle was established that elementary parts, quite distinct in a physiological sense, may be developed according to the same laws. This was the theme of the first section of this work. The course of development of the cells of cartilage and of the cells of the chorda dorsalis was compared with that of vegetable cells. Were the cells of plants developed merely as infinitely minute vesicles which progressively expand, were the circumstances of their development less characteristic than those pointed out by Schleiden, a comparison, in the sense here required, would scarcely have been possible. We endeavoured to prove in the first section that the complicated process of development in the cells of plants recurs in those of cartilage and of the chorda dorsalis. We remarked the similarity in the formation of the cell-nucleus, and of its nucleolus in all its modifications, with the nucleus of vegetable cells, the pre-existence of the cell-nucleus and the development of the cell around it, the similar situation of the nucleus in relation to the cell, the growth of the cells, and the thickening of their wall during growth, the formation of cells within cells, and the transformation of the cell-contents just as in the cells of plants. Here, then, was a complete accordance in every known stage in the progress of development of two elementary parts which are quite distinct, in a physiological sense, and it was established that the principle of development in two such parts may be the same, and so far as could be ascertained in the cases here compared, it is really the same.

18"But regarding the subject from this point of view we are compelled to prove the universality of this principle of development, and such was the object of the second section. For so long as we admit that there are elementary parts which originate according to entirely different laws, and between which and the cells which have just been compared as to the principle of their development there is no connexion, we must presume that there may still be some unknown difference in the laws of the formation of the parts just compared, even though they agree in many points. But, on the contrary, the greater the number of physiologically different elementary parts, which, so far as can be known, originate in a similar manner, and the greater the difference of these parts in form and physiological signification, while they agree in the perceptible phenomena of their mode of formation, the more safely may we assume that all elementary parts have one and the same fundamental principle of development. It was, in fact, shown that the elementary parts of most tissues, when traced backwards from their state of complete development to their primary condition are only developments of cells, which so far as our observations, still incomplete, extend, seemed to be formed in a similar manner to the cells compared in the first section. As might be expected, according to this principle the cells, in their earliest stage, were almost always furnished with the characteristic nuclei, in some the pre-existence of this nucleus, and the formation of the cell around it was proved, and it was then that the cells began to undergo the various modifications, from which the diverse forms of the elementary parts of animals resulted. Thus the apparent difference in the mode of development of muscular fibres and blood-corpuscles, the former originating by the arrangement of globules in rows, the latter by the formation of a vesicle around a globule, was reconciled in the fact that muscular fibres are not elementary parts co-ordinate with blood-corpuscles, but that the globules composing muscular fibres at first correspond to the blood-corpuscles, and are like them, vesicles or cells, containing the characteristic cell-nucleus, which, like the nucleus of the blood-corpuscles, is probably formed before the cell. The elementary parts of all tissues are formed of cells in an analogous, though very diversified manner, so that it may be asserted, <u>that there is one universal principle of development for the elementary parts of organisms, however different, and that this principle is the formation of cells</u>. This is the chief result of the foregoing observations.

19"The same process of development and transformation of cells within a structureless substance is repeated in the formation of all the organs of an organism, as well as in the formation of new organisms; and the fundamental phenomenon attending the exertion of productive power in organic nature is accordingly as follows: <u>a structureless substance is present in the first instance, which lies either around or in the interior of cells already existing; and cells are formed in it in accordance with certain laws, which cells become developed in various ways into the elementary parts of organisms.</u>

20"The development of the proposition, that there exists one general principle for the formation of all organic productions, and that this principle is the formation of cells, as well as the conclusions which may be drawn from this proposition, may be comprised under the term <u>cell-theory</u>, using it in its more extended signification, whilst in a more limited sense, by theory of the cells we understand whatever may be inferred from this proposition with respect to the powers from which these phenomena result."

21Schwann's theory is significant both in its correctness in certain points and its errors. Modern biology does agree that all the parts of organisms are either made of, or develop from, cells. It radically disagrees with Schwann's picture of new-cell formation. As a matter of fact, after only a dozen years, the cytologist, Robert Remak, would pretty well discredit the idea that cells form in any other way than through cell division.

22 While we are on the subject of Schwann, however, it is interesting to note how he connects theory with a major philosophical issue of the day.

23 "The various opinions entertained with respect to the fundamental powers of an organized body may be reduced to two, which are essentially different from one another. The first is, that every organism originates with an inherent power, which models it into conformity with a predominant idea, arranging the molecules in the relation necessary for accomplishing certain purposes held forth by this idea. Here, therefore, that which arranges and combines the molecules is a power acting with a definite purpose. A power of this kind would be essentially different from all the powers of inorganic nature, because action goes on in the latter quite blindly. A certain impression is followed of necessity by a certain change of quality and quantity, without regard to any purpose. In this view, however, the fundamental power of the organism (or the soul, in the sense employed by Stahl) would, inasmuch as it works with a definite individual purpose, be much more nearly allied to the immaterial principle, endued with consciousness which we must admit operates in man.

24 "The other view is, that the fundamental powers of organized bodies agree essentially with those of inorganic nature, that they work altogether blindly according to laws of necessity and irrespective of any purpose, that they are powers which are as much established with the existence of matter as the physical powers are." . . .

25 "The first view of the fundamental powers of organized bodies may be called the <u>teleological</u>, the second the <u>physical</u> view.

"In physics, all those explanations which were suggested by a teleological view of nature, as "horror vacui," and the like, have long been discarded. But in animated nature, adaptation--individual adaptation--to a purpose is so prominently marked, that it is difficult to reject all teleological explanations. Meanwhile it must be remembered that those explanations, which explain at once all and nothing, can be but the last resources, when no other view can possibly be adopted; and there is no such necessity for admitting the teleological view in the case of organized bodies. The adaptation to a purpose which is characteristic of organized bodies differs only in degree from what is apparent also in the inorganic part of nature; and the explanation that organized bodies are developed, like all the phenomena of inorganic nature, by the operation of blind laws framed with the matter, cannot be rejected as impossible. Reason certainly requires some ground for such adaptation, but for her it is sufficient to assume that matter with the powers inherent in it owes its existence to a rational Being. Once established and preserved in their integrity, these powers may, in accordance with their immutable laws of blind necessity, very well produce combinations, which manifest, even in a high degree, individual adaptation to a purpose. If, however, rational power interpose after creation merely to sustain, and not as an immediately active agent, it may, so far as natural science is concerned, be entirely excluded from the consideration of the creation."

26 Schwann concludes his great study with an effort to explain cell formation as if it were a modified form of crystal-formation. The effort is not very successful but it is historic in stimulating later workers to more successful attempts at physico-chemical explication.

27 The cell theory, even after the correction of its major errors, did not gain immediate acceptance. There was a great deal of interest in the idea that life resides in the apparently homogeneous background substance ("hyaloplasm") which cells seem to contain. Some scientists agreed that not the hyaloplasm but the visibly-structured "ergastoplasm" was the living part. In either case, many were of the opinion that there are <u>subvisible living units</u> ("micromeres") that make up the living part of the cell. More than twenty famous biologists come forward with micromeritic units of life.

28 We illustrate with selections from one such theory, that of the important late 19th century physiologist, Max Verworn who calls living micromeres "biogens."

> 29 "A long time ago Pflüger, as has been seen elsewhere, called attention to this important difference between the proteid in dead and that in living cell-substance in his valuable work upon oxidation in living substance, and distinguished clearly between living proteid and dead proteid. The fundamental difference between the two consists in the fact that the atoms of the dead proteid molecule are in a condition of stable equilibrium, while the living proteid molecule possesses a very labile constitution.
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> 30 . . ."The great lability that distinguishes it from other proteids, can be conditioned only by an essentially different constitution. Further, critics will rightly object to the terming of this hypothetical compound a 'living proteid molecule,' for there is a certain contradiction in calling a molecule living. The word "living" can be applied only to something that exhibits vital phenomena. Hence, the expression 'living substance' is well justified, for vital phenomena may be observed in living substance as a whole. But a molecule cannot exhibit vital phenomena, at least as long as it exists as such; for if any changes appear in it it is no longer

the original molecule; and, if it continues unchanged, vital phenomena are not present in it. The latter, which are based upon chemical processes, can be associated only with the construction or the destruction of the molecule in question; and thus the application of another name to the compound that is at the focus of life is doubly justified. In order to distinguish this body, therefore, from dead proteid and to indicate its high significance in the occurrence of vital phenomena, it appears fitting to replace the term 'living proteid' with that of biogen.

31"The metabolism of living substance, upon which all life is based, is conditioned by the existence of certain very labile compounds, which stand next to the proteids and on account of their elementary significance in life are best termed biogens. To a certain degree the biogens are continually undergoing spontaneous decomposition, just as is the case with other organic bodies, e.g., prussic acid. . . . In this respect the biogens can be compared to explosive substances, the atoms of which possess likewise very labile equilibrium and which upon receiving violent shocks explode, i.e., rearrange their atoms into more stable compounds; . . .. But, in contrast to other explosive bodies, we must evidently ascribe to the biogens the peculiarity that in decomposition the whole molecule is not destroyed, but that certain groups of atoms, which are formed by rearrangement, are split off, while the residue is again built up into a complete biogen molecule at the expense of the materials found in its vicinity, ... The substances still present in the living substance in addition to the biogens are merely 'satellites' of the biogen molecule, and either serve for its construction or are derived from its transformations. Thus far no substances have been made known in living matter, which can stand in any nearer or more remote relations to the biogens. Nevertheless, from the variety in the decomposition-products that are excreted by different kinds of cells in metabolism, it must be concluded with great probability that biogen molecules have not in all cells exactly the same chemical composition, but that there are various biogen bodies, and even that the biogens not only of different cells, but of the various differentiations of the same cell, such as exoplasm, myoids or contractile fibres, muscle-fibrillae, cilia, etc., have different constitutions, although they agree in essential structure. The biogens, therefore, are the real bearers of life. Their continual decomposition and reformation constitutes the life-process, which is expressed in the manifold vital phenomena."

32During the twentieth century the debate concerning the unit of life has continued. The question is whether anything less than a cell - e.g. a virus particle, a gene, etc. - should be thought of as living. The answer depends, in part, on our definition of life. A majority of biologists would define life rather amply, would not admit the individual particle or macromolecule to the designation living, and would say that life goes on only in intact cells. Until an agreement is reached on the definition of life, the question is open.

Historic Studies on Nerves

In this paper, we wish to show the beginning of the break-through that occurred in the early nineteenth century after a very long period of stagnation in the investigation of nerve-function. It was largely due to the paper part of which we shall read here that a modern science of neurology became possible. Galen (175 A.D.) did surgical operations (on wounded soldiers and gladiators, among others) and distinguished between sensory and motor nerves. After that, there was no significant progress in the study of nerves until the sixteenth century when the great anatomist Vesalius (1543) traced out the nerve connections and got an accurate general idea of the gross topography of the brain. But, almost no branch of biology advanced so slowly as neurology, so that Bell (1810) is justified in the following complaint.

> 1"The want of any consistent history of the brain and nerves, and the dull unmeaning manner which is in use of demonstrating the brain, may authorize any novelty in the manner of treating the subject."

A major problem of nerve function is: how are the nerves and brain organized to permit sensory discrimination? How do we distinguish sight from sound, and one sound from another? Note how Bell begins.

> 2"The prevailing doctrine of the anatomical schools is, that the whole brain is a common sensorium [i.e. any part of it can receive any and all sorts of incoming impulses] ; that the extremities of the nerves are organized, so that each is fitted to receive a peculiar impression [today we would say stimulus] ; or that they are distinguished from each other only by delicacy of structure, and by a corresponding delicacy of sensitivity; that the nerve of the eye, for example, differs from the nerve of touch only in the degree of its sensibility [sensitivity]. It is imagined that impressions [today we should say impulses] thus differing in kind, are carried along the nerves to the sensorium, and presented to the mind; and that the mind, by the same nerves which receive sensation, sends out the mandate of the will to the moving parts of the body.

> 3"It is further imagined, that there is a set of nerves, called vital nerves [i.e. the visceral or autonomic system] , which are less strictly connected with the sensorium, or which have upon them knots [today, ganglia] , cutting off the course of sensation, and thereby excluding the vital motions from the government of the will.

> 4"This appears sufficiently simple and consistent until we begin to examine anatomically the structure of the brain, and the course of the nerves - then all is confusion: the divisions and subdivisions of the brain, the circuitous course of nerves, their intricate connections, their separation and re-union, are puzzling in the last degree, and are indeed considered as things inscrutable. Thus it is that he who knows the parts the best, is most in a maze, and he who knows least of anatomy, sees least inconsistency in the commonly received opinion."

Note now the break in the chain of thought, contrasting what follows in paragraphs 5, 6, and 7. The main thing to be on the lookout for is <u>to what Bell ascribes our power of discrimination</u>.

5"In opposition to these opinions, I have to offer reasons for believing that the cerebrum and cerebellum are different in function as in form; that the parts of the cerebrum have different functions; and that the nerves which we trace in the body are not single nerves possessing various powers, but bundles of different nerves, whose filaments are united for the convenience of distribution, but which are distinct in office, as they are in origin from the brain.

6"That the external organs of the senses have the matter of the nerves [today, sensory cells] adapted to receive certain impressions [stimuli], while . . . corresponding organs of the brain are put in activity by [particular] external excitement[s]: that the idea of perceptions [discrimination] is according to the part of the brain to which the nerve is attached. . .:

7"That the nerves of sense, the nerves of motion, and the vital nerves, are distinct through their whole course, though they seem sometimes united in one bundle; and that they depend for their attributes on the organs of the brain to which they are severally attached."

Paragraph 9 starts a new line of thought. Be sure you see what the function of paragraph 9 is.

9"The view which I have to present will show why there are divisions and many distinct parts in the brain; why some nerves are simple in their origin and distribution, and others intricate beyond description. It will explain the apparently accidental connection between the twigs of nerves. It will do away with the difficulty of conceiving how sensation and volition should be the operation of the same nerve at the same moment. It will show how a nerve may lose one property and retain another; and it will give an interest to the labors of the anatomist in tracing nerves."

Paragraphs 10, 11, and 12 give three items of information to be used in constructing a theory of sensory discrimination.

10"It is admitted that neither bodies nor the images of bodies enter the brain. It is indeed impossible to believe that color can be conveyed along a nerve; or the vibration in which we suppose sound to consist can be retained in the brain; but we can conceive, and have reason to believe, that an impression is made upon the organs of the outward senses, when we see, or hear, or taste.

11"In this inquiry, it is most essential to observe, that while each organ of sense is provided with a capacity of receiving certain changes to be played upon it, as it were, yet each is utterly incapable of receiving the impression destined for another organ of sensation.

12"It is also very remarkable that an impression made on two different nerves of sense, though with the same instrument, will produce two distinct sensations; and the ideas resulting will only have relation to the organ affected.

"As the announcing of these facts forms a natural introduction to the anatomy of the brain, which I am about to deliver, I shall state them more fully."

Bell thinks that (a) each sense organ is normally activated by only one sort of stimulus ("impression") but that (b) the conscious sensation produced by that nerve depends on the brain region to which it is attached. He illustrates (but does not fully prove) the former point with respect to the tongue.

13"There are four kinds of papillae on the tongue, but with two of those only do we have to do at present. Of these, the papillae of one kind form the seat of the sense of taste; the other papillae (more numerous and smaller) resemble the extremities of the nerves in the common skin, and are the organs of touch in the tongue. When I take a sharp steel point and touch one of these papillae, I feel the sharpness. The sense of touch informs me of the shape of the instrument. When I touch a papilla of taste, I have a sensation similar to the former. I know not that a point touches the tongue, but I am sensible of a metallic taste, and the sensation passes backward on the tongue.

He now turns to the second point and begins by refuting the idea that we distinguish sight from touch by virtue of the extra sensitivity of the optic nerve.

14"In the operation of couching the cataract, the pain of piercing the retina with a needle is not so great as that which proceeds from a grain of sand under the eyelid. And although the derangement of the stomach sometimes marks the injury of an organ so delicate, yet the pain is occasioned by piercing the outward coat, not by the affection of the expanded nerve of vision.

15"If the sensation of light were conveyed to us by the retina, the organ of vision, in consequence of that organ being as much more sensible than the surface of the body as the impression of light is more delicate than that pressure which gives us the sense of touch; what would be the feelings of a man subjected to an operation in which a needle were pushed through the nerve? Life could not bear so great a pain.

16"But there is an occurrence during this operation on the eye, which will direct us to the truth: when the needle pierces the eye, the patient has the sensation of a spark of fire before the eye."

The latter point suggests that a given nerve can be affected by more than one sort of stimulus. This gives a way of deciding whether the conscious sensation depends (a) on the sort of stimulus applied or (b) the part of the brain that receives the impulse.

> 17"This fact is corroborated by experiments made on the eye. When the eyeball is pressed on the side, we perceive various colored light. Indeed, the mere effect of a blow on the head might inform us, that sensation depends on the exercise of the organ effected, not on the impressions conveyed to the external organ; for by the vibration caused by the blow, the ears ring and the eye flashes light, while there is neither light nor sound present.
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> 18"It may be said that there is here no proof of the sensation being in the brain more than in the external organ of sense. But when the nerve of a stump is touched, the pain is as if in the amputated extremity."

In a famous experiment, Bell discovers that the dorsal and ventral roots of the spinal nerves have different functions.

> 19"Next, considering that the spinal nerves have a double root, and being of the opinion that the properties of the nerves are derived from their connections with the parts of the brain, I thought that I had an opportunity of putting my opinion to the test of experiment, and of proving at the same time that nerves of different endowments were in the same cord, and held together by the same sheath.
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> 20"On laying bare the roots of the spinal nerves, I found that I could cut across the posterior fasciculus of nerves, which took its origin from the posterior portion of the spinal marrow, without convulsing the muscles of the back; but that on touching the anterior fasciculus with the point of a knife, the muscles of the back were immediately convulsed."

The ventral root of the nerve is, then, motor. Other experiments presently convince him that the <u>dorsal</u> root is sensory.

Investigation of Enzyme Action

Background

[1]Aristotle (ca. 360 B.C.) and Galen (ca. 180 A.D.) thought that the food we eat is transformed into tissue through a sequence of changes caused in it by the transforming influence of the stomach (food ⟶ chyle), liver (chyle ⟶ blood), and organs (blood ⟶ tissue). Galen said each of these organs had a certain "faculty" for changing the substances presented to it.

[2]A more experimental approach was tried in the mid-eighteenth century when the French physicist René de Réaumur performed two sorts of experiments on buzzards and falcons. He enclosed meat in a perforated lead tube, let the bird swallow the tube, recovered it and found the meat inside the tube had been dissolved. Something, he thought, must have entered the tube and dissolved the meat. To test this hypothesis he enclosed a sponge in the tube, recovered it, and was able to squeeze from the sponge a fluid. He hoped that this fluid would dissolve meat and, though the experiment failed, clung to the idea that he had discovered a digestive fluid. Time was to uphold this belief.

[3]In 1837, Schwann convinced himself that the fermentive transformation of sugar into alcohol is caused by a microscopic plant present in the fermenting system. Reporting his experiments, Schwann says:

> [4]"Four flasks were filled with a mixture of cane sugar and brewer's yeast, and were sealed. All were immersed in boiling water long enough (10 minutes) to heat them to the same temperature. After removal and cooling, the flasks were inverted under mercury and air was introduced into them, until the flasks were about 1/4 to 1/3 filled with air. In one case the air had been led in through a thin glass tube heated red hot. The air entering the other flask was not so heated. Tests showed that such heating does not alter the usual 19.4% of oxygen present in air. . . . In 4 to 6 weeks, fermentation commenced in the flask that had received unheated air . . .. The other flasks, after two to three months, are unaltered." Schwann concludes that "in alcoholic fermentation (as in putrefaction) not oxygen but a heat-labile substance in air is responsible."
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> [5]"We are brought to the conclusion that alcoholic fermentation is probably a breakdown of sugar occasioned by the growth of infusoria or some sort of plant . . .. The brewer's yeast showed, under the microscope, its familiar granular appearance, always found in fermentation, here converted into chains. Some were round; most were

oval, light yellow, single or - usually - in chains of two to eight or more. In sum, their appearance was entirely like that of many of the jointed fungi, and it is indubitably a plant . . . more like a fungus than an alga, since green pigment is lacking."

[6]Though upheld by experiments of the French scientist Cagniard-Latour (1838), Schwann's idea was not generally accepted. The influential German chemist, Liebig, opposed it. He insisted on the historic view according to which fermentation is a self-propagating chemical reaction. "The cause of fermentation," says Liebig (1839), is the ability of certain chemical substances, when decomposing or combining, to force or allow adjacent matter to undergo a similar sort of change." Liebig had to acknowledge the presence of microscopic granules where fermentation is going on but refused to admit that they caused it. He thought that during fermentation, yeast decomposes and induces decomposition in other substances nearby, e.g., the decomposition of sugar into alcohol.

[7]Liebig was opposed by the great French biochemist (later, bacteriologist) Louis Pasteur. Pasteur showed that, far from decomposing, yeast (or some related organism) grows while fermentation proceeds. He commences his work with the fermentative transformation of sugar into lactic acid (1857).

[8]To secure this reaction we mix sugar solution, chalk, and a protein. As the fermentation proceeds, a gray deposit is formed at the upper surface of the fermenting solution. Pasteur adds a bit of this gray matter to a sterile solution of protein, chalk and sugar. Again the deposit appears (at the same rate that the chalk disappears).

[9]When examined microscopically, the gray substance looks like yeast, though its grains are smaller. Pasteur discovers that a tiny fleck of this gray substance transferred to a similar solution of sugar and some protein substance induces in it a lively production of lactic acid and appears to multiply, and presently deposits a gray ring in the new flask comparable to that in the old.

[10]A few years later he publishes the following abstract of a report on alcoholic fermentation. It is historic in proving the possibility of life in the absence of air (anerobic life).

<u>Influence of Oxygen on the Development of Yeast and on Alcoholic Fermentation</u>
by Louis Pasteur, Paris, 1861

[11]"M. Pasteur gives the result of his researches on the fermentation of sugar and the development of yeast-cells,

according as that fermentation takes place apart from the influence of free oxygen or in contact with that gas. His experiments, however, have nothing in common with those of Gay-Lussac, which were performed with the juice of grapes crushed under conditions where they would not be affected by air, and then brought into contact with oxygen.

[12]"Yeast, when perfectly developed, is able to bud and grow in a saccharine and albuminous liquid, in the complete absence of oxygen or air. In this case but little yeast is formed, and a comparatively large quantity of sugar disappears--sixty or eighty parts for one of yeast formed. Under these conditions fermentation is very sluggish.

[13]"If the experiment is made in contact with the air, and with a great surface of liquid, fermentation is rapid. For the same quantity of sugar decomposed much more yeast is formed. The air with which the liquid is in contact is absorbed by the yeast. The yeast develops very actively, but its fermentative character tends to disappear under these conditions; we find, in fact, that for one part of yeast formed, not more than from four to ten parts of sugar are transformed. The fermentative character of this yeast nevertheless, continues, and produces even increased effects, if it is made to act on sugar apart from the influence of free oxygen.

[14]"It seems, therefore, natural to admit that when yeast functions as a ferment by living apart from the influence of air, it derives oxygen from the sugar, and that this is the origin of its fermentative character.

[15]"M. Pasteur explains the fact of immense activity at the commencement of fermentations by the influence of the oxygen of the air held in solution in the liquids, at the time when the action commences. The author has found, moreover, that the yeast of beer sown in an albuminous liquid, such as yeast-water, still multiplies, even when there is not a trace of sugar in the liquid, provided always that atmospheric oxygen is present in large quantities. When deprived of air, under these conditions, yeast does not germinate at all. The same experiments may be repeated with albuminous liquid, mixed with a solution of non-fermentable sugar, such as ordinary crystallized milk-sugar. The results are precisely the same.

[16]"Yeast formed thus in the absence of sugar does not change its nature; it is still capable of causing sugar to ferment, if brought to bear upon that substance apart from air. It must be remarked, however, that the development of yeast is effected with great difficulty when it has not a fermentable substance for its food. In short, the yeast of beer acts in exactly the same manner as an ordinary plant, and the analogy would be complete if ordinary plants had such an affinity for oxygen as permitted them to breathe by appropriating this element from unstable compounds, in which case, according to M. Pasteur, they would appear as ferments for those substances.

[17]"M. Pasteur declares that he hopes to be able to realize this result, that is to say, to discover the conditions under which certain inferior plants may live apart from air in the presence of sugar, causing that substance to ferment as the yeast of beer would do."

[18]Pasteur's work had a transforming influence on the history of biology. He effectively demonstrated, on good experimental evidence, that living micro-organisms can cause (a) fermentation, (b) putrefaction and (c) disease. The repercussions of these discoveries were both theoretically and practically revolutionary. They made it possible to understand and control industrial fermentations (especially the manufacture of beer and wine), to find ways of preserving food and other organic materials (as exemplified by the "Pasteurization" of milk), and to fight infectious diseases. Closely linked with Pasteur's discovery that micro-organisms can cause putrefaction came his personal conviction and ultimate convincing demonstration that the reverse is not true. Micro-organisms cannot arise spontaneously in putrescing materials.

[19]Nevertheless, Pasteur was in error on one point, and this is a little surprising in so good a chemist. He believed that, to cause fermentation, micro-organisms must necessarily be alive. He saw fermentation as a vital activity of the living cell. This idea was often debated, and was effectively countered by the following paper published a generation later by the German biochemist Eduard Buchner (see below).

Alcoholic Fermentation Without Yeast Cells
by Eduard Buchner

Abridged from Berichte deutsche Chemische Gesellschaft, Vol. 30, pp. 117-124 (1897). Translated by M. L. Gabriel, GREAT EXPERIMENTS IN BIOLOGY, (C) 1955. Here used by special permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey.

[20]"Separation of the fermentation process from living yeast cells has up to now not been successfully accomplished; in the following communication an experiment is described that solves this problem.

[21]"One thousand grams of brewer's yeast, cleaned as for pressing into cakes, but without the addition of potato starch, is carefully mixed with an equal weight of quartz sand* and 250 grams of diatomaceous earth, and then ground until the mass becomes moist and plastic. To this dough, 100 gms of water are added and the dough is wrapped in a cloth and

*Glass powder, because of its mild alkaline reaction, is less suitable.

gradually brought under a pressure of 4-500 atmospheres. Three hundred ccm of juice are thus obtained. The remaining cake is once again ground, strained and mixed with 100 gms of water. Subjected once more to the same pressure in the hydraulic press, it yields 150 cc more of juice. Therefore, out of a kilogram of yeast one obtains 500 cc of juice which contains about 300 cc of cellular material. To remove a slight remaining turbidity, the juice is finally shaken up with 4 gms of fuller's earth and filtered through filter paper, the first part of the filtrate being refiltered repeatedly.

22"The juice thus obtained has the appearance of a clear but opalescent yellow liquid with a pleasant yeasty smell . . ..

23"The most interesting property of the juice is the fact that it is capable of fermenting carbohydrate. When it is mixed with an equal volume of a concentrated cane sugar solution a steady evolution of carbon dioxide begins in as little as 1/4-1 hour, and continues for days. Exactly the same results are obtained with glucose, fructose, and maltose; on the other hand, no fermentation takes place in mixtures of juice with saturated lactose or mannitose, just as these substances are not fermented by living brewer's yeast cells. Mixtures of juice and sugar solution that have been allowed to ferment for several days and placed in an ice chest gradually become turbid, without giving evidence of the presence of any microscopic organisms; on the other hand, at a magnification of 700 times, a fairly large number of particles of albuminoids are visible, the formation of which is probably due to the acid arising during the course of fermentation. Saturation of the mixture of juice and saccharose solution with chloroform does not inhibit the fermentation, but it leads prematurely to the separation of a small amount of albumin. Neither is the power of fermentation destroyed by filtration of the juice through a sterilized Berkefeldt filter of diatomaceous earth, which certainly retains all yeast cells; a mixture of a quite clear filtrate with sterilized cane sugar solution begins to ferment, although with a delay of about one day, even at the temperature of the ice chest. If a parchment paper bag filled with juice is suspended in thirty-seven per cent cane sugar solution, the outer surface of the bag becomes covered after several hours with innumerable tiny gas bubbles, naturally an active evolution of gas could also be observed in the inner surface as a consequence of the inward diffusion of sugar solution. Further experiments will be necessary to decide whether the agent responsible for fermentation has the capacity to diffuse through parchment paper, as would seem to be the case . . ..

[24]"The following conclusions may be drawn with respect to the theory of fermentation. In the first place it has been demonstrated that for the production of the fermentation process no such complicated apparatus is necessary as is represented by the yeast cell. It is much more likely that the agent of the juice which is active in fermentation is a soluble substance, doubtless an albuminoid substance; this may be designated as zymase.

[25]"The view that an albuminoid substance of a specific nature derived from the yeast cells is responsible for fermentation was already expressed in 1858 by M. Traube as the enzyme or ferment theory, and later was especially defended by F. Hoppe-Seyler. However, the separation of such an enzyme from the yeast cell has heretofore never been accomplished.

[26]. . ."It is possible that the fermentation of the sugar by the zymase takes place inside the yeast cells; it is more probable though that the yeast cells secrete this albuminoid substance into the sugar solution, where it causes the fermentation. If so, the process in alcoholic fermentation is perhaps to be regarded as a physiological act only insofar as it is living yeast cells that secrete the zymase."

[27]Buchner's discovery had two main effects. First, it suggested that when living things cause fermentation (or putrefaction) they do so by producing a particular substance (like Buchner's "zymase") which is directly responsible for the transformation in question. Second, it initiated a search for comparable "enzymes." The existence of many was soon established, some were isolated in a pure state, their activities began to be investigated. The outcome was that, by about 1925, it became apparent that the vast array of chemical changes underlying the visible signs of life are all enzyme-controlled reactions. Further, each such change is controlled by a specific enzyme that has no effect on other changes. In a subsequent study, we shall learn some of the ways in which the actions of enzymes were explored.

Discovery and Demonstration of the Circulation of the Blood

In ca. 175 A.D., Galen developed a theory of blood movement which was largely accepted until 1628 A.D. Its overthrow by William Harvey did more than any other single thing to put biology on a sound scientific footing. Here, briefly, is Galen's view which Harvey overthrew.

Absorbed food travels in intestinal veins to the liver where it is transformed into blood. Blood now travels from the liver to the vena cava. There some enters the right ventricle of the heart; the rest enters the veins which convey it all through the body. At the tips of the veins some of it gets through into the arteries. The blood that enters the heart has two destinations. Some of it goes through pores in the interventricular partition to the left ventricle and from there via the arteries to the body at large. The rest goes via the pulmonary artery to the lung, and some of it (Galen doesn't say how much) passes over into the pulmonary vein. To complete the picture, the lungs send air, via the pulmonary vein, to the heart. There some of this air "fans" the (invisible) fire that burns there. The rest is converted into "vital spirit" and is conveyed by the arteries to various parts of the body. The proper function of the various organs depends on the presence in them of vital spirit. At the tips of the arteries, some vital spirit moves over to the veins in exchange for blood.

Harvey began lecturing on the circulatory system around 1610, first published his theory in a book of about 60 pages in 1628. This book, Anatomical Investigations of the Motion of the Heart and of the Blood, is considered one of the great works in the history of science, partly because of the author's pioneering use of (a) experimentation and (b) measurement. The following are excerpts from crucial parts of Harvey's text.

Harvey begins by discussing what we call the pulmonary circulation. Be sure to note where Harvey discontinues the discussion of the pulmonary circulation to turn to other matters. As you read about this ask yourself two questions: first, is the belief in the pulmonary circulation new with Harvey? Second, does he present evidence for it and, if so, what evidence (in other words is this a descriptive or an argumentative exposition)?

> [1]"No one denies that all the ingested nourishment may pass through the liver to the vena cava in man and all large animals. If nutrition is to proceed, nutriment must reach the veins, and there appears to be no other way. Why not hold the same reasoning for the passage of blood through the lungs of adults, and believe it to be true, with Columbus, that great anatomist, from the size and structure of the pulmonary vessels, and because the pulmonary vein and corresponding ventricle are always filled with blood, which must come from the veins and by no other route except through the lungs? He and I consider it evident from dissections and other reasons given previously.

Query: why, in the preceding paragraph does Harvey talk about the passage of food through the liver? Note: the next paragraph introduces a <u>kind</u> of evidence which Harvey himself is not especially enthusiastic about.

> 2"Those who will agree to nothing unless supported by authority, may learn that this truth may be confirmed by the words of Galen himself, that not only may blood be transmitted from the pulmonary artery to the pulmonary vein, then into the left ventricle, and from there to the arteries, but that this is accomplished by the continual beat of the heart and the motion of the lungs in breathing."

The following two paragraphs contain a further exposition of the Galenic view, and a certain elaboration on that view. When you get to the end of paragraph 4, be sure you can specify what Harvey has added to Galen's conception.

> 3"There are three sigmoid or semilunar valves at the opening of the pulmonary artery, which prevent blood forced into this pulmonary artery from flowing back into the heart. Galen clearly explains the functions of these valves.

> 4"Galen proposes this argument to explain the passage of blood from the vena cava through the right ventricle to the lungs. By merely changing the terms, we may apply it more properly to the transfer of blood from the veins through the heart to the arteries. From the words of that great Prince of Physicians, Galen, it seems clear that blood filters through the lung from the pulmonary artery to the pulmonary vein as a result of the heart beat and the movement of the lungs and thorax. The heart, further, continually receives blood in its ventricles, as into a cistern, and expels it. For this reason, it has four kinds of valves, two regulating inflow, and two outflow, so blood will not be inconveniently shifted back and forth like Euripus, neither flowing back into the part from which it should come, nor quitting that to which it should pass, lest the heart be wearied by vain labor and respiration be impeded. Finally, our assertion is clearly apparent, that the blood continually flows from the right to the left ventricle, from the vena cava to the aorta, through the porosities of the lung."

Toward the end of the next paragraph Harvey weighs, and chooses between, two theories of function of the pulmonary artery. Be sure you know what the two are, which he chooses, and what induces him to make the choice.

> 5"It is evident from dissection that this occurs through wide open channels in all animals before birth, and from Galen's words and what has been said previously it is equally manifest that it occurs in adults by tiny pores and vascular openings

through the lungs. So it appears that, whereas one ventricle of the heart, the left, suffices for distributing blood to the body, and drawing it from the vena cava, as is the case in all animals lacking lungs, Nature was compelled, when she wished to filter blood through the lungs, to add the right ventricle whose beat should force blood from the vena cava through the lungs into the left ventricle. Thus the right ventricle may be said to be made for the sake of transmitting blood though the lungs, not for nourishing them. It is entirely unreasonable to assume that the lungs need so much more abundant nutriment, and coming directly from the heart, so much purer and more spiritous blood than either the very refined substances of the brain, or the very brilliant and perfect structure of the eyes, or the flesh of the heart itself which is adequately nourished by the coronary artery."

The next paragraph is a bridge to a new topic. It reveals something of the state of scientific freedom at the time, and ends with a quotable and poignant affirmation.

6"So far we have considered the transfer of blood from the veins to the arteries, and the ways by which it is transmitted and distributed by the heart beat. There may be some who will agree with me on these points because of the authority of Galen or Columbus or the reasons of others. What remains to be said on the quantity and source of this transferred blood, is, even if carefully reflected upon, so strange and undreamed of, that not only do I fear danger to myself from the malice of a few, but I dread lest I have all men as enemies, so much does habit or doctrine once absorbed, driving deeply its roots, become second nature, and so much does reverence for antiquity influence all men. But now the die is cast; my hope is in the love of truth and in the integrity of intelligence."

Not unusually, a scientific paper contains first, a statement of preliminary observations; second, the identification of a problem arising out of these observations (frequently the problem arises because the observations seem not to be in agreement with some existing theory); third, the statement of a new theory or a modification of the old one; and fourth, a more or less argument in favor of the new theory. Harvey's paper follows this outline fairly well. Hence, you should decide which of the ensuing paragraphs (7-25) plays each of the above four roles.

7"First I seriously considered in many investigations how much blood might be lost from cutting the arteries in animal experiments. Then I reflected on the symmetry and size of the vessels entering and leaving the ventricles of the heart, for Nature, making nothing in vain, would not have given these vessels such relative greatness uselessly. Then I thought of the arrangement and structure of the valves and the rest of the heart. On these and other such matters I pondered often and deeply. For a long time I turned over in my mind such questions as, how much blood is transmitted, and how short a time does its passage take. Not deeming it possible for the digested food mass to furnish such an abundance of blood, without totally draining the veins or rupturing the arteries, unless it somehow got back to the veins from the arteries and returned to the right ventricle of the heart, I began to think there was a sort of motion as in a circle."

Queries: What is the role of each point made in the preceding paragraph (7)?

8"This I afterwards found true, that blood is pushed by the beat of the left ventricle and distributed through the arteries to the whole body, and back through the veins to the vena cava, and then returned to the right auricle, just as it is sent to the lungs through the pulmonary artery from the right ventricle and returned from the lungs through the pulmonary vein to the left ventricle, as previously described.

9"The vessels for the conduction of blood are of two sorts, the vena cava type and the aortic type. These are to be classified, not on the basis of structure or make-up, as commonly thought with Aristotle, for in many animals, as I have said, the veins do not differ from the arteries in thickness of tunics, but on the basis of difference in function or use. Both veins and arteries were called veins by the ancients, and not unjustly, as Galen notes. The arteries are the vessels carrying blood from the heart to the body, the veins returning blood from the body to the heart, the one the way from the heart, the other toward the heart, the latter carrying imperfect blood unfit for nourishment, the former perfected, nutritious blood."

Queries: What is the role of the preceding paragraphs (8 and 9)? What is the connection of paragraph 8 to paragraph 7? Of paragraph 9 to paragraph 8? Harvey now enters upon a new part of his exposition. Be alert to see how the next paragraphs (10-14) fit the scheme of the paper as a whole.

10"If anyone says these are empty words, broad assertions without basis, or innovating without just cause, there are three points coming for proof, from which I believe the truth will necessarily follow and be clearly evident.

11"First, blood is constantly being transmitted from the vena cava to the arteries by the heart beat in such amounts that it cannot be furnished by the food consumed, and in such a way that the total quantity must pass through the heart in a short time.

12"Second, blood is forced by the pulse in the arteries continually and steadily to every part of the body in a much greater amount than is needed for nutrition or than the whole mass of food could supply.

13"And likewise third, the veins continually return this blood from every part of the body to the heart.

14"These proved, I think it will be clear that the blood circulates, passing away from the heart to the extremities and then returning back to the heart, thus moving in a circle."

Having told what points he wants to prove, Harvey now begins the proof itself. This is one of the first serious applications of mathematics to physiology. What specified point does he establish in paragraph 15?

15"Let us consider, arbitrarily or by experiment, that the left ventricle of the heart when filled in diastole, contains two or three ounces, or only an ounce and a half. In a cadaver I have found it holding more than three ounces. Likewise let us consider how much less the ventricle contains when the heart contracts or how much blood it forces into the aorta with each contraction, for, during systole, everyone will admit something is always forced out . . . and apparent from the structure of the valves. As a reasonable conjecture suppose a fourth, fifth, sixth, or even an eighth part is passed into the arteries. Then we may suppose in man that a single heart beat would force out either a half ounce, three drams, or even one dram of blood, which because of the valvular block could not flow back that way into the heart."

What specific point does he establish (or endeavor to establish) in paragraphs 16-18?

16"The heart makes more than a thousand beats in a half hour, in some two, three, or even four thousand. Multiplying by the drams, there will be in half an hour either 3,000 drams, 2,000 drams, five hundred ounces, or some other such proportionate amount of blood forced into the arteries by the heart, <u>but always a greater quantity than is present in the whole body</u>. Likewise in a sheep or dog, suppose one scruple goes out with each stroke of the heart, then in half an hour 1,000 scruples or about three and a half pounds of blood would be pumped out. But as I have determined in the sheep, the whole body does not contain more than four pounds of blood.

17"On this assumption of the passage of blood, made as a basis for argument, and from the estimation of the pulse rate, it is apparent that the entire quantity of blood passes from the veins to the arteries through the heart, and likewise through the lungs.

18"But suppose this would not occur in half an hour, but rather in an hour, or even in a day, it is still clear that more blood continually flows through the heart than can be supplied by the digested food or be held in the veins at any one time."

The ensuing two paragraphs are, essentially, an extension of the preceding two.

> [19]"It cannot be said that the heart in contracting sometimes pumps and sometimes doesn't, or that it propels a mere nothing or something imaginary. This point has been settled previously, and besides, it is contrary to common sense. If the ventricles must be filled with blood in cardiac dilatation, something must always be pushed out in contraction, and not a little amount either, since the passages are not small nor the contractions few. This quantity expelled is some proportion of the contents of the ventricle, a third, a sixth, or an eighth, and an equivalent amount of blood must fill it up in diastole, so that there is a relation between the ventricular capacity in contraction and in dilatation. Since the ventricles in dilating do not become filled with nothing, or with something imaginary, so in contracting they never expel nothing or something imaginary, but always blood in an amount proportionate to the contraction."
>
> [20]"So it may be inferred that if the heart in a single beat in man, sheep, or ox, pumps one dram, and there are 1,000 beats in half an hour, the total amount pumped in that time would be ten pounds five ounces; if two drams at a single stroke, then twenty pounds ten ounces; if half an ounce, then forty-one pounds eight ounces; and if one ounce, then a total of eighty-three pounds four ounces, all of which would be transferred from the veins to the arteries in half an hour."

Next comes an extension of his general hypothesis.

> [21]"Meanwhile I know and state to all that the blood is transmitted sometimes in a larger amount, other times in a smaller, and that the blood circulates sometimes rapidly, sometimes slowly, according to temperament, age, external or internal causes, normal or abnormal factors, sleep, rest, food, exercise, mental condition, and such like."

Among the sorts of evidence scientific authors bring to bear are the following: (a) the results of experiments performed with a specific view to testing the author's hypothesis; (b) observable facts (not necessarily experimental) which the author's hypothesis "explains" or would have led one to predict. In the concluding paragraphs, Harvey adduces both these sorts of evidence. As you read, be sure to note which is which.

> [22]"The reason is now apparent why so much blood is found in the veins in anatomical dissection, and so little in the arteries, so much in the right side of the heart, so little in the left. This fact probably led the ancients to believe that arteries contained only spirits during an animal's life. The reason for the difference is probably as follows. There is no other passage from the veins to the arteries except through the heart and lungs, so when an animal expires and the lungs stop moving, the blood is prevented from passing from the pulmonary artery to the pulmonary vein and then into the left ventricle of the heart. This is like what was noted previously in the embryo, where

the transit is prevented by the lack of motion in the lungs and the opening and closing of its tiny pores. The heart, however, does not stop at the same time as the lungs, but outlives them and continues to beat. The left ventricle and the arteries continue to send blood to the rest of the body and into the veins, but, receiving none from the lungs, they soon become empty.

[23]"I have often noticed in dissecting veins, that no matter how much care I take, it is impossible to pass a probe from the main venous trunks very far into the smaller branches on account of the valvular obstructions. On the contrary it is very easy to push it in the opposite direction, from the branches toward the larger trunks. In many places a pair of valves are so placed that when raised they join in the middle of the vein, and their edges are so nicely united that one cannot perceive any crack along their junction. On the other hand, they yield to a probe introduced from without inwards and are easily released in the manner of flood-gates opposing a river flow. So they intercept, and when tightly closed, completely prevent in many places a flow of blood back from the heart and vena cava. They are so constituted that they can never permit blood to move in the veins from the heart upwards to the head, downwards toward the feet, or sidewise to the arms. They oppose any movement of blood from the larger veins toward the smaller ones, but they favor and facilitate a free and open route starting from the small veins and ending in the larger ones.

[24]"This fact may be more clearly shown by tying off an arm of a subject as if for blood-letting. There will appear at intervals knots, or swellings, like nodules, not only where there is branching, but also where none occurs. These are caused by the valves, appearing thus on the surface of the hand and arm. If you will clear the blood away from a nodule or valve by pressing a thumb or finger below it, you will see that nothing can flow back, being entirely prevented by the valve, and that the part of the vein between the swelling and the finger, disappears, while above the swelling or valuve it is well distended. Keeping the vein thus empty of blood, if you will press downwards against the valve, by a finger of the other hand on the distended upper portion, you will note that nothing can be forced through the valve. The greater effort you make the more the vein is distended toward the valve, but you will observe that it stays empty below it.

Life Existing Independently in an "Internal Environment"

1 Claude Bernard was a great physiologist who experimented and taught in France during the middle decades of the nineteenth century. The following lecture (1878) summarizes some of his life-work and thought.

2 "Constant or Free Life. . . . Constant, or free, life is the third[1] form of existence and pertains only to those animals which are highest in organization. With these animals, life is never, under any circumstance, found to be suspended. It pursues a course which is constant and apparently indifferent to alterations in the cosmic environment and changes in the material conditions surrounding the animal. Organs, mechanisms, tissues function in an apparently stable manner, without evincing such considerable variations as appear among animals with variable life. This comes about because, actually, the internal environment which surrounds organs, tissues, and tissue elements does not change; atmospheric variations are checked by it, so that, it may truthfully be said, the physical conditions of the environment are, for the higher animal, constant. It is enveloped in an internal environment which acts for it as an atmosphere of its own in the midst of an ever changing outer cosmic environment. The higher organism has, in effect, been placed in a hot house. Here it is beyond the reach of the perpetual changes of the cosmic environment. It is not bound up in them; it is free and independent.

3 "I believe I was the first to insist upon this idea that there are for the animal really two environments: an external environment in which the organism is situated, and an internal environment in which the tissue elements live. Thus life goes on for it not in the external environment,--(atmospheric air for the aërial animal, fresh or salt water for the aquatic one),--but in the liquid internal environment formed by the circulating organic liquid which surrounds and bathes all the anatomical elements of the tissues. It is the lymph, or the plasma, the liquid part of the blood, which, among the higher animals, penetrates the tissues, and makes up the ensemble of all interstitial liquids, and is the outward expression of all local nutritional activity and is the source and common ground of every fundamental exchange. A complex organism must be considered as a collection of simple beings,--*viz*., the anatomical elements which live in the liquid internal environment. . .

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[1] The other two forms of life, in addition to *la vie constante*, are *la vie oscillante* (as in cold-blooded animals) and *la vie latente* (as in spores and encysted microbes.)

Water

4. . ."It is the nervous system, as we have said, which makes up the machinery of compensation between acquisitions and losses. The sensation of thirst which is under the dependence of this system always makes itself felt at times when the proportion of liquid diminishes in the body after some such condition as hemorrhage or abundant sweating; the animal finds itself compelled to repair, by ingestion of liquids, the losses which it has sustained. But this very same ingestion is also regulated, in the sense that it will not augment, beyond a certain degree, the quantity of water which exists in the blood; the urinary excretions and others eliminate the surplus somewhat like an overlfow device. The mechanisms which cause the quantity of water to vary and which re-establish it are very numerous. They set in operation the large number of secretory devices as well as those of respiration, ingestion, and circulation, which transports the ingested, absorbed liquids. These mechanisms are varied but concur in the same result: namely, the presence of water in the internal environment in a set proportion, a necessary condition for the maintenance of free life.

5"It is not only for water that these compensatory mechanisms exist. We recognize them equally well for the majority of mineral or organic substances contained in solution in the blood. We know that the blood does not take on appreciable quantities of sodium chloride, for example; the excess, beyond a certain limit, is carried off with the urine. I have also discovered the same thing as regards sugar which, remaining normal in the blood, is, beyond a certain amount, rejected by the urine.

Heat

6"We know that there exists for each organism, elementary or complex, limits of external temperature between which their functioning is possible, and a middle-point which corresponds to the maximum of vital energy. Moreover, this is true not only for creatures which have achieved maturity but also for the egg and embryo. All these beings manifest variable life, but for the higher, so-called warm-blooded animals, the temperature compatible with manifestations of life is narrowly fixed. This fixed temperature maintains itself in the internal environment, despite the most extreme climatic variations, and assures continuity and independence of existence. There is, in a word, among animals possessing constant and free life, a heat producing property which does not exist among animals with oscillatory life.

[7]"For this function there exists a group of mechanisms governed by the nervous system. There are thermic nerves, and vasomotor nerves which I have demonstrated, whose activity produces either elevation or depression of temperature depending upon circumstances.

[8]"Heat production is due, in the living world as in the inorganic world, to chemical phenomena. Such is the great law made known to us by Lavoisier and Laplace. It is in the chemical activity of the tissues that the higher organism discovers a source for that heat which it keeps, in its internal environment, at a practically fixed degree, 38 to 40 degrees for mammals, 45 to 47 degrees for birds. Calorific regulation is accomplished as I have said by means of two sorts of nerves: (1) The nerves which I have called thermic, which belong to the greater sympathetic system and which in some way bridle the chemico-thermal activities for which the living tissues are the seat. When these nerves act, they diminish interstitial combustions and lower the temperature; when their influence is weakened, by the suppression of their action, or, by the antagonism of other nervous influences, then the combustions are heightened and the temperature of the internal environment rises considerably; (2) The vasomotor nerves which, accelerating circulation at the periphery of the body or in the central organs, likewise participate in the mechanism of equilibration of animal heat.

Oxygen

[9]"The manifestations of life demand for their production the intervention of air, or better, of its active element, oxygen, in a soluble form and in such condition as to facilitate its arrival within the actual organism. Moreover, it is necessary, up to a certain point, that this oxygen exist in fixed proportions in the internal environment: amounts too small and too great are equally incompatible with vital function. . . .

[10]"But it is possible for there to be in the animal itself mechanisms to establish the compensation when it is not done outside and to assure the penetration into the internal environment of the amount of oxygen necessary for vital function. We are here referring to the quantitative variations which may be experienced by the hemoglobin, a substance actively absorbent of oxygen,--variations still little known but which certainly also play their part.

[11]"All these mechanisms like the preceding ones are effective only within rather restricted limits; they are distorted and rendered powerless in extreme conditions. They are regulated by the nervous system. When air is rarefied due to

any cause, such as an ascension in a balloon or in the mountains, the respiratory movements become more ample and frequent, and compensation is established. Nevertheless the mammals, man included, cannot long sustain this compensatory struggle when the rarefaction is exaggerated,--when, for example, they find themselves carried to altitudes higher than 5000 meters.

Reserves

12"Finally, the animal must have, for the maintenance of life, reserve materials which assure a constancy of the composition of its internal environment. The higher organisms secure with their diet the material contents of their internal environment but since they cannot secure an identical or exclusive diet, there must be in them certain mechanisms which draw from these variable nutriments similar materials and which regulate the proportion in which each of them must enter the blood.

13"I have shown, and we will see later, that nutrition is not direct, as accepted chemical theories teach us, but that, on the contrary, it is indirect and is accomplished through reserves. This fundamental law is a consequence of the variety of the diet, as opposed to the constancy of the (internal) environment. Briefly, one does not live upon his actual food substance, but only upon those which one has previously eaten, modified, and somehow brought into existence by the act of assimilation. The same is true of respiratory combustion. It is by no means direct, as we shall show later.

14"There are, then, reserves, prepared from nutrients and expended at each instant in greater or less proportion. In this way, vital activities lead to the destruction of provisions which have their origin, to be sure, in the first place outside the body, but which have been elaborated under the influence of the tissues of the organism, and which, poured into the blood, assure the constancy of its physicochemical constitution.

Conclusion

15"We have successively examined the three general forms in which life appears:--latent life, oscillatory life, constant life,--in order to see whether, in any of them, we would find an interior vital principle capable of causing manifestations of life, independent of the exterior physicochemical conditions. The conclusion to which we find ourselves led is easy to discern. We see that in latent life the being is dominated by exterior physicochemical conditions to such a point that every vital manifestation can be stopped. In oscillating life, although the living creature is not absolutely submitted to these conditions, yet it remains so bound up in them that it undergoes all their variations. In constant life, the creature appears to be free, and the vital manifestations seem to be effective and controlled by an internal vital principle, entirely free from the influence of external physicochemical conditions. This appearance is an illusion. Quite to the contrary, it is exactly in the mechanism of constant or free life that these narrow relationships are particularly evident. We cannot therefore admit in living organisms a free vital principle struggling against the influence of physical conditions. The opposite has been proved, and thus all of the contrary conceptions of the vitalists are seen to be overthrown."

The Story of Diabetes

1When the physiologist wishes to investigate the activity of an organ of unknown function, he sometimes follows the method of experimental ablation: he takes the organ out and watches to see what will happen. Two German workers, von Mering and Minkowski, followed this procedure with the pancreas. The pancreas contains two sorts of tissue. There are first hundreds of pear-shaped sacks which pour their secretions into tubes which converge to form the pancreatic duct. These secreted matters consist of digestive enzymes which travel to the duodenum and further hydrolyze the already partially digested food. Between these sacks (acini) are isolated islands of rather undifferentiated cells whose function was, in the 1880's, mysterious.

2An accidental discovery had something to do with solving the mystery. A laboratory attendant, taking care of the animal cages, reported that ants were attracted to the cages of pancreatectomized dogs. Investigation showed that these dogs exhibited glycosuria (sugar in the urine) and that the dogs exhibited other effects equally symptomatic of diabetes. These investigators guessed that this might be caused by a pancreatic failure of some sort. Since the pancreas itself is not a sugar depot, it was suspected that the pancreas might produce a substance which, travelling through the blood, affected sugar metabolism elsewhere in the body.

3Many workers tried to cure experimental diabetes by injecting pancreatic extracts, variously prepared, but all equally without success. There was one exception. Another German worker during the second decade of our own century, tried to get the pancreas to store up its hypothetical solution by ligating its veins for a few hours before removal of the pancreas. Extracts of this pancreas so treated showed a limited ability to lower the sugar-content of urine in pancreatectomized dogs. When the extract proved dangerously toxic to diabetic persons, the investigation was discontinued.

4Other workers were only semi-successful in the search for antidiabetic pancreatic extracts. But their experiments suggested that possibly when the pancreas is extracted its hypothetical hormone is brought into contact with and destroyed by one of its digestive enzymes.

5The matter stood there until ca. 1920 when a young Canadian physician noted a report in the scientific literature that when the pancreatic duct is ligated the backed-up enzyme appears to destroy the digestive part of the gland but not the is island tissue. Struck by the possibility that here was a way of getting island-extract free of digestive enzymes he travelled to McGill University and in association with two other workers (best, Collip) began to experiment.

Banting, Best, and Collip: 1921

6(In full) "The hypothesis underlying our experiments was that the usual extracts of pancreas do not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because this is destroyed by the digestive enzymes also present in such extracts. To circumvent this difficulty we have taken advantage of the fact that the acinous, but not the insular, cells become degenerated in 7 to 10 weeks after ligation of the ducts.

7"A neutral or faintly acid extract of the degenerated gland, kept at a low temperature, was therefore prepared and its effect on pancreatic diabetes investigated. Ten weeks after ligation of the pancreatic ducts, the degenerated gland was removed and extracted with icecold Ringer's solution. This extract injected intravenously or subcutaneously invariably caused marked reduction of the percentage of sugar in the blood and the amount of sugar excreted in the urine. Extracts of liver, spleen, or boiled extract of degenerated pancreas have no effect.

8"Further investigations have shown the following: a, incubation of the extract in alkaline reaction for 2 hrs., with pancreatic juice, removes its effect; b, glucose given intravenously or per os is retained by diabetic animals if adequate doses of the extract are also administered; c, the clinical condition of the animal is improved by the extract; d, hemoglobin estimations before and after administration of the extract are identical; e, neutral extract kept in cold storage retains its potency for at least 7 days; f, subcutaneous injections have a less rapid but more prolonged effect. Rectal injections are not effective.

9"The experiments have been repeated on ten animals, several of which were under observation for over 2 weeks.

J. B. Collip: 1922

10"The demonstration by Banting and Best that extracts of pancreas, prepared with certain precautions, contain a substance having the power to lower the blood sugar and to raise the sugar tolerance, in diabetes, both in dogs and man, warranted an attempt, to isolate this substance in a sufficiently pure state for repeated subcutaneous or intravenous administration in man. The problem was to remove most of the protein and salts and all the lipoid material from the extracts without destroying the active principle. In the endeavor to solve this problem, various methods were tried and the following was found to be most satisfactory.

[11]There follows a detailed account of the steps in the extractive process. We are interested only in the fact that the purified extract proved largely non toxic to human beings in whom, within a year, diabetes was being partly controlled through the administration of extract of pancreatic island tissue (insulin). Subsequent developments in this story will be treated in lecture.

THE ORIGIN OF SPECIES
Charles Darwin, London, 1859

Darwin presents his views rather fully and we may dispense for the most part with explanatory comment. On the Origin of Species was published in successive editions, beginning in 1859. Each chapter is devoted to a category of evidence massive in its development (Darwin collected evidence over a twenty-five year period before he was willing to publish). The following excerpts are from a recapitulation contained in the final chapter.

[1]"Under domestication we see much variability caused, or at least excited, by changed conditions of life; but often in so obscure a manner, that we are tempted to consider the variations as spontaneous. . ..

[2]"Variability is not actually caused by man; he only unintentionally exposes organic beings to new conditions of life, and then nature acts on the organization and causes it to vary. But man can and does select the variations given to him by nature, and thus accumulates them in any desired manner.

[3]"There is no reason why the principles which have acted so efficiently under domestication should not have acted under nature. In the survival of favored individuals and races, during the constantly recurrent Struggle for Existence, we see a powerful and everacting form of Selection. The struggle for existence inevitably follows from the high geometrical ratio of increase which is common to all organic beings. This high rate of increase is proved by calculation--by the rapid increase of many animals and plants during a succession of peculiar seasons, and when naturalized in new countries. More individuals are born than can possibly survive. A grain in the balance may determine which individuals shall live, and which shall die--which variety or species shall increase in number, and which shall decrease, or finally become extinct. As the individuals of the same species come in all respects into the closest competition with each other, the struggle will generally be most severe between them; it will be almost equally severe between the varieties of the same species, and next in severity between the species of the same genus. On the other hand the struggle will often be severe between beings remote in the scale of nature. The slightest advantage in certain individuals, at any age or during any season, over those with which they come into competition, or better adaptation in however slight a degree to the surrounding physical conditions, will, in the long-run, turn the balance.

[4]"With animals having separated sexes, there will be in most cases a struggle between the males for the possession of the females. The most vigorous males, or those which have most successfully struggled with their conditions of life, will generally leave most progeny. But success will often

depend on the males having special weapons or means of defense or charms; and a slight advantage will lead to victory. . .."

Mere modification does not in itself lead to the creation of new species (speciation). The several species with a genus, for example, are distinct and not continuously integrated. Note what Darwin has to say on this subject.

[5]"As each species tends by its geometrical rate of reproduction to increase inordinately in number; and as the modified descendants of each species will be enabled to increase by as much as they become more diversified in habits and structure, so as to be able to seize on many and widely different places in the economy of nature, there will be a constant tendency in natural selection to preserve the most divergent offspring of any one species. Hence, during a long-continued course of modification, the slight differences characteristic of varieties of the same species, tend to be augmented into the greater differences characteristic of the species of the same genus. New and improved varieties will inevitably supplant and exterminate the older, less improved, and intermediate varieties; and thus species are rendered to a large extent defined and distinct objects. Dominant species belonging to the larger groups within each class tend to give birth to new and dominant forms; so that each large group tends to become still larger, and at the same time more divergent in character. But as all groups cannot thus go on increasing in size, for the world would not hold them, the more dominant groups beat the less dominant. This tendency in the large groups to go on increasing in size and diverging in character, together with the inevitable contingency of much extinction, explains the arrangement of all forms of life in groups subordinate to groups, all within a few great classes, which has prevailed throughout all time. This grand fact of the grouping of all organic beings under what is called the Natural System, is utterly inexplicable on the theory of creation."

Here occurs a break in the flow of thought and introduction of a new part of the paper.

[6]"Many other facts are, as it seems to me, explicable on this theory. How strange it is that a bird, under the form of a woodpecker, should prey on insects on the ground; that upland geese, which rarely or never swim, should possess webbed feet; that a thrush-like bird should dive and feed on subaquatic insects; and that a petrel should have the habits and structure fitting it for the life of an auk! and so in endless other cases. But on the view of

each species constantly trying to increase in number, with natural selection always ready to adapt the slowly varying descendants of each to any unoccupied or ill-occupied place in nature, these facts cease to be strange, or might even have been anticipated.

[7]"We can to a certain extent understand how it is that there is so much beauty throughout nature; for this may be largely attributed to the agency of selection. That beauty, according to our sense of it, is not universal, must be admitted by every one who will look at some venomous snakes, at some fishes, and at certain hideous bats with a distorted resemblance to the human face. Sexual selection has given the most brilliant colors, elegant patterns, and other ornaments to the males, and sometimes to both sexes, of many birds, butterflies, and other animals. With birds it has often rendered the voice of the male musical to the female, as well as to our ears. Flowers and fruit have been rendered conspicuous by brilliant colors in contrast with the green foliage, in order that the flowers may be easily seen, visited and fertilized by insects, and the seeds disseminated by birds. How it comes that certain colors, sounds, and forms should give pleasure to man and the lower animals, that is, how the sense of beauty in its simplest form was first acquired, we do not know any more than how certain odors and flavors were first rendered agreeable . . ..

[8]"Glancing at instincts, marvellous as some are, they offer no greater difficulty than do corporeal structures on the theory of the natural selection of successive, slight, but profitable modifications. We can thus understand why nature moves by graduated steps in endowing different animals of the same class with their several instincts. I have attempted to show how much light the principle of gradation throws on the admirable architectural powers of the hive-bee. Habit no doubt often comes into play in modifying instincts; but it certainly is not indispensable, as we see in the case of neuter insects, which leave no progeny to inherit the effects of long-continued habit. On the view of all the species of the same genus having descended from a common parent, and having inherited much in common, we can understand how it is that allied species, when placed under widely different conditions of life, yet follow nearly the same instincts; why the thrushes of tropical and temperate South America, for instance, line their nests with mud like our British species. On the view of instincts having been slowly acquired through natural selection, we need not marvel at some instincts being not perfect and liable to mistakes, and at many instincts causing other animals to suffer.

[9]"If we admit that the geological record is imperfect to an extreme degree, then the facts, which the record does give, strongly support the theory of descent with modification. . .. The fact of the fossil remains of each formation

being in some degree intermediate in character between the fossils in the formations above and below, is simply explained by their intermediate position in the chain of descent.

10"Looking to geographical distribution, if we admit that there has been during the long course of ages much migration from one part of the world to another, owing to former climatical and geographical changes and to the many occasional and unknown means of dispersal, then we can understand, on the theory of descent with modification, most of the great leading facts in distribution. We can see why there should be so striking a parallelism in the distribution of organic beings throughout space, and in their geological succession throughout time; for in both cases the beings have been connected by the bond of ordinary generation, and the means of modification have been the same. We see the full meaning of the wonderful fact, which has struck every traveller, namely, that on the same continent, under the most diverse conditions, under heat and cold, on mountain and lowland, on deserts and marshes, most of the inhabitants within each great class are plainly related; for they are the descendants of the same progenitors and early colonists.

11"On this view of migration, with subsequent modification, we see why oceanic islands are inhabited by only few species, but of these, why many are peculiar or endemic forms.

12"It is a rule of high generality that the inhabitants of each area are related to the inhabitants of the nearest source whence immigrants might have been derived. We see this in the striking relation of nearly all the plants and animals of the Galapagos Archipelago, of Juan Fernandez, and of the other American islands, to the plants and animals of those of the mainland; and of those of the Cape de Verde Archipelago, and of the other African islands to the African mainland. It must be admitted that these facts receive no explanation on the theory of creation.

13"But the chief cause of our natural unwillingness to admit that one species has given birth to other and distinct species, is that we are always slow in admitting great changes of which we do not see the steps. The difficulty is the same as that felt by so many geologists, when Lyell first insisted that long lines of inland cliffs had been formed, and great valleys excavated, by the agencies which we still see at work. The mind cannot possibly grasp the full meaning of the term of even a million years; it cannot add up and perceive the full effects of many slight variations, accumulated during an almost infinite number of generations.

[14]"Although I am fully convinced of the truth of the views given in this volume under the form of an abstract, I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine. It is so easy to hide our ignorance under such expressions as the 'plan of creation,' 'unity of design,' etc., and to think that we give an explanation when we only restate a fact. Any one whose disposition leads him to attach more weight to unexplained difficulties than to the explanation of a certain number of facts will certainly reject the theory. A few naturalists, endowed with much flexibility of mind, and who have already begun to doubt the immutability of species, may be influenced by this volume; but I look with confidence to the future, to young and rising naturalists, who will be able to view both sides of the question with impartiality. Whoever is led to believe that species are mutable will do good service by conscientiously expressing his conviction; for thus only can the load of prejudice by which this subject is overwhelmed be removed.

[15]"It is interesting to contemplate a tangled bank, clothed with plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent on each other in so complex a manner, have all been produced by laws acting around us. These laws, taken in the largest sense, being Growth with Reproduction; Inheritance which is almost implied by reproduction; Variability from the indirect and direct action of the conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a struggle for Life, and as a consequence to Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms. Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, while this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been and are being evolved."

Classic Studies in Immunology

The history of folk medicine provides a number of examples of intentional immunization. Children or other susceptible persons would be permitted to acquire a (hopefully mild) infection on the (usually justified) supposition that they would thus be rendered immune.

A case in point arises in connection with smallpox. This is a virus disease. Viruses are self-replicating infectious agents that can multiply exclusively in living cells. The virus particle has recently been shown to consist typically of a nucleic acid core surrounded by a coating of protein. But our present interest is in smallpox long before there was any information about the nature of infectious agents.

Thus disease existed in the past both endemically and epidemically. Trustworthy estimates are hard to obtain, but it is clear that smallpox killed some tens of millions of Europeans and Asians during the eighteenth century. Europeans then infected the North American Indians (a possible partial factor in the Indians' inability to resist European aggression).

In various sectors of the Far and Middle East, it was by then realized that the disease exists in one or more less than normally virulent forms which confer subsequent immunity against the disease in general. This led to the practice of inoculation which spread from Turkey into Europe around 1700. But the practice was both risky and controversial until the critical experiments performed in the late 1780's and 1790's by an English country doctor, Edward Jenner.

[1]Jenner writes, in 1798, that ". . . what renders the cow-pox virus so extremely singular is that the person who has been thus affected is forever after secure from the infection of the smallpox; neither exposure to the variolous effluvia, nor the insertion of the matter into the skin, producing this distemper.

[2]"In support of so extraordinary a fact, I shall lay before my reader a great number of instances (of which we give here one example.

[3]"Case II. Sarah Portlock, of this place, was infected with the cow-pox when a servant at a farmer's in the neighborhood, twenty-seven years ago.

[4]"In the year 1792, conceiving herself, from this circumstance, secure from the infection of the smallpox, she nursed one of her own children who had accidentally caught the disease, but no indisposition ensued. During the time she remained in the infected room, variolous matter was inserted into both her arms, but without any further effect than in the preceding case.

After detailing other cases pointing to the same conclusion, Jenner reports his famous experiment on a little boy named Phipps.

[5]"The more accurately to observe the progress of the infection I selected a healthy boy, about eight years old, for the purpose of inoculation for the cow-pox. The matter was taken from a sore on the hand of a dairymaid, who was infected by her master's cows, and it was inserted, on the 14th of May, 1796, into the arm of the boy by means of two superficial incisions, barely penetrating the cutis, each about half an inch long.

[6]"On the seventh day he complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite, and had a slight headache. During the whole of this day he was perceptibly indisposed, and spent the night with some degree of restlessness, but on the day following he was perfectly well.

[7]"The appearance of the incisions in their progress to a state of maturation were much the same as when produced in a similar manner by variolous matter. The only difference which I perceived was in the state of the limpid fluid arising from the action of the virus, which assumed rather a darker hue, and in that of the efflorescence spreading round the incisions, which had more of an erysipelatous look than we commonly perceive when variolous matter has been made use of in the same manner; but the whole dies away (leaving on the inoculated parts scabs and subsequent eschars) without giving me or my patient the least trouble.

[8]"In order to ascertain whether the boy, after feeling so slight an affection of the system from the cow-pox virus, was secure from the contagion of the smallpox, he was inoculated the 1st of July following with variolous matter, immediately taken from a pustule. Several slight punctures and incisions were made on both his arms, and the matter was carefully inserted, but no disease followed. The same appearances were observable on the arms as we commonly see when a patient has had variolous matter applied, after having either the cow-pox or smallpox. Several months afterwards he was again inoculated with variolous matter, but no sensible effect was produced on the constitution.

In conclusion, Jenner compares his method with that already in use.

[9]"Should it be asked whether this investigation is a matter of mere curiosity, or whether it tends to any beneficial purpose, I should answer that, notwithstanding the happy effects of inoculation, with all the improvements which the practice has received since its first introduction in this country, it not very unfrequently produces deformity

of the skin, and sometimes, under the best management, proves fatal.

10"These circumstances must naturally create in every instance some degree of painful solicitude for its consequences. But as I have never known fatal effects arise from the cow-pox, even when impressed in the most unfavourable manner, producing extensive inflammations and suppurations on the hands; and as it clearly appears that this disease leaves the constitution in a state of perfect security from the infection of the smallpox, may we not infer that a mode of inoculation may be introduced preferable to that at present adopted, especially among those families which, from previous circumstances, we may judge to be predisposed to have the disease unfavourably? It is an excess in the number of pustules which we chiefly dread in the smallpox; but in the cow-pox no pustules appear, nor does it seem possible for the contagious matter to produce the disease from effluvia, or by any other means than contact, and that probably not simply between the virus and the cuticle; so that a single individual in a family might at any time receive it without the risk of infecting the rest or of spreading a distemper that fills a country with terror."

* * * * * * * *

Immunology enters an entirely new phase after the clear demonstrations by Louis Pasteur (ca.) and Robert Koch (1882) that the causal agents in certain diseases are either bacteria or the much smaller entities termed viruses. In a famous "laboratory accident" Pasteur discovered that when chicken cholera germs are allowed to stand about for a time they lose their capacity to infect a healthy animal when injected. Further, birds inoculated with weakened germs proved subsequently resistant to fresh and virulent germs. Pasteur wondered whether he had discovered a method of artificial immunization (i.e. through the injection of attentuated germs that had lost their pathogenic, but had retained their immunogenic, capacity).

Experiments on another seriously epidemic disease, anthrax, which had fatal effects on various domesticated animals, proved the correctness of Pasteur's supposition. In a dramatic public demonstration, Pasteur proved the immunity of sheep and cattle, previously injected with attenuated germs, to a new and virulent injection.

In the case of hydrophobia, a deadly virus disease, Pasteur tried to weaken the germ by drying tissues containing a heavy infection. In a paper which is one of the great classics of medical history, he describes the outcome.

11"After what might be called innumerable trials I achieved a prophylactic method, both prompt and practical, the success of which in dogs has been so frequent and so sure that I have confidence in the applicability of it generally to all animals and to man himself.

12"This method rests essentially on the following facts:

"The inoculation into a rabbit by trepanation, under the dura mater, of a rabic spinal cord of a dog with street rabies, always gives to these animals a case of rabies after an average incubation period of around a fortnight.

13"If one passes the virus from this first rabbit to a second, from the second to a third, and so on, according to the foregoing procedure there soon is manifested a tendency, increasing in distinctness, toward a diminution of the incubation period of rabies in the rabbits successively inoculated.

14"After twenty to twentyfive passages from rabbit to rabbit one encounters incubation periods of eight days which remain during a new series of twenty to twentyfive passages. Then one attains an incubation period of seven days which recurs with striking regularity during a new series of up to ninety passages.

Pasteur turns now to his method of attentuation, and the results obtained in animal subjects and a very famous human subject.

15"If one detaches portions of these cords several centimeters long, utilizing the greatest precautions for purity which it is possible to realize, and if one suspends these in dry air, gradually their virulence diminishes until it finally disappears entirely. The time for extinction of virulence varies very little with the thickness of the pieces, but markedly with the external temperature. The results constitute the <u>scientific</u> point in our method.

16"These facts established, here is a method for rendering a dog refractory to rabies in a relatively short time.

17"In a series of flasks in which the air is kept dry by pieces of potash placed on the bottom of the vessel, one suspends each day a section of fresh rabic cord from a rabbit dead of rabies, developt after seven days' incubation. Likewise daily, one inoculates under the skin of a dog one full Pravaz syringe of sterilized bouillon in which one has dispersed a small fragment of one of these dessicated cords, commencing with a cord whose order number places it sufficiently far from the day of operation so that we are sure that it is not at all virulent. Previous experiments have established what may be considered safety in this matter. On the following days one proceeds in the same way with more recent cords, separated by an interval of two days, until one arrives at a last very virulent cord which has only been in the flask for a day or two.

18"At this time the dog is refractory to rabies. One is able to inoculate him with rabic virus under the skin or even on the surface of the brain without rabies declaring itself.

19"By applying this method, I finally had fifty dogs of every age and breed all refractory without encountering a single failure when unexpectedly there presented themselves at my laboratory upon the sixth of last July three persons from Alsace:

20"Theodore Vone, a petty merchant grocer of Meissengott near Schlestadt, bitten in the arm July 4th by his own dog which had gone mad;

21"Joseph Meister, aged nine years, likewise bitten on the 4th of July at 8 o'clock in the morning by the same dog. This child, thrown to the earth by the dog, had numerous bites on his hand, legs, and buttocks, some of them very deep and making walking difficult. The chief wounds had been cauterized with carbolic acid only twelve hours after the accident, at 8 in the evening of July 4th, by Dr. Weber of Ville;

22"The third person who had herself received no bites was the mother of little Joseph Meister.

23"At the autopsy of the dog, struck down by its master, the stomach of the dog was found full of straw, hay, bits of wood. The dog had been quite mad. Joseph Meister had been dragged from under the dog covered with saliva and blood.

24"M. Vone had on his arm some marked contusions, but he assured me that his shirt had not been pierced by the fangs of the dog. Since he had nothing to fear I told him he could leave for Alsace the same day, and he did so. But I kept with me little Joseph Meister and his mother.

25"Now it happened that it was also on exactly July 6th that the Academy of Science was holding its weekly meeting; I saw there our colleague M. le Dr. Vulpian and told him what had happened. M. Vulpian, as well as Dr. Grancher, were good enough to accompany me at once to Joseph Meister and to confirm the condition and number of his wounds. He had no less than fourteen of them.

26"The opinions of our colleague and of Dr. Grancher were to the effect that, from the intensity and number of his bites, Joseph Meister had been practically fatally exposed to the inception of rabies. I then communicated to M. Vulpian and M. Grancher the new results I had obtained in the study of rabies since my lecture in Copenhagen a year before.

27"The death of this child appearing to be inevitable, I decided, not without deep and acute anxiety, as you will well imagine, to try with Joseph Meister the method which had so often proved successful with dogs.

28"My fifty dogs, it is true, had not been bitten before I commenced to make them refractory, but I knew that this circumstance need not preoccupy me for I had previously already obtained the refractory state in dogs after their being bitten in a large number of cases. I had already presented evidence this year to the rabies Commission of this new and important forward step.

29"Therefore, on July 6th, at 8 in the evening, sixty hours after the bites of July 4th, and in the presence of Drs. Vulpian and Grancher, Joseph Meister was inoculated under the skin of the hypochondrium, right side, with one half of a Pravaz syringe of cord of a rabbit dead of rabies June 21st and since then preserved in a flask of dry air, namely, for fifteen days.

30"The days following, new inoculations were made, always in the hypochondrial region according to the conditions which I give in the following table:

July	time	cord taken	dried for
7th	9 am	June 23rd	14 days
7th	6 pm	June 25th	12 days
8th	9 am	June 27th	11 days
8th	6 pm	June 29th	9 days
9th	11 am	July 1st	8 days
10th	11 am	July 3rd	7 days
11th	11 am	July 5th	6 days
12th	11 am	July 7th	5 days
13th	11 am	July 9th	4 days
14th	11 am	July 11th	3 days
15th	11 am	July 13th	2 days
16th	11 am	July 15th	1 day

31"In this way I carried to 13 the number of inoculations and to 10 the number of days of treatment. I will explain later that a fewer number of inoculations would have sufficed. But you will understand that in this first attempt I felt obliged to act with the most particular circumspectness.

32"Each of the cords employed was also inoculated by trepanation into two new rabbits so as to follow the virulence of the materials we were injecting into the human subject.

33"Study of these rabbits made it possible to verify that the cords of July 6th, 7th, 8th, 9th, and 10th were not virulent, for they did not produce rabies in the rabbits. The cords of July 11th to 16th were all virulent, and the proportion of virulent substance present grew daily greater. Rabies declared itself after seven days' incubation for rabbits of July 15th and 16th; after eight days for those of the 12th and 14th; after fifteen days for those of July 11th.

34"During the last days, I had inoculated into Joseph Meister the very most virulent strain of rabies virus, a strain which taken from dogs and reinforced by many passages from rabbit to rabbit gives rabies to rabbits in seven days, to dogs in eight to ten. I felt justified in undertaking to do so because of what happened to the fifty dogs to which I previously referred.

35"When the immune state has been attained one can without fear inoculate the strongest virus in any quantity whatever. It has always seemed to me that this would have no other effect than to consolidate the refractory state.

36"Thus, Joseph Meister escaped not only the rabies to which his bites might have given rise but also the virus which I injected as a control upon the immunity got by treatment, and the rabies which I injected was stronger than the street strain.

37"The final inoculation of this very virulent material has likewise the advantage of cutting down the time during which one need be apprehensive about the aftereffects of a bite. For if the rabies is going to be able to appear, then it will appear much sooner from the injected virus than from the weaker virus of the bite. After the middle of August, I looked forward with confidence toward the future soundness of Joseph Meister. Today as well, after a lapse of three months and three weeks since the accident, his health leaves nothing to be desired . . ..

Pasteur makes a guess as to the mechanism underlying his results and cites a second case of immunizing a human subject.

38"M. Raulin, my old teacher, now professor of the Faculty of Lyon, has established, in a very remarkable thesis which he defended at Paris, March 22, 1870, that the growth of aspergillus niger develops a substance which partially arrests the growth of this mold when the culture medium does not contain iron salts.

39"Could it not be that the rabies virus is composed of two distinct substances so that in addition to that which is living and able to reproduce in the nervous system, there is another having the faculty when present in suitable amounts of stopping the development of the foregoing? I will examine this third interpretation of the method of prophylaxy in rabies with all the attention it deserves in my next communication. . ..

40"Last Tuesday, October 20th, with the obliging assistance of MM. Vulpian and Grancher, I had to start treating a youth of 15 years, bitten six days before on both hands and in very serious condition.

41"I shall not delay in informing the Academy of the outcome from this new attempt.

[42]"Probably it will not be without emotion that the academy will hear the account of the couragious act and presence of mind of this boy whom I started treated Tuesday last. He is a shepherd, fifteen years old, named Jean-Baptiste Jupille, from Villers-Farlay (Jura) who, on seeing a dog of suspicious actions and great size leap upon a group of six small friends of his, all younger than he was, lept forward, armed with his whip, in front of the animal. The dog seized Jupille's left hand in his mouth. At this, Jupille knocked the dog down, held him down, opened his mouth with his right hand, meanwhile receiving several new bites, and then, with the thong of his whip bound the dog's muzzle and dispatched the dog with one of his wooden shoes."

<u>Abstracts from comments succeeding the reading of Pasteur's paper</u>

VULPIAN:

"The Academy will not be astonished if, as a member of the Section on Medicine and Surgery, I seek the chair's recognition to express the feelings of admiration which M. Pasteur's communication inspires in me. The sentiments will be shared, I am sure, by the entire medical profession. Etc.

LARREY:

"- - - - - I therefore take the honor of moving that the Academy recommend to the French Academy that this young shepherd has, in giving so generous an example of courage, rendered himself deserving of a 'prize of virtue.'

BOULEY (President of the Academy):

"The Communication which we have just heard permits the Academy, and I might even say humanity, to conceive new hopes.

"Likewise the date of October 27, 1885, will remain as one of the most memorable, if it is not the most memorable, in the history of scientific conquests and in the Annals of the Academy."

The Search for an Explanation of Heredity

[1] There was a great deal of speculation about, but not much actual progress in understanding, inheritance until the third quarter of the nineteenth century. In antiquity, two views were put forward and variations of these were contested for over 2,000 years. The Greek atomists developed the notion that material particles representative of the various parts of the body crowded into the sexual products of the male and female, became mixed together, and somehow arranged themselves to form a preliminary sketch of the new organism, this sketch subsequently developing and differentiating into a fully organized individual. This theory, of representative particles coming from various parts of the body, acquired the name pangenesis. Probably, its chief authors were Leucippus and Democritus (ca. 400 B.C.). An alternate view was developed, primarily, by Aristotle (ca. 360 B.C.), which is not easy for a person with the modern scientific perspective to understand. Aristotle believed that in reproduction the female contributed merely the nourishment for the new individual whereas the male contributed what Aristotle called the "form." By this he meant that the male sexual product contained the potentiality for organizing the nutritive matter supplied by the female. But the organization was present in the male sexual product only potentially, and not actually.

[2] A somewhat prophetic idea was put forward in the eighteenth century by a French physicist, mathematician, and philosophical biologist, Moreau de Maupertuis, who was, in essence a pangenesist. He thought that particles collected from all parts of the male and female bodies at the moment of conception, and mingled to form a new individual, or sketch of a new individual, in the female uterus. He believed these particles were endowed with "memory, aversion, and desire." In other words, they remembered where they had come from, they had an aversion for particles coming from other parts of the body, and they had a desire to line up near particles coming from neighboring parts of the body. Maupertuis believed that the particles sometimes experienced "accidents" which caused unprecedented differences - very much like modern mutations - between offspring and their parents. He believed that an accumulation of these differences could lead to the establishment of new species and that perhaps all species arose in this manner, namely through descent with change from pre-existing species. Therefore, Maupertuis was one of several eighteenth century precursors of the theory of evolution. His ideas were countered by others who believed, somewhat after the manner of Aristotle, that the sexual products contain the future individual only "potentially" rather than actually.

[3]The first important modern insight into hereditary processes came through the work of an Austrian monk, Gregor Mendel, who in 1866 published

Experiments on Plant Hybridization

[4]Mendel's experiments involve the inbreeding and crossbreeding of plants, especially plants of the pea family. In some of his experiments, he crossed two inbred strains which were entirely similar to each other. In other experiments he crossed inbred strains which differed from each other with respect to one specific characteristic such as flower color, seed color, condition of the seed coat (whether wrinkled or smooth). He says:

> [5]"If two plants [strains] which differ constantly in one or several characters be crossed, numerous experiments have demonstrated that the[ir] common characters are transmitted unchanged to the hybrids and their progeny; but each pair of differentiating characters, on the other hand, unite in the hybrid to form a new character, which in the progeny of the hybrid is usually variable. The object of the experiment was to observe these variations in the case of each pair of differentiating characters, and to deduce the law according to which they appear in the successive generations. The experiment resolves itself, therefore, into just as many separate experiments as there are constantly differentiating characters presented in the other experimental plants."

[6]One might suspect that the offspring of strains differing with respect to some specific characteristic might be intermediate in character between their parents. Note, however, what Mendel actually found to be the case.

> [7]"Experiments which in previous years were made with experimental plants have already afforded evidence that the hybrids, as a rule, are not exactly intermediate between the parental species. With some of the more striking characters, those for instance which relate to the form and size of the leaves, the intermediate indeed is nearly always to be seen;

in other cases, however, one of the two parental characters is so preponderant that it is difficult or quite impossible to detect the other in the hybrid.

[8]"This is precisely the case with the Pea hybrids. This circumstance is of great importance in the determination and classification of the forms under which the offspring of the hybrids appear. Henceforth in this paper those characters which are transmitted entire or almost unchanged in the hybridization and therefore in themselves constitute the character of the hybrid, are termed the dominant, and those which become latent in the process recessive."

[9]In his first set of experiments Mendel inbred dominantly-appearing off-spring of two different strains. That is, he placed the pollen of these plants on the pistils of the same plant, so that self-fertilization occurred. He then collected and examined the seeds, and planted some, and summarized the results as follows:

F_2: The First Generation From the Hybrids

[10]"In this generation there reappear, together with the dominant characters, also the recessive ones with their peculiarites fully developt, and this occurs in the definitely expressed average proportion of three to one, so that among each four plants of this generation (an average of) three display the dominant character and one the recessive. This occurs without exception for all the characters which were investigated in these experiments. The angular, wrinkled form of the seed, the green color of the albumen, the white color of the seed coats and the flowers, the constrictions of the pods, the yellow color of the unripe pod, of the stalk, of the calyx, and of the leaf venation, the umbel-like form of the inflorescence, and the dwarfed stem, all reappear in the numerical proportion given, without essential alteration. Transitional forms were not observed in any experiment." [This is followed by the statistical basis for

the above statement of the 3:1 ratio with details for each character]

[11]Mendel next self-fertilized some of the plants that he obtained in the above manner and made a striking discovery. He found that plants that appeared dominant, when self-fertilized, did not all behave in the same way. Apparently their dominant appearance could mean two different things as far as their genetic constitution was concerned. Reporting these experiments, Mendel says:

> [12]"The dominant character can have a <u>double signification</u> viz., that of a parental character, or a hybrid character. In which of the two significations it appears in each separate case can only be determined by the following generation. As a parental character it must pass over unchanged to the whole of the off-spring; as a hybrid character on the other hand it must maintain the same behavior as in the first (F_2) generation.
>
> <u>F_3: The Second Generation From the Hybrids</u>
>
> [13]"Those forms which in the first generation (F_2) exhibit the recessive character do not further vary in the second generation (F_3) as regards this character; they remain constant in their off-spring.
>
> [14]"It is otherwise with those which possess the dominant character in the first generation (F_2). Of these two-thirds yield offspring which display the dominant and recessive characters in the proportion of 3 to 1, and thereby show exactly the same ratio as the hybrid forms, while only one-third remains with the dominant character constant. The separate experiments yielded the following results: . . . [Here follows a detailed account of experiments with statistical results providing the basis for the foregoing statement].
>
> [15]"In these experiments a certain number of the plants came constant with the dominant character. For the determination of the

proportion in which the separation of the forms with the constantly persistent character results, our first two experiments were of special importance, since in these the largest number of plants can be compared (1,084). The ratios 1.93 to 1 and 2.13 to 1, for these experiments, gave together almost exactly the average ratio of 2 to 1. The sixth experiment (100 plants) gave quite concordant results. Experiment 5 which showed the greatest departure was repeated and then in lieu of the ratio of 60 to 40, that of 65 and 35 resulted. The average ratio of 2 to 1 appears therefore as fixed with certainty. It is therefore demonstrated that, of those forms which possess the dominant character in the first generation, two-thirds have the hybrid character, while one-third remains constant with the dominant character.

16"The ratio of 3 to 1, in accordance with which the distribution of the dominant and recessive characters results in the first generation resolves itself therefore in all experiments into the ratio of 2:1:1 if the dominant character be differentiated according to its significance as a hybrid character or a parental one. Since the members of the first generation (F_2) spring directly from the seed of the hybrids (F_1), it is now clear that the hybrids form seeds having one or other of the two differentiating characters, and of these one-half develop again the hybrid form, while the other half yield plants which remain constant and receive the dominant or the recessive characters (respectively) in equal numbers."

17Mendel now takes two steps. First, he asks himself what his results could mean in terms of the actual material content of the sex cells. Second, as we shall see, this leads him to experiment with plant strains differing in two characteristics instead of merely one. He says:

18". . . So far as experience goes, we find it in every case confirmed that constant progeny can only be formed when the egg-cells and the fertilizing pollen are of like character, so that both are provided with the material for creating quite similar individuals, as is the case with the normal fertilization of pure species. We must therefore regard it as certain that exactly similar factors must be at work also in the production of the constant forms in the hybrid plants. Since the various constant forms are produced in one plant, or even in one flower of a plant, the conclusion appears logical that in the ovaries of the hybrids there are formed as many sorts of egg-cells, and in the anthers as many sorts of pollen cells, as there are possible constant combination forms, . . .

[19]"In point of fact it is possible to demonstrate theoretically that this hypothesis would fully suffice to account for the development of the hybrids on the average in equal numbers.

[20]"In order to bring these assumptions to an experimental proof, the following experiments were designed. Two forms which were constantly different in the form of the seed and the color of the albumen were united by fertilization.

[21]"If the differentiating characters are indicated as A,B,a,b, we have:

AB, seed parent	ab, pollen parent
A, form round	a, form wrinkled
B, albumen yellow	b, albumen green

The artificially fertilized seeds were sown together with several seeds of both original stocks, and the most vigorous examples were chosen for the reciprocal crossing. There were fertilized: 1 the hybrids with the pollen of AB 2 the hybrids with the pollen of ab 3 AB with the pollen of the hybrids 4 ab with the pollen of the hybrids.

[22] "For each of these four experiments all of the flowers on three plants were fertilized. If the above theory be correct, there must be developt on the hybrids egg and pollen cells of the forms AB, Ab, aB, and ab and there would be combined: 1 egg cells AB, Ab, aB, and ab with pollen cells AB 2 the same with pollen cells aB 3 egg cells AB with the pollen cells AB, Ab, aB, and ab 4 egg cells ab with the pollen cells AB, Ab, aB, and ab. From each of these experiments there could then result only the following forms: 1 AB, ABb, AaB, AaBb 2 AaBb, Aab, aBb, ab 3 AB, ABb, AaB, AaBb 4 AaBb, Aab, aBb, ab. The crop fulfilled these expectations perfectly." (Here follow detailed data obtained in the many experiments and summarized by the foregoing statement).

[23] Mendel's work was published in an obscure journal, was not widely read, and curiously was apparently not appreciated by those who did read it. Only in the year 1900, thirty-four years after Mendel published, was his work "rediscovered" by three different scientists seeking to understand the hereditary process. They recognized Mendel's genius and the true - though preliminary - insight which he had into the mechanism of inheritance. Mendel's experiments immediately began to be repeated and extended and, presently, to be correlated with the visible aspects of reproduction made through microscopic examination of the sex cells (mitosis and meiosis).

Spontaneous Generation

[1]Historical studies show that biologists return, in era after era, to the investigation of certain persistent, fundamental problems. The spontaneous generation problem became acute in the seventeenth century, the prevailing opinion until then having been that, under the proper conditions, the proper sorts of nonliving matter can generate living beings spontaneously. There are numerous allusions to spontaneous generation, for example, in the scientific literature of antiquity. Our information about the pre-Socratics is fragmentary, but we know that both Anaximander and Empedocles spoke of elements as undergoing organization to give rise to the first living things. They and other pre-Socratics undoubtedly supposed that this happened not only in the beginning but often thereafter.

[2]Aristotle was, in any case, quite specific on the point, asserting that animals arise in two ways, biogenetically (through reproduction) and spontaneously (through the operation of natural forces in nonliving matter - matter, especially, where decay is going on, such as dead bodies or dung). Epicurus (as represented by Lucretius) was equally definite, and said that the warmth of the sun and moisture of the rain, give rise to living things in rotting earth or manure.

[3]Both in early Christian times, and later during the Middle Ages, ecclesiastical thought supported the idea of spontaneous generation, and reconciled it with religious doctrine. In the fourth century, Basil the Great and St. Augustine, major founders of the Greek and Latin churches respectively, both subscribed to this mode of origin of living things, and so did the thirteenth century scholastic Albertus Magnus, and his student Thomas Aquinas. Lay thought was equally congenial to the theory. Many of the alchemists - including Paracelsus - thought of minerals and other things that we consider nonliving as very much alive. Some of them set themselves the problem of inducing spontaneous generation artificially; Paracelsus gives the formula for creating a human fetus (homunculus), de novo, in a bottle.

[4]We must be careful, however, not to confuse two rather different ideas about the appearance of life in previously nonliving matter. To be precise at least three views are theoretically tenable. One may believe, first of all, that no living thing ever arises except through the reproductive activity of some other, pre-existent living thing or things. This principle - omne vivum e vivo - acquired increasing acceptance over a two hundred year period (1680-1880), and is sometimes known as the principle of biogenesis. Or, second, one may suppose that chemical elements, behaving as such, have occasionally and quite accidentally acquired the organization that is needed for the manifestation of life. This is spontaneous generation in the strict sense.

This differs from a third opinion according to which some adventitious (and usually, supernatural) agency is supposed to intervene, and arrange the elements in the requisite pattern. Such intervention is conventionally spoken of as special creation - though that term has also been used to suggest the creation of life not out of preexistent matter but rather out of nothing at all.

5 In the early seventeenth century, Francis Bacon revived the Aristotelian dichotomy (see above) and divided reproductive processes into two sorts, copulative and putrefactive. This was in about 1610. Not long thereafter the great iatrochemist van Helmont, though a pious man who often mixed his religious with his scientific theories, argued for spontaneous generation partly on experimental grounds. He recommended a mixture of dirty rags with wheat grains or cheese as an experimentally tested method for generating mice!

6 The fact that excremental and decaying matter often swarms with fly larvae (maggots) certainly added credence to the association of generation with corruption, and it was on maggots, in fact, that the first good experimental work on spontaneous generation was done. The experimenter in question was the Italian poet and physician Francesco Redi (1688). Harvey had objected to the idea that full-fledged organisms could spring fully developed from mud or dung, and insisted that complex living forms usually start life as some sort of seminal matter or undifferentiated germ; but such seminal matter, he supposed, could arise spontaneously provided conditions were right. On the latter point, Redi begs to differ. He writes as follows:

> 7 "Although content to be corrected by any one wiser than myself, if I should make erroneous statements, I shall express my belief that the Earth, after having brought forth the first plants and animals at the beginning by order of the Supreme and Omnipotent Creator, has never since produced any kinds of plants or animals, either perfect or imperfect, and everything which we know in past or present times that she has produced, came solely from the true seeds of the plants and animals themselves, which thus, through means of their own, preserve their species. And, although it be a matter of daily observation that infinite numbers of worms are produced in dead bodies and decayed plants, I feel, I say, inclined to believe that these worms are all generated by insemination and that the putrefied matter in which they are found has no other office than that of serving as a place, or suitable nest where animals deposit their eggs at the breeding season, and in which they also find nourishment; otherwise, I assert that nothing is ever generated therein. . ..

[8] "In being thus, as I have said, the dictum of ancients and moderns, and the popular belief, that the putrescence of a dead body, or the filth of any sort of decayed matter engenders worms; and being desirous of tracing the truth in the case, I made the following experiment:

[9] "At the beginning of June I ordered to be killed three snakes, the kind called eels of Aesculapius. As soon as they were dead, I placed them in an open box to decay. Not long afterwards I saw that they were covered with worms of a conical shape and apparently without legs. These worms were intent on devouring the meat, increasing meanwhile in size, and from day to day I observed that they likewise increased in number; but, although of the same shape, they differed in size, having been born on different days. But all, little and big, after having consumed the meat, leaving only the bones intact, escaped from a small aperture in the closed box, and I was unable to discover their hiding place. Being curious, therefore, to know their fate, I again prepared three of the same snakes, which in three days were covered with small worms. These increased daily in number and size remaining alike in form, though not in color. Of these, the largest were white outside, and the smallest ones, pink. When the meat was all consumed, the worms eagerly sought an exit, but I had closed every aperture. On the nineteenth day of the same month some of the worms ceased all movements, as if they were asleep, and appeared to shrink and gradually to assume a shape like an egg. On the twentieth day all the worms had assumed the egg shape, and had taken on a golden white color, turning to red, which in some darkened, becoming almost black. At this point the red, as well as the black ones, changed from soft to hard, resembling somewhat those chrysalides formed by caterpillars, silkworms, and similar insects. My curiosity being thus aroused, I noticed that there was some difference in shape between the red and the black eggs (pupae), though it was clear that all were formed alike of many rings joined together; nevertheless, these rings were more sharply outlined, and more apparent in the black than in the red, which last were almost smooth and without a slight depression at one end, like that in a lemon picked from its stalk, which further distinguished the black egg-like balls. I placed these balls separately in glass vessels, well covered with paper, and at the end of eight days, every shell of the red balls was broken, and from each came forth a fly of gray color, torpid and dull, misshapen as if half finished, with closed wings; but after a few minutes they commenced to unfold and to expand in exact proportion to the tiny body, which also in the meantime had acquired symmetry in all its parts. Then the whole creature, as if made anew, having lost its gray color, took on a most brilliant and vivid green; and the whole body had expanded and grown so that it seemed incredible that it could ever have been contained in the small shell. Though the red eggs (pupae) brought forth green flies at the end of eight days, the black ones labored fourteen days to produce certain large black flies striped with white, having a hairy abdomen, of the kind that we see daily buzzing about the butchers' stalls.

10"Having considered these things, I began to believe that all worms found in meat were derived directly from the droppings of flies, and not from the putrefaction of the meat, and I was still more confirmed in this belief by having observed that, before the meat grew wormy, flies had hovered over it, of the same kind as those that later bred in it. Belief would be vain without the confirmation of experiment, hence in the middle of July I put a snake, some fish, some eels of the Arno, and a slice of milk-fed veal in four large, wide-mouthed flasks; having well closed and sealed them, I then filled the same number of flasks in the same way, only leaving these open. It was not long before the meat and the fish, in these second vessels, became wormy and flies were seen entering and leaving at will; but in the closed flasks I did not see a worm, though many days had passed since the dead flesh had been put in them. Outside on the paper cover there was now and then a deposit, or a maggot that eagerly sought some crevice by which to enter and obtain nourishment. Meanwhile the different things placed in the flasks had become putrid. . .

11"Leaving this long digression and returning to my argument, it is necessary to tell you that although I thought I had proved that the flesh of dead animals could not engender worms unless the semina of live ones were deposited therein, still, to remove all doubt, as the trial had been made with closed vessels into which the air could not penetrate or circulate, I wished to attempt a new experiment by putting meat and fish in a large vase closed only with a fine Naples veil, that allowed the air to enter. For further protection against flies, I placed the vessel in a frame covered with the same net. I never saw any worms in the meat, though many were to be seen moving about on the net-covered frame. These, attracted by the odor of the meat, succeeded at last in penetrating the fine meshes and would have entered the vase had I not speedily removed them. It was interesting, in the meanwhile, to notice the number of flies buzzing about which, every now and then, would light on the outside net and deposit worms there. I noted that some left six or seven at a time there and others dropped them in the air before reaching the net. . .."

12Shortly before Redi's experiments, the microscope had come actively into use and had revealed - especially to the Dutch observer van Leeuwenhoek - a new world of microscopic beings. Leeuwenhoek discovered both infusoria (protozoa) and bacteria as well as microscopic plants. One of the richest sources of such organisms, as it turned out, was precisely the sort of material where spontaneous generation had always seemed to occur, namely in decaying plant and animal matter. Micro-organisms appeared in infusions even when they were covered with gauze, and the suspicion quickly spread that they arose there by spontaneous generation. This hypothesis was argued pro and con throughout the middle years of the eighteenth century. At that time, experimental biology declined and arm-chair speculation was in style, but there were at least a few physiologists who preferred experimental procedures. One of these was the Irish cleric, J. T. Needham, who approached the spontaneous generation problem in an experimental and at least semi-scientific spirit, though not, as we shall see, without a strong component of speculative interpretation. Note the experimental method of his approach, and the rather extreme conclusions that his experimental findings engender.

> [13]". . . For my purpose, therefore, I took a Quantity of Mutton-Gravy hot from the Fire, and shut it up in a phial, clos'd up with a Cork so well masticated, that my Precautions amounted to as much as if I had sealed my Phial hermetically. I thus effectually excluded the exterior Air, that it might not be said my moving Bodies drew their Origin from Insects, or Eggs floating in the Atmosphere . . . I neglected no Precaution, even as far as to heat violently in hot Ashes the Body of the Phial, that if any thing existed, even in that little portion of Air which filled up the Neck, it might be destroyed, and lose its productive Faculty. Nothing therefore could answer my Purpose of excluding every Objection, better than hot roast-Meat Gravy secured in this manner, and exposed some Days to the Summer-Heat; and as I determined not to open it, till I might reasonably conclude, whether, by its own Principles, it was productive of any thing, I allow'd sufficient Time for that Purpose to this pure unmix'd Quintessence, if I may so call it, of an animal body . . . .. My Phial swarm'd with Life, and microscopical Animals of most Dimensions, from some of the largest I had ever seen, to some of the least. The very first Drop I used, upon opening it, yielded me Multitudes perfectly form'd, animated, and spontaneous in all their Motions: . . .
>
> [14]"I shall not at this present time trouble you with a Detail of Observations upon three or four Scores of different Infusions of animal and vegetable Substances, posterior to these upon Mutton-Gravy; all which constantly gave me the same Phaenomena with little Variation, and were uniform in their general Result: These may better appear at length upon some other Ocasion; let it suffice for the present to take notice, that the Phials, clos'd or not clos'd, the Water previously boil'd or not boil'd, the Infusions permitted to teem, and then plac'd upon hot Ashes to destroy their Productions, or proceeding in their Vegetation without Intermission, appear'd to be so nearly the same, that, after a little time, I neglected every Precaution of this kind, as plainly unnecessary . . . ..
>
> [15]". . . It seems plain therefore, that there is a vegetative Force in every microscopical Point of Matter, and every visible Filament of which the whole animal or vegetable Texture consists: And probably this Force extends much farther; . . .

[16]"Hence it is probable, that every animal or vegetable substance advances as fast as it can in its Resolution to return by a slow Descent to one common Principle, the Source of all, a kind of universal Semen; whence its Atoms may return again, and ascend to a new Life."

[17]Needham supposed (a) that he had heat-killed any living organisms that had happened to be in his flasks, (b) that he had prevented others from entering from outside, and (c) that the thus decontaminated fluid had given rise to living things completely anew. It seemed to him that he had saved the day for spontaneous generation. But opponents, such as the Italian Abbot Spallanzani, were not slow to point to the shortcomings of Needham's method. Had Needham left the flasks in the ashes long enough to kill all of the organisms present there? Had his corks been really sterile? Spallanzani performed a series of experiments in which eleven different sorts of substances were boiled for periods varying for one or two minutes to several hours. He completely prevented the entrance of organisms from the air by a method indicated in the following:

Lazaro Spallanzani. Tracts on the nature of animals and vegetables; "Observations and Experiments upon the Animalcula of Infusions," Edinburgh, 1799.

[18]"I hermetically sealed vessels with the eleven kinds of seeds mentioned before [kidney-beans, vetches, buckwheat, barley, maize, mallow, beet, peas, lentils, beans, hemp]. To prevent the rarefaction of the internal air, I diminished the thickness of the necks of the vessels, till they terminated in tubes almost capillary, and, putting the smallest part to the blowpipe, sealed it instantaneously, so that the internal air underwent no alteration. . . . I took nine vessels with seeds, hermetically sealed. I immersed them in boiling water for half a minute. I immersed another nine for a whole minute, nine more for a minute and a half, and nine for two minutes. Thus, I had thirty-six infusions. That I might know the proper time to examine them, I made similar infusions in open vessels, and, when these swarmed with animalcula, I opened those hermetically sealed. . . . I examined the infusions, and was surprised to find some of them an absolute desert; others reduced to such a solitude, that but a few animalcula, like points, were seen, and their existence could be discovered only with the greatest difficulty. The action of heat for one minute, was as injurious to the production of the animalcula, as of two. The seeds producing the inconceivably small animalcula, were, beans, vetches, buckwheat, mallows, maize, and lentils. I could never discover the least animation in the other three infusions. I thence concluded, that the heat of boiling water for half a minute, was fatal to all animalcula of the largest kind; even to the middle-sized, and the smallest, of those which I shall term animalcula of the higher class,

to use the energetic expression of M. Bonnet; while the heat of two minutes did not affect those I shall place in the lower class [undoubtedly bacteria - ed.] . . .

[19]"Boiling half an hour was no obstacle to the production of animalcula of the lower class; but boiling for three quarters, or even less, deprived all the six infusions of animalcula.

[20]"Two important consequences thence arise. The first evinces the extreme efficacy of heat to deprive infusions in close vessels of a multitude of animated beings; for, in open vessels, are always seen a vast concourse of animalcula. The second consequence concerns the constancy of animalcula of the lower class appearing in infusions boiled in close vessels; and the heat of 212°, protracted an hour, has been no obstacle to their existence . . ..

[21]"We are therefore induced to believe that those animalcula originate from germs there included, which, for a certain time, withstand the effects of heat, but at length yield under it; and, since animalcula of the higher classes only exist when the heat is less intense, we must imagine they are much sooner affected by it, than those of the lower classes. Whence we should conclude, that this multitude of the superior animalcula, seen in the infusions of open vessels, exposed not only to the heat of boiling water, but to the flame of a blowpipe, appears there, not because their germs have withstood so great a degree of heat, but because new germs come to the infusions, after cessation of the heat . . ..

[22]"The idea, that animalcula come from the air, appears to me to be confirmed by undoubted facts. I took sixteen large and equal glass vases: four I sealed hermetically; four were stopped with a wooden stopper, well fitted; four with cotton; and the four last I left open. In each of the four classes of vases, were hempseed, rice, lentils, and peas. The infusions were boiled a full hour, before being put into the vases. I begun the experiments 11. May, and visited the vases 5. June. In each there were two kinds of animalcula, large and small; but in the four open ones, they were so numerous and confused that the infusions, if I may use the expression, rather seemed to teem with life. In those stoppered with cotton, they were about a third more rare; still fewer in those with wooden stoppers; and much more so in those hermetically sealed . . ..

[23]"The number of animalcula developed, is proportioned to the communication with the external air. The air either conveys the germs to the infusions, or assists the expansion of those already there. . ..

[24]"These facts fully convinced me, that vegetable seeds never fail to produce animalcula, though exposed to any degree of heat; whence arises a direct conclusion, that the <u>vegetative</u>

power is nothing but the work of imagination; and if no animalcula appear in vessels hermetically sealed and kept an hour in boiling water, their absence must proceed from some other cause."

[25]Spallanzani's experiments were persuasive but, as it turned out, not decisive. They were still open to the possibility that the prolonged boiling had destroyed the pretended "vegetative power" of the fluids, or impaired the life-sustaining power of the air in the flask. What was needed, then, was an experiment to show that boiled fluids can easily support life and that micro-organisms will appear if such fluids are exposed to ordinary air, but not if the air has been rendered bacteria free. This was accomplished, only in 1860, as part of the ambitious and successful experimental program of Louis Pasteur.

[26]Pasteur conducted a number of fairly decisive experiments. In one he drew a current of ordinary air through a wad of guncotton, dissolved the guncotton, and noticed a "dust" of particles at the bottom of the solution chamber. This, on microscopic examination, turned out to have micro-organisms in it - killed, of course, but unmistakable. In another experiment he drew

(a) preheated air and
(b) ordinary air

through a wad of cotton which was then allowed to drop into a broth previously sterilized through long boiling. He developed a way of introducing into these flasks a stream of air previously heated and then cooled. In case (b) but not in case (a) the broths developed populations of micro-organisms. Query: How do these results affect the argument that heating kills the "vegetative power" of the fluids or the "life-supporting power" of air?

[27]In another, admirably simple experiment, Pasteur prepared some sealed flasks containing unsterilized broth. The flasks had long, much-twisted necks. After submitting the flasks to prolonged boiling, he set them aside to cool, and then broke off the tip of each flask to let in a current of air. Certain flasks were similarly treated except that they were not boiled. In the latter, the broth soon swarmed with micro-organisms, but the boiled flasks still exist, a hundred years later, on the shelves of Institut Pasteur in Paris; they have remained entirely sterile. Occasionally, as an experiment, one of these flasks has been tilted and then returned to its upright position; the broth thus comes momentarily into contact with the walls of the neck of the flask. In such cases, the broth soon develops a copious population of micro-organisms. How would you interpret this result?

Final queries: After Pasteur announced his results, belief in spontaneous generation died out in scientific circles. Had Pasteur proved that spontaneous generation never occurs? never has occurred? could not possibly occur? What did he prove?

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