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THE HARVEY LECTURES

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1911-1912

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PROF. JAMES J. PUTNAM
PROF. WILLIAM T. SEDGWICK
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PREFACE

While the Harvey Society becomes responsible to a larger audience each year, the prestige and character given to its undertaking by the generous services of the lecturers makes the work of arranging for the annual series and the publication of the volume progressively easier.

The lectures of Dr. Flexner, Prof. Kossel, Prof. Richards, Prof. Chittenden, and Prof. Thayer have not appeared in previous publications.

The Editor acknowledges gratefully the courtesy of the Editors of the *Johns Hopkins Hospital Bulletin*, the *Boston Medical and Surgical Journal*, the *Journal of Infectious Diseases*, the *Popular Science Monthly*, and the *American Naturalist*, in allowing our republication of the lectures of Prof. Verworn, Prof. Putnam, Prof. Sedgwick, Prof. Cannon, Prof. Jennings, and Prof. Osborn respectively.

The Society is indebted to Dr. H. D. Dakin for his translation of Prof. Kossel's lecture, which was delivered in German.

Haven Emerson, Secretary,
120 East 62d St., New York.

September, 1912.

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LOCAL SPECIFIC THERAPY OF INFECTIONS*

SIMON FLEXNER, M.D.

THE specific treatment of infectious diseases has, as you are aware, made great progress during the last two decades. In this time some of the most potent curative agents have been perfected and introduced into practical medicine. However, the achievements of an earlier period in this field should not be minimized. One has merely to allude to the examples of quinine and mercury, to be reminded of the discovery of two of the most perfect drugs for the conquest of specific infections that are still at our disposal. Moreover, these specific remedies date from a period anterior to the present one, in which new remedies are worked out in the laboratories before they are applied to the relief of human suffering. Since the experimental method in medicine is responsible for the recent great advances that have been made, it will be of some interest to refer in passing to the circumstance that the discovery of quinine and mercury was not through magic or intuition but also by experimentation, but in this instance the experiments were conducted upon sick human beings. That is to say, the adoption of these drugs represents merely a selection out of countless hundreds of substances that had at one time or another been tested against the diseases malaria and syphilis.

We are to consider briefly the subject of a specific form of treatment of disease that is distinguished by the peculiarity that it comes to be applied locally to the focus of infection. In order that we may appreciate the purpose of this method, and also the nature of the method itself, it will be necessary to lay before you a few general data concerning the subject of infection and of recovery from that condition.

---

* Delivered October 7, 1911.

In the pursuit of knowledge of the subject of infection, no aspect of the problem has been more enlightening and rewarding than that relating to the reasons for spontaneous recovery from infectious disease. The leading physicians have rarely failed to appreciate the unexcelled power of Nature herself to heal her self-inflicted wounds, and to recognize that many diseases tend of themselves, when not quickly fatal, to progress toward recovery. There resides, therefore, within the animal body, a set of potential forces capable, when aroused, of exercising a highly effective control over disease. You are familiar with the fact that these powers have been traced to a group of substances contained within the blood and passing from the blood into the lymph, where they exert influence on the cells composing the organs and on parasites in the interstices of their tissues.[1] What these substances consist of has already been ascertained in good part, so that they may be classed briefly into soluble, complex chemical bodies, probably of protein nature, that are contained dissolved in the fluids, and of certain mobile white cells, the so-called leucocytes or phagocytes. In virtue of the soluble form and the motility of the cells, these healing substances are able to reach most parts of the body where their special properties may be exerted. Moreover, not only are these curative substances, technically called "immunity principles," preformed in all individuals in which they operate against intending infection, but they

[1] The native curative powers of the blood have been invoked to heal local diseases through the creation of a condition of artificial hyperæmia or congestion. "All organs that functionate are hyperæmic during activity. In every form of growth and regeneration local hyperæmia is present and in a degree corresponding to the rapidity and energy of the growth. . . . . All reactions to foreign substances, whether crude bodies or minute parasites or their chemical products, are associated with hyperæmia. There is no lesion which the body tries to and is capable of removing by rendering harmless, that produces anæmia. Hence if we accept the reactions of the body as useful efforts of Nature, we must admit that hyperæmia is the most common of all autocurative agents" (Bier, Hyperæmia, Translation by G. A. Bleck).

become quickly increased in amount when an infection has been established; and the ultimate issue of the condition in spontaneous recovery or the reverse depends upon the degree of this response to infection and the competency of the curative principles evoked to reach and to suppress the infectious agent.

These principles come to operate equally against all classes of microbic parasites, whether protozoa, bacteria, or that remarkable class the import of which we are just learning—the so-called submicroscopic or filterable organisms or viruses.[2] But the effectiveness of their operation is determined not only by the intrinsic qualities of parasite and of host, but also in a high degree by the manner of location and distribution of the parasites themselves within the infected host. Whether they have a general distribution throughout the blood and tissues or whether they are confined within a pathological process in the interior of an important organ or part, may be the factor determining whether not only the native curative principles shall gain ready access to them, but whether also extraneous curative agents introduced into the body shall be able to reach the seat of disease.

The parasite, struggling to survive, withdraws, at one time,

[2] A number of diseases of the higher animals, including man, and one disease of plants (the mosaic disease of tobacco) have, within ten years, been traced to submicroscopic parasites. It is indeed not remarkable that the present microscopes should have failed to define the limits of organized nature. Whether we shall ever invent instruments capable of resolving and rendering visible these minute particles of living matter is a question impossible to answer. Even doubling the potential power of the microscope by the device of employing, for photographic purposes, the ultraviolet rays of the spectrum has failed to bring them into view. Their place in nature is not accurately established. Some, as the parasite causing yellow fever, that passes a stage of its existence in mosquitoes, probably are protozoal; others, as the parasite of pleuropneumonia of cattle, that can be propagated in artificial cultures, probably are bacterial. It can hardly be doubted that they are living organisms, since they are capable of transmission from animal to animal, in which they produce infection, through an indefinite series.

into situations to which the curative substances gain access imperfectly and with difficulty, causing thereby local infections more or less cut off from the general circulation and the curative agents purveyed by the blood. This is the condition met with in massive inflammations, in abscess formation, and in infections of specialized portions of the body—such as the great serous cavities—that receive normally a modified and dilute lymph secretion.

It is the lymph that carries the protective as it does the nutritive principles for the tissues and organs; and hence this fluid provides the essential safeguard against infection. Moreover, the quality of lymph in the several serous cavities is not the same, but is, indeed, peculiar for each cavity, and the lowest limit of strength is reached by the cerebrospinal fluid —regarded as the lymph of the brain and spinal cord, which is almost devoid of protein matter.[3] As the protein moiety of the lymph carries the immunity principles, it follows that the serous cavities are really less well supplied with them, and the subarachnoid space of the central nervous system the least well of all. These considerations are not without high importance as affecting the provisions for warding off intending infection, and especially for controlling and abating an established infection. Since the anatomical structure decides the quality of the lymphatic fluid in health, it also determines it

[3] The notion that the cerebrospinal fluid is the lymph of the central nervous system is open to discussion. Mott (The Lancet, 1910) suggests that it "may serve as the ambient fluid of the neurons and play the part of lymph to the central nervous system." The fluid arises from the choroid plexus and escaping from the foramina of Magendie and Luschka into the subarachnoid spaces occupies them all and communicates, probably, with a "canalicular system surrounding the cells and vessels of the brain" (Mott). Thus this fluid should provide the most direct path for the penetration of active substances to the nervous tissues; and in fact it has been established by experiment that chemical bodies act upon the nerve cells with greater energy and certainty when introduced directly into the cerebrospinal fluid. The hen, indeed, is not subject to the effects of tetanus toxin injected into the blood, while it suffers from tetanus when it is injected into the subarachnoid spaces (Behring).

in disease, and thus by regulating the composition of this fluid commands the issue of the pathological process. Under such circumstances the parasite that becomes localized in these cavities is insured a potential advantage against the host.

The parasites possess, moreover, an advantage of regulation within themselves to preserve them from extinction—they are capable of altering rapidly, not their form and external appearances, but their chemical reactions and probably chemical structure when too closely pressed and menaced. The change consists in the development of a state of effective resistance, called "fastness," to injurious chemical agents, whether the immunity principles of the blood or other substances. The new qualities acquired have been viewed as the result of mutation among the parasites, and the mutants have been observed to transmit the new characters through an indefinite number of generations. It is precisely this property of mutation that we are learning to hold accountable for the troublesome or dangerous relapses that occur in many of the parasitic diseases, commonly for example in malaria, sleeping sickness, spirochætal infection, to mention only a few.[4] Finally, the so-called chronic carrier of infectious organisms, who is being recognized as a serious menace to the health of society and is sincerely to be pitied, is to be regarded often as the victim of this form of mutation among the micro-organisms which at one time caused him to be ill, but to which he, but not his fellows, has become adapted. In the successful exploitation of specific therapeutic measures account must obviously be taken of the biologi-

[4] This parasitic mutation or "fastness" is more readily developed against serum immunity principles (antibodies) than against chemical agents of the nature of drugs, but once produced, the latter effect is the more difficult to remove. Serum fastness may be overcome by the superinfection of an animal that has recovered from infection with the corresponding "fast" strain, through which reversion to the normal type may be accomplished; while chemical mutation is overcome solely, apparently, through sexual conjugation of protozoal parasites in the body of an appropriate insect host (Ehrlich, Folia Serologica, 1911, p. 697).

cal conditions described as well as others that may in time be discovered.

Manifestly, therefore, the bringing of the parasitic causes of microbic diseases under the influence of curative agents will be more readily and certainly accomplished when they are widely disseminated throughout the body than when they are hidden away within an organ or in the interior of a serous cavity. Hitherto the most effective agents of specific treatment have been just those that operated against the generalized infections, of which examples are such drugs as quinine in its action against the malarial parasite, and mercury in its effect on the spirochætal cause of lues. The same result is now being achieved by salvarsan, recently discovered by Ehrlich, in respect to its application to a number of spirochætal affections in man and the domestic animals; while the control of diphtheria by antitoxin, perhaps the most perfect example of all, consists essentially in the neutralization of a universally distributed toxic or poisonous agent that is directly the cause of the serious effects of the disease. When, in generalized infections, the surviving micro-organisms escape from the blood and tissues, as sometimes happens in luetic or other diseases, to aggregate in special situations and local pathological products that are reached imperfectly by the lymph, then the specific drug or other agents assert their curative powers with far more difficulty and far less certainty.

Medicine is now armed with a number of specific remedies for serious diseases, consisting partly of chemical compounds of known composition and partly of more complex serum products of unascertained nature. The number of drugs is potentially greater than the number of sera and is capable of almost unlimited expansion, so that doubtless therapeutics will be greatly enriched by future discovery in this fascinating field. That many immune sera are capable of being prepared artificially is also certain, but the degree of their applicability will need to be worked out in any given instance. It is already clear that the immune sera closely resemble the natural defences against infection and its consequences, so that it follows that

they are essentially non-foreign bodies, and thus, technically, ideal agents with which to combat disease. They are, in essence, so precisely fashioned as to operate exclusively against the agents of infection, and thus to pass over without molestation the sensitive cells of the organs. In fact, their action is less specific than this statement implies, because, as now manufactured, they carry with them in the natural serum of animals certain alien substances that do effect, in some degree, the host himself. A factor that bears upon the production of curative immune sera as well as upon specific drugs is that of fastness or mutation of the micro-organisms within the body. Experiment has already disclosed the high importance of this unexpected phenomenon of infection. In the choice of especially fashioned drugs the two properties that now determine availability for practical medical employment are, first, a low degree of toxicity for the organs of the host, and second, absence of the tendency to produce fast strains of the parasite upon which they exert their influence.

We have still to learn the extent to which specific drug treatment of the infections is capable of altering the state of the acquired immunity to infectious diseases that protects, in some instances, from second attacks of maladies. Important facts bearing on this subject are already appearing in connection with the more energetic modes of treatment recently introduced for the spirochætal infections. It seems that possibly the refractory state in these infections is the result of an enduring sub-infection, the complete removal of which exposes the individual to reinfection.[5] In a similar manner it would appear that in the suppression of microbic agents of disease by the body's forces through a process of immunization, the serum products are more varied and complex than are produced in the

[5] Ehrlich (loc. cit.) explains this phenomenon in a slightly but not fundamentally different manner. He accounts for the decreasing number of spirochætæ, as the disease advances, by a wiping out of the parasites through the action of the successive specific antibodies formed. The fresh outbreaks or relapses, then, are caused by mutants or fast strains that are immune to the antibodies thus far elaborated,

course of artificial immunization of animals that are destined to yield sera to be employed passively, by injection, in the treatment of their corresponding diseases; and that this greater complexity arises from the circumstance that in the suppression of the micro-organisms in the infected body, not only the normal strains but also the mutants are successively overcome, with the result that a series of immune principles, each directed against its particular variety of parasite, is elaborated. Diseases of a relapsing character are accountable for on the basis of the conception that each successive relapse coincides with the appearance of a new mutant of the infecting organism; and the typical disease of this class, relapsing fever, so-called, is characterized by the ability of its spirochætal cause to undergo at most three or four mutations that in turn lead to an equal number of relapses, which, if survived, are followed by an enduring disappearance of the infection. Hence in the artificial production of curative sera we shall have to take account of the mutants or fast strains of the micro-organisms used for immunization purposes. This result is not necessarily accomplished, although it may be promoted by selecting cultures from many different sources. What is required is that we shall learn to distinguish the fast strains or mutants outside the body in cultures and even, indeed, to create them at will so that they may be employed for enriching the sera produced in animals that will thus be better adapted to their purpose of suppressing the parasitic causes of disease.

The successful issue of specific therapeutics, toward which goal our hopes have been eagerly turned by the triumph of experimental medicine, will be secured not only by the production of more perfect instruments for the suppression of the microbic causes of disease, but also through a more effective

and the subsidence of the lesions depends on the production of antibodies for the new strain. During the actual existence of the syphilitic infection insusceptibility to reinfection is secured by the presence of antibodies in the blood to which the strain of spirochætæ, intending to infect, is not immune. But once the disease is actually terminated and all the antibodies have been discharged, reinfection with a normal strain becomes possible.

application of the curative agents themselves to the seat of disease.

I have alluded to the circumstance that the infectious agent may be strengthened in its attack by confinement within the organism, through which confinement it is preserved from injury by the defensive principles in the blood and lymph. Now no group of infections is in position better to secure this protection than that located within the membranes surrounding the brain and spinal cord, the fluid contents of which are so poor in defensive principles; and for this reason, and for the reason also that the subarachnoid spaces in these membranes are in such intimate association with the peri-cellular spaces about the sensitive nerve-cells, the consequences of meningeal infections are highly serious. To endeavor to reach the infections seated in the membranes by means of the general blood and lymph circulation is futile because of the established fact that not only are the large protein molecules, which include the immunity principles, not secreted within the membranes, but also because highly diffusible salts tend as well to be excluded. But what cannot be thus accomplished by indirection can, in this important instance, be achieved by direction. No operation is simpler in competent hands than lumbar puncture, so-called, which came into use originally to provide cerebrospinal fluid for purposes of diagnosis and now promises to be of far greater value in affording the means of local specific treatment of meningeal infections. How valuable this route may be for the introduction of curative agents is illustrated best at the moment, perhaps, by the convincing results that have been obtained in the treatment of epidemic cerebrospinal meningitis by the antimeningitis serum. This therapeutic agent is utterly without effect on the local infection when introduced directly or indirectly into the blood, but it has proven of unmistakable value when injected into the seat of the disease by lumbar puncture. The latest figures relating to its employment are, and should be, the most favorable to its action, since the methods of production and administration have been improved through experience; and, therefore, it is

a source of gratification that in the recent French epidemic of meningitis the gross mortality among cases treated by serum injections begun in the first three days of illness fell below 10 per cent.

The results secured in epidemic meningitis have suggested the extension of the method of direct local specific treatment to still other kinds of infection of the meninges. Meningitis is now known to be caused by a number of micro-organisms, including the streptococcus, staphylococcus, pneumococcus, the bacillus of tuberculosis and of influenza. Generally speaking, all these inflammations are highly fatal in character. There is still doubt whether recovery from tuberculous meningitis ever takes place; the number of recoveries from pneumococcus meningitis is surely very few; and while we are just learning the extent to which influenzal meningitis prevails, we can already predict that the infection is not only not infrequent, but it is highly fatal in character. Many cultures of influenza bacilli have slight or non-appreciable action on animals, and cannot, therefore, be employed for purposes of artificial immunization; but cultures obtained from cases of influenzal meningitis not only can be used for preparing an immune serum, but also produce, when injected into monkeys, a form of meningitis that in its nature, course, and fatal effects cannot be distinguished from the spontaneous human affection. This experimental fatal disease, like epidemic meningitis, can be controlled by the intraspinal injection of an anti-influenzal serum. The degree of applicability of this serum to the treatment of spontaneous disease in human beings is still to be determined; but in view of its highly fatal character it should be tried. Undoubtedly, it will be necessary to apply the serum early and by repeated injection to secure beneficial results; and the early application will be dependent upon prompt bacteriological diagnosis, which can be made by immediate microscopical examination of the cerebrospinal fluid.[6]

Influenzal meningitis, as it occurs spontaneously or is produced experimentally, is attended by an invasion of the blood

[6] See Wollstein: Jour. Exp. Med., 1911, xiv, p. 73.

with the influenza bacilli which sometimes appear there in large numbers. It is important, therefore, to consider the consequences of the bacteræmia, as it is called, upon the local treatment of the meningeal infection. Now, fortunately, the difficulties surrounding the passage of the antiserum from the blood into the cerebrospinal fluid are sharply contrasted with the ease with which the antiserum escapes from the meninges into the blood. This discrepancy is explained by the fact that while the fluid on entry is in the nature of a secretion from the choroid plexus, the escape is by way of the veins in the membranes themselves.

While, therefore, it is impractical to bring the antiserum into the meninges from the blood, the reverse effect is readily accomplished; and thus it comes about that in such secondary infections of the circulation with bacteria as are being here considered, the suppression of the local development not only stops the eruption of bacilli that causes the blood infection, but the passage of the antiserum from the membranes into the blood arrests their development there.

Probably recovery from any local bacterial infection is not wholly accounted for by the several activities of blood-serum and phagocytes that are usually invoked to account for the phenomenon. This restricted view leaves out of consideration certain definite chemical substances that are always present in a focus in which tissues and cells are disintegrating. That some of these substances are injurious to bacteria we now know. While the nature of the so-called stabile bacterial substances yielded by extraction of the somatic cells is still doubtful, it would appear that among them are certain soaps yielded by disintegration of the neutral and higher phosphorized fats contained within protoplasm. That soaps are injurious to bacteria has been abundantly proven; so that the view should be entertained that the degeneration of leucocytes and tissues which results from a local bacterial infection may not be entirely to the advantage of the parasitic agent, but is also of use to the body in assisting it to overcome the bacteria, since the cells brought to death and disintegration by the parasites yield

chemical substances that themselves exert a destructive action upon the infecting bacteria.

The application of these considerations to the treatment of a typical pneumococcus infection, such as the experimentally produced pneumococcus meningitis in the monkey, has been rewarded with significant results. We are still ill-informed of the factors which control resistance to and recovery from a local pneumococcus infection. The decrease in number of the organisms that takes place as recovery progresses in lobar pneumonia, for example, has not been shown to depend either on phagocytosis or on serum solution of the bacteria. It is a highly suggestive fact that the pneumococcus differs from most bacteria by reason of its solubility in chemical solutions, such as those containing bile-acids and, as has been recently discovered, soaps. The effect of soap is peculiar in that exposure of the pneumococci to its weak action merely modifies the texture without altering the growing properties in cultures, so that when the soaped pneumococci are next exposed to blood and serum, and especially to an antipneumococcus serum, they suffer complete dissolution. These conditions are, indeed, present in a local pneumococcus infection since soaps are produced there, and during its progress immunity principles appear in the blood and lymph.[7]

By employing a suitable combination of sodium oleate and antipneumococcus serum, experimental pneumococcus infections of the meninges can be controlled and abolished. Through this means monkeys that would surely have succumbed have been repeatedly restored to health. But the successful employment of the soap and serum mixture rests upon the overcoming of the property that the soap possesses of uniting with the protein of the antiserum and thus being rendered inert and withheld from acting upon the pneumococcus. This obstacle is the common one on which so many high hopes of the chemical suppression of infections, by what is termed "internal antisepsis," have been wrecked. Luckily, in this instance, it has been proven that the soap portion can be kept apart from the

[7] See Lamar: Jour. Exp. Med., 1911, xiii, p. 1.

protein moiety of the serum by introducing a second protective chemical body, itself innocuous, into the mixture. When minute quantities of boric acid are thus introduced, the soap is isolated and left in condition to exert its injurious action upon the pneumococci, for which organisms it appears to have a greater affinity than for ordinary protein matter. Whether among the products of local tissue disintegration a similar separation of the soap and serum elements is secured has not been ascertained; but we should consider factors that possibly suffice to overcome this initial impediment to the bactericidal action of the soaps, among which are the proximity of the bacteria to the nascent fatty acids and soaps and the natural occurrence within the exudate of chemical bodies that have the effect of removing the protein inhibition.[8]

The antisera and the chemical disintegration products of cells do not exhaust the list of defensive agents that operate against infection, for there remain the living leucocytes themselves. Certain bacterial infections that have not thus far been made to respond to the dissolved immunity principles may still be subject to influence by the white cells of the blood. Hence the effort has been made, and with an encouraging degree of success, to control experimentally produced tuberculous pleurisy in the dog by the repeated injection of living leucocytes;[9] and the observation made upon this condition has been extended to include experimental tubercular meningitis produced likewise in the dog, the course of which it has also been found possible to affect in a favorable manner.[10] In the pneumococcus and tubercular infections just considered, as in the influenzal bacillus affection already mentioned, the general infection of the blood and organs has been suppressed or much reduced by the local specific treatment.

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[8] The fatty acids and soaps are yielded by the dissolution of the neutral and the higher phosphorized fats contained within the cellular protoplasm in which other colloidal bodies of a protecting nature may well be stored.

[9] See Opie: Jour. Exp. Med., 1908, x, p. 419.

[10] See Manwaring: idem, 1912, p. 1.

Although the treatment of these tuberculous affections with leucocytes is still in the experimental stage and is not yet ready for application to medical practice, it has been described in this connection in order that there might be brought under review the diverse means that are at present invocable in the efforts to determine the conditions that underlie the therapeutic control of varied infectious processes.

Finally, the application of the principle of the local treatment of infections holds out hope of some measure of therapeutic control, at least, of that serious and menacing disease, now in the foreground of interest for physicians and public alike, namely, epidemic poliomyelitis. The propagation of the disease in monkeys has led to the elucidation of its cause and pathology, while at the same time it has exposed it to therapeutic experimentation. The cause of the malady is an exceedingly minute parasite—submicroscopic and filterable—which probably gains access to the spinal cord and brain by way of the meninges and through the lymphatic connections that surround the olfactory filaments that terminate in the nasal mucosa and are in direct communication with the subarachnoid spaces. The lesions of the meninges constitute an important effect of the infection, and especially of those prolongations of the meninges about the veins and arteries that enter the spinal cord and bulb and support the perivascular lymphatics. The lymphatics and, indeed, the subarachnoid spaces in general, comprise a system of communicating channels charged with cerebrospinal fluid that extend to the pericellular spaces and therefore penetrate to the nerve-cells. Consequently a parasitic or toxic agent that gains access to the cerebrospinal fluid is capable of ready transportation to all parts of the nervous system; and by utilizing the same route it is obviously possible to distribute what may prove to be a soluble antagonistic and therapeutic agent.

Recent experiments have shown unmistakably that spontaneous recovery from poliomyelitis is brought about by a set of immunity reactions that involve the formation in the blood of soluble principles or antibodies for the parasitic

virus. Similar principles are formed in inoculated monkeys; and they can be used successfully, up to a certain point, when injected into the spinal canal by lumbar puncture, in preventing the development, after an intracerebral inoculation of the virus, of experimental poliomyelitis. This effect has not yet been accomplished by the introduction of large quantities of immune blood into the circulation, a result that was predictable in view of the location of the pathological process that leads to the paralysis in the meninges.

It is not excluded that epidemic poliomyelitis may be subject to effective treatment by drugs. There is, indeed, one drug—urotropin, or hexamethylenamin—that does exert some action even when administered by the mouth, since it presents the exceptional instance of a chemical body being excreted into the cerebrospinal fluid.[11] But its powers are limited. However, as the drug is constituted in a manner that permits of many modifications of its composition without the sacrifice of its central structure through which formaldehyde may be liberated, it has been found readily possible to prepare a number of derivatives far exceeding urotropin in activity, some of which have been applied to the treatment of experimental poliomyelitis with a hopeful measure of success. These new compounds, it should be added, require to be injected into the spinal membranes and act best in conjunction with an immune serum.[12] They are subject to rapid dissociation, upon which phenomenon probably their high activity depends; and

[11] See Crowe: Bull. Johns Hopkins Hosp., 1909, xx, p. 102.

[12] The advantage to be secured against the parasites by employing more than one antagonistic agent results, first, from the circumstance that an antibody or drug will operate with greater effect against an already injured than against a normal parasite, and second, because mutation in two directions is less readily effected than in one direction. Hence a fortunate combination of serum antibodies and a drug offers, theoretically, a favorable means of overcoming an infecting micro-organism. Ehrlich (loc. cit.) recommends the simultaneous employment of two curative substances, one of which is especially chosen to injure the protoplasm and the other the nuclei of the parasites.

the dissociation proceeds somewhat more slowly in the presence of the colloidal constituents of the immune serum that itself carries a small amount of healing substances. This is obviously no more than a beginning in the effort to accomplish therapeutic control of this protean and serious disease, the natural history and significance of which are just beginning to be appreciated; but the outlook for its conquest is at the moment made hopeful through the utilization of the method of the local specific treatment of infections.

The arguments that have been presented and the examples adduced would seem to possess not only theoretical but also established value in justifying the further pursuit of the measure of opposing local infection by local specific remedies. In the effort to combat the infectious processes account will have to be taken, in any given instance, of the peculiarities of the infecting parasite, as well as the particular anatomical and physiological adjustments of the infected parts, that together constitute the foundation upon which effective specific therapeutic effort must ultimately come to rest.

THE CHEMICAL COMPOSITION OF THE CELL*

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WHEN, in response to your President's invitation, I attempt to put before you a bird's-eye view of some of the problems which are occupying the attention of biochemists at the present time, I am very cognizant of the difficulties of my task. The anatomist, the pathologist, and the clinician can present his observations to you directly, but this is not possible for the chemist. The phenomena which the chemist studies are only intelligible when considered with the help of a special nomenclature, based upon chemical theories. His results are expressed in a special language in which the letters of the alphabet are represented by elements, the words by chemical formulæ. He makes use of theoretical conceptions when he assumes certain spatial relations for atoms and molecules that we can neither see nor feel. He discusses the arrangement in space of things which are inaccessible to our direct observation. These peculiarities make the presentation of his results specially difficult.

When, notwithstanding, I draw your attention to these lines of investigation, it is with the profound conviction of their great importance. It may be truly said that to-day the eyes of the biologist and the pathologist are directed hopefully toward chemistry. Everyone who is engaged upon the investigation of the processes of life in the cell, with the problems of fertilization, or of contractility, with the phenomena of nutrition, respiration, or growth, comes to the conclusion that all these manifestations of life are ultimately to be referred to chemical changes, and it is chemistry that must bring us the

* Delivered October 14, 1911.

solution of the most important of the mysteries of life which are accessible to investigation. When we consider the extraordinary results of chemistry obtained during the last century, we may well be inclined to expect even more wonderful results in the future, but it is certain that they cannot be obtained at once. It requires long and intensive work to develop from the elementary chemistry of to-day a higher chemical science capable of analyzing those complex chemical processes which together constitute life.

To-day we are concerned with the question as to how far chemistry has been of service in promoting our knowledge of the processes of life. How may chemistry concern itself with the fundamental questions of physiology? What are the biochemical problems which we may successfully attack in the present state of our knowledge? The medical student begins his studies with anatomy, and the biochemist who investigates the finest details of metabolic changes must begin in a similar fashion. First of all, he must concern himself with questions relating to the presence, distribution, and properties of certain chemical constituents of the animal body. Only when this has been accomplished is it possible for him to approach the chemical processes taking place between these different constituents, which together form the basis of metabolic changes.

Moreover, the chemical consideration of the various substances present in the body resembles anatomical studies in that both of them are concerned with spatial relationships. I have already referred to the fact that we think of the atoms as arranged in definite positions in space. These arrangements of the atoms, which together make up the "formula," give to the chemist a presentation of the properties of a substance. When we have obtained such a formula, we can predict to a certain extent how a substance will behave in certain chemical reactions and with certain chemical reagents, and also its behavior toward the chemical actions which are operative in the living organism. If, for example, we find in a chemical formula the group COOH, we infer that the substance possesses the property of an acid, while the group NH_2 is indicative of basic qualities. We learn also whether it is attacked by oxygen with

ease or with difficulty, and whether its decomposition by one or other ferment is probable. Thus the foundation for our biochemical considerations is derived from chemical formulæ, just in the same way as physiological and pathological considerations are derived from anatomical representations.

I should like to carry the comparison between anatomical and biochemical investigations still further. Laws governing the anatomical relationships of the human body and also the sciences of pathology and physiology have entered upon a new era, since it has been possible to determine certain cellular units in plant and animal tissues which act as centres for development, for nutrition, and for numerous other special functions. Through the determination of these units it has been possible to define more exactly many physiological and pathological processes, and also to compare them with one another and so make them more intelligible.

Biochemical investigations require the consideration of similar units. So long as one considers the mass of living substance as a whole, an analysis of its activity can scarcely be undertaken. Such an analysis is only possible through the isolation of certain units capable of chemical investigation and to whose activity the individual functions of living substances may be referred. I wish to speak of these units, which I shall refer to as the " Bausteine " or building-stones of protoplasm.

The word " Baustein " indicates that these units may be united to form larger structures and that their union takes place according to a determined plan or architectural idea. Through the union of these Bausteine larger aggregates are formed which we call either proteins, fats, nucleic acids, phosphatides, or polysaccharides, as the case may be.

On the other hand Bausteine are not the smallest units of the living tissue, for they are themselves composed of a certain number of atoms of different kinds, commonly of carbon, hydrogen, nitrogen, oxygen, or sulphur. They are, however, not only anatomical or structural units but also physiological units.

If we wish to obtain a clear picture of the chemical changes occurring in living substances, we must study the behavior of these Bausteine. It is with them that we must work in our

studies of physiological combustion and of all the processes bound up with the production and destruction of organic substances in the animal cells.

In one relation my choice of the term Baustein is not applicable. The Bausteine or building-stones of a house are uniform, but the Bausteine of living substances possess a great diversity. They differ among themselves as much as the stones of a colored mosaic, and in addition, they are of different sizes. At times, however, we find aggregates which are formed by the repeated combination of a single type of Baustein, but in general the most varied types of Bausteine are intermingled according to a definite plan.

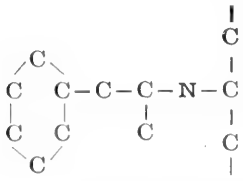
We may ask ourselves what are the reasons for ascribing to these atomic groups which I term Bausteine a certain individuality, and for singling them out as units from the more complex aggregates of atomic compounds which we find in living substance. The conception of these atomic groups as Bausteine is due to their internal stability and also to the coherence of the carbon atoms which makes them relatively stable in metabolism. The carbon atoms which go toward the building up of the Bausteine are arranged either in the form of chains or of rings. Where one Baustein is united to another we find another atom such as oxygen, nitrogen, or sulphur taking part in the union. These latter elements may be regarded in a sense as the mortar of the Bausteine. In the following diagram I try to make this clear.

TABLE I

(1) $-C-C-C-C-C-C-O-C-C-C-C-C-C-$

(2) $C-N-C-C-C-C-C-$

(3)



(4) $C-C-C-S-S-C-C-C$

The above representation is intended to convey the mode of union of two Bausteine with one another, and the binding atoms are indicated in heavier type. One must remember that the scaffolding or " carbon-skeleton " of the Bausteine may greatly vary in size. The union of two Bausteine, each containing six carbon atoms, is shown in the first example, while in the second a Baustein with only one carbon atom is united with one containing five carbon atoms, while the third formula represents a Baustein possessing a skeleton of nine carbon atoms partly arranged in the form of a ring united with a side-chain of three carbon atoms. Finally, in the fourth formula, we have two chains each containing three carbon atoms. The union of the Bausteine in the first case is effected by an oxygen atom, in the second and third, by a nitrogen atom, and in the last case by means of two sulphur atoms.

We have here four characteristic types of combination such as are to be found in every living part of animal and vegetable organisms. It is possible for a much greater number of Bausteine to be united in a similar fashion, so that aggregates may be formed containing several hundred carbon atoms. The resolution of such large structures can be relatively easily accomplished at the places indicated in heavy type. This change is brought about especially by the ferments present in the animal and vegetable organisms.

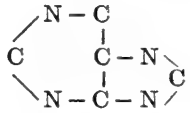
Our food contains principally Bausteine united in large aggregates and not in the form of single units. Through the secretion of the salivary glands, stomach, pancreas, and intestine, these combinations are to a large extent completely resolved, and when necessary their disintegration may be made more complete by other ferments present in the tissues. But on the other hand, these large structures may be equally readily built up from the individual Bausteine. The union of Bausteine, " the building-up," requires the expenditure of a very small amount of energy, as is also the case with their decomposition, " their break-down," which leads to a very slight liberation of energy.

In addition to these Bausteine, composed of directly united

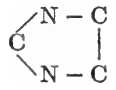
carbon atoms, we have a second form in which the carbon atoms are not directly united. This is made clear in the following formulæ:

TABLE II

I



II



According to what has been previously stated, Formula I shows us three different Bausteine, since the union of the carbon atoms is interrupted at three different places by nitrogen atoms. In Formula II we might assume the presence of two Bausteine. As a matter of fact I prefer in both cases to consider the whole group as a single Baustein, for by the closing of the ring the union of the atoms is made so firm that they possess marked resistance to the decompositions of the organism and the whole system reacts as a unit both within and without the living organism. I found the first grouping as a characteristic constituent of cell nuclei. It is also found, however, in uric acid, and since we find it in the urine, we may regard this as proof of the stability of this ring-system. The substance whose atomic linking is represented in Formula II was found by me in the proteins and is known as histidine.

I have just spoken of the multiplicity of these Bausteine and illustrated it with different formulæ. The variety is so great that it is necessary for us to limit ourselves for the present to the more important types. Our choice has, however, certain restrictions. We find that certain individual Bausteine are present in all living cells capable of developing, and these recur in unchanged or but slightly changed form throughout the animal and vegetable world. We ascribe to these Bausteine a fundamental biological importance, in contrast to others which occur only in certain orders or families, or possibly only in individual species.

So far we have only considered the carbon skeleton, which is contained in these substances; their real character is de-

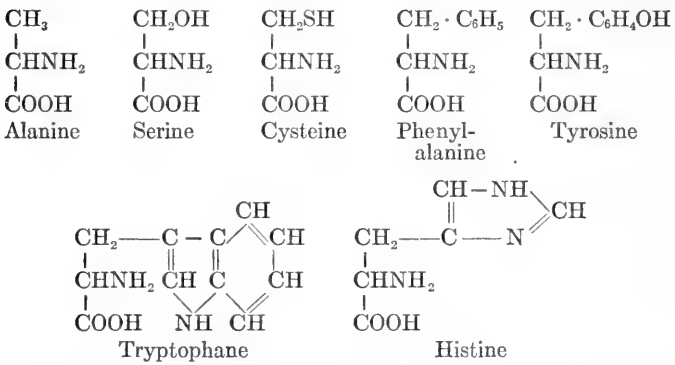
pendent upon other atoms which are attached to this scaffolding of carbon. In the foregoing tables only the carbon atoms have been inserted, while further on we shall find that the printed formulæ have their skeletons to a certain extent provided so to say with flesh and blood. By the attachment of oxygen and hydrogen atoms to a chain of three, five, or six carbon atoms, substances are formed which are known as *polyatomic alcohols*. By the addition of oxygen in a somewhat different manner we obtain *saccharides*, the biological importance of which is recognized by everyone. By the accumulation of oxygen at a particular point in the molecule, the whole complex assumes acid properties, and in this way the *organic acids* are formed, the higher members of the series being found as Bausteine of all living cells. As examples of these substances I may mention butyric, palmitic, stearic, and oleic acids. I have already mentioned the fact that the union of nitrogen and hydrogen atoms gives us the *amino group*, and this, when attached to a carbon scaffolding, confers basic properties upon it. Basic Bausteine of this kind can as a matter of fact be found in all parts of the living organism. As an example we may mention the *amidine group* which may be converted into urea through the entrance of oxygen and hydrogen. The *amino-acids* form a group possessing a very wide distribution and apparently concerned with most important biochemical functions. The amino-acids possess at the same time the properties of both acids and bases. A glance at the following table shows us that they contain both the carboxyl and amino groups.

The number of amino-acids which are found in protoplasm is very considerable. They form a series constructed according to a common plan, and are known as homologous substances. The simplest member of this group is amino-acetic acid or glycocoll. If we replace a hydrogen atom of glycocoll by the group CH_3, we obtain another substance which is known as alanine, and this body possesses special interest.

There are many Bausteine which may be regarded as alanine derivatives. All of these derivatives may be regarded as

formed by the substitution of hydrogen atoms. *Serine* for example, by the entrance of (OH), *cysteine,* by the introduction of (SH). If the group C_6H_5, the so-called phenyl group, is introduced, we obtain *phenylalanine,* while the oxyphenyl group leads to *tyrosine.* Other groups, such as "indol" and "iminazol" as substituents of alanine, lead to the formation of *tryptophane* and *histidine* respectively.

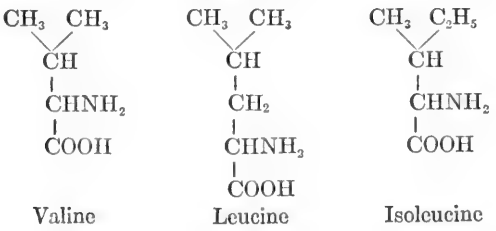
TABLE III



It is thus seen that we have a large number of Bausteine which resemble each other in general structure but which apparently subserve different physiological functions.

The two last-mentioned substances, tryptophane and histidine, both of which contain five carbon atoms directly united with each other, form a connecting link with those amino-acids containing more than four carbon atoms of which *valine* is the first representative. Its composition is shown in the following table:

TABLE IV



Together with the valine we find in the above table two other Bausteine, *leucine* and *isoleucine*, which differ from each other by the form of their carbon skeletons.

The multiplicity of these chemical forms is increased by the fact that the number of COOH and NH_2 groups attached to one and the same carbon chain may vary. We find, for example, in the adjoining table, two amino-acids, one of them *glutamic acid* containing two COOH groups, the other *ornithine* containing only one COOH group but two NH_2 groups. Naturally the characters of these two Bausteine are altogether different. The first is an acid, while in the second substance basic properties predominate.

TABLE V

$CH_2 \cdot NH_2$	COOH
|	|
CH_2	CH_2
|	|
CH_2	CH_2
|	|
$CHNH_2$	$CHNH_2$
|	|
COOH	COOH
Ornithine	Glutamic Acid

But I do not wish to weary you with the further enumeration and closer characterization of these substances. I will only say that in the amino-acids we have a group of which it may be well said:

"Alle Gestalten sind ähnlich und keine gleichet der andern
Und so deutet das Chor auf ein geheimes Gesetz."

In the living cell these substances are found partly in the *free state*, but chiefly in combination. Under normal conditions they do not accumulate in the free state to any considerable extent, but this does frequently happen under pathological conditions. I need only mention the appearance of cystine, glucose, and the higher fatty acids in certain abnormalities of metabolism. It is also well known that these substances are often stored up in considerable amount in ripening seeds.

Other considerations confirm us in the belief that the Bausteine of protoplasm play an independent rôle in the organism. A particularly instructive and well-known example is the formation of hippuric acid following the introduction of benzoic acid into the animal body. This change is brought about so that the glycocoll or amido-acetic acid is attached to the benzoic acid administered. Thus we see that the glycocoll not only appears as a chemical unit when we decompose animal tissue by artificial means, but also that it can react as a unit in the processes taking place in the living body.

The same thing is true in the case of some other amino-acids, such as ornithine and cystine, and in the case of certain other Bausteine of protoplasm, such as glucose, for example. All these substances may react, at least to some extent, in the free state, as does glycocoll. They may attach themselves to substances which may be introduced into the animal body, and thus it is certain that they may react as independent groups in metabolic processes.

As I have previously said, in most cases these Bausteine are found not as chemical individuals but as parts of a larger complex. Thus are formed the most various substances which we know as fats, carbohydrates, phosphatides, and proteins. I have already spoken of their different types of union. In some cases we find the Bausteine united to the larger complexes by means of oxygen, in other cases by sulphur or nitrogen. In those cases where the union is effected by means of nitrogen we find that one of the three valences of nitrogen is united with one of another Bausteine, while the third valence is attached to hydrogen. The linkage is thus effected by an NH group or "imino-group." When a large number of amino-acids are joined to each other in this fashion there are formed large aggregates which are known as albumins or proteins.

The fats present a very simple form of union in which the triatomic alcohol, glycerin, is united with three fatty acid molecules. The phosphatides form a more complex group and apparently contain combinations of most varied kind, of which some are still unknown to us. In the carbohydrates we also

find the linkage brought about by oxygen. These Bausteine have a skeleton containing five or six carbon atoms which are bound together in large or small numbers. The linkage by sulphur is only met with in exceptional cases as in the proteins together with the imide forms. These imide linkages are the predominant form present in the proteins. An example is shown in the following formula representing the combination of a glycocoll with an alanine molecule:

$$NH_2 \cdot CH_2 \cdot CO\ NH \cdot \underset{\displaystyle CH_3}{\underset{|}{CH}} \cdot COOH$$

Glycylalanine

The larger groups formed by the union of many Bausteine are those which the chemist first encounters in his analyses. Thus up to the present it has been customary to consider the proteins, polysaccharides, fats, and phosphatides as the physiological units rather than the protoplasmic Bausteine. When, therefore, I regard the smaller protoplasmic fragments as the reacting units, I find myself to a certain extent in opposition to the usual point of view, and this conception of mine should not be generally adopted without further consideration.

As a matter of fact, when we consider the physiological rôle of the larger aggregates, such as the proteins, it is necessary for us to distinguish between those functions which may be considered as due to the sum of the individual Bausteine and those which depend on the mode of union of these Bausteine. In the latter case it is the particular formation of the whole molecule which is of importance. This latter is obviously the case where the form of living parts is dependent upon the constituents, as, for example, is the case with cellulose, chitin, and the horny substance of the skin. In other cases it would appear that the function of certain substances is not dependent upon their chemical composition, but it is rather their physical consistence that renders them of value to the organism. In these cases the proteins function as a whole, and probably this is also the case with the muscle proteins concerned with the transmission of mechanical and thermal stimuli.

This is true, too, of the proteins of other parts concerned with the reception and distribution of stimuli.

There are many other important functions which are dependent upon the chemical peculiarities of the whole molecule. As an example I may mention the taking up of oxygen by the coloring matter of the red blood-cells. The large protein molecules are so arranged that they easily react to feeble chemical influences, and this reactivity is undoubtedly related to their physiological rôle.

The foregoing examples differ from those cases in which we find large molecules, especially in the case of the carbohydrates and proteins, which are to be regarded simply as storage forms of the smaller active components. The proteins, the polysaccharides, and other similar aggregates act in this manner when they are employed as foodstuffs. The particular forms of combination which are characteristic of the large molecules are destroyed in the process of digestion. Specific ferments decompose the polysaccharides; others the fats or phosphatides; others the nucleic acid; and still others resolve the proteins into their Bausteine. The individuality of the proteins is completely lost save for the quantitative relations of the Bausteine, which undergo absorption and are utilized for the various purposes of the body.

We may regard the storage of carbohydrates, fats, and proteins in the same way. They form a reserve of nutrient material which is attacked and utilized according to the necessities of the organism. At certain times ferments come into play in the tissues which decompose the larger aggregates into their Bausteine, which then play a part in metabolism as individual units. Glycogen, for example, which is readily stored up as the result of a generous diet, at other times is resolved into glucose molecules, that is to say into its Bausteine. Proteins in the same way are decomposed by active tissue ferments into their Bausteine, which are then utilized in the course of metabolism.

The importance of this resolution into Bausteine can only be fully appreciated when one considers that out of these same

Bausteine entirely new structures may be built up in other parts of the organism. For example, if an animal is fed with fat, the fat is resolved into its Bausteine in the intestinal canal, but it may be resynthesized, on absorption. Fat in the process of transportation through the intestinal wall may be compared to a portable house which may be taken apart in one place to be reconstructed in another.

When the proteins undergo a similar process, involving their decomposition and subsequent re-formation, a change in the character of the synthesized protein may be effected. Thus the body is able to build its own protein substances from foreign proteins. This reconstruction of the proteins is so interesting and so physiologically important that I should like to make further reference to it. I should like to compare this rearrangement which the proteins undergo in the animal or vegetable organism to the making up of a railroad train. In their passage through the body parts of the whole may be left behind, and here and there new parts added on. In order to understand fully the change we must remember that the proteins are composed of Bausteine united in very different ways. Some of them contain Bausteine of many kinds. The multiplicity of the proteins is determined by many causes, first through the differences in the nature of the constituent Bausteine; and secondly, through differences in the arrangement of them. The number of Bausteine which may take part in the formation of the proteins is about as large as the number of letters in the alphabet. When we consider that through the combination of letters an infinitely large number of thoughts may be expressed, we can understand how vast a number of the properties of the organism may be recorded in the small space which is occupied by the protein molecules. It enables us to understand how it is possible for the proteins of the sex-cells to contain, to a certain extent, a complete description of the species and even of the individual. We may also comprehend how great and important the task is to determine the structure of the proteins, and why the biochemist has devoted himself with so much industry to their analysis.

The first step in these lengthy investigations consists in the determination of the quantitative relations which the Bausteine in the protein molecules bear to each other—how much of one and how much of another Baustein is present in the large protein molecule. Methods have been worked out for the determination of some of the amino-acids, to estimate the quantity of leucine, alanine, histidine, and lysine in different proteins. The results of these analyses are presented in such a way that one may see the percentage quantity of any particular Baustein in the different proteins.

This represents merely the beginning of our investigations, and may be compared to a man attempting to read a book in some foreign language who at first can only determine the numerical relation between the different letters of the alphabet in each section of the book.

I should like to illustrate this by an example. It has been possible to remove from proteins some large fragments and successfully investigate their constitution. In this way the relative position of individual Bausteine in the protein molecule can be determined, and this again may be compared to the deciphering of separate syllables. Furthermore, it has been possible to reconstruct artificially such compounds and compare the synthetic with the natural products. In this way a knowledge of the chemical make-up of the protein substances may be slowly gained. On the other hand it is possible to find in nature substances which may be regarded as simplified proteins, and the constitution of these is more readily investigated than the complex typical proteins. The following is an example of their formation:

Observations upon the life-history of the Rhine salmon show that this fish at certain times lives in the sea; at others in fresh water. During the period of life in the sea, he eats freely and devotes himself to the acquisition of a sufficient quantity of protein in his body to serve him for a long time (on an average about ten months) in the river, where the formation and storing of the sexual products take place. While in fresh water he takes no food of any kind, and the proteins

of the body muscles are used up to a large extent, while the male or female sexual products are being formed. During this time the animal may be compared to a patient in whose body is formed a tumor, the tissue material of which is slowly gathered from the whole body. By the beginning of November the development of the sexual products has reached its high point. If at this time we kill the male animal and compare the protein of the newly-formed male sexual products with the protein which in the course of the development of the testicles has disappeared from the muscles, we find a peculiar relationship. Of twenty Bausteine present in the used-up protein, only four or five kinds are present in the newly-formed proteins. We must conceive of the process as taking place first of all by the resolution of the protein into its individual Bausteine. Some of these Bausteine are completely decomposed during the starvation period of the animal and others of special kinds remain protected from decomposition and are united to form a new protein substance—the so-called salmine.

Similar transformations of proteins into other protein substances possessing totally different characters from the original one take place when foreign proteins are used for food. In the seeds of many plants proteins are contained which differ in their composition from the proteins of the animal organism. This difference is due to the absence of certain Bausteine which are present in the animal protein. Moreover, they possess different solubility relationships. Zein, the protein of maize, is an example of this kind. If a young goose is fed for several months with maize so that its body substance is materially increased, we find on investigation of its organs that the Bausteine of the maize have been used for the synthesis of a new animal protein. This process of reconstruction is seen to occur when a mammal such as a dog or mouse is given only Bausteine instead of intact protein substances. In this case it is possible to demonstrate the formation of the proteins characteristic of the animal's own body.

Similar phenomena are observed in the case of other chemical constituents of the tissues, such as carbohydrates and fats.

It has long been known that glucose when introduced into the body leads to glycogen formation, while fatty acids unite with glycerine and are built up into fats.

Thus far we have been considering the Bausteine, the nature of their union, and their formation from large groups, without considering the questions of their origin and of their significance in metabolism. I propose to touch on these problems but lightly.

When in the seventies the early observations upon the structure of the cell nucleus were made, it was correctly believed that a most important step forward had been taken. The histological structure of the nucleus and its changes in form were rightly considered characteristic of the individuality of the organs. These nuclei are found throughout the whole world of living organisms, and form an "Einheit in der Vielheit" of living phenomena. Karyokinesis is brought into relation with the function of cell division and growth of living substance. It is obvious that it would be of even greater importance if we could correlate the changes in chemical structure with these histological peculiarities. It would give us a deeper insight into the significance of these parts of the living substance if we could determine a particular atomic grouping which would be typical for the cell nucleus or for its functions.

It seems to me that such a determination may be derived from investigations upon the chemistry of these elementary parts. If we compare the atomic groupings of the cytoplasm with those of the karyoplasm, we find that long carbon chains either free from or poor in nitrogen predominate in the first. This is also the case with the fatty acids and the carbohydrates. Furthermore, the proteins of the cytoplasm are to a large extent made up of the union of monamino-acids which contain only one nitrogen atom in a large series of carbon atoms. Such is the case, for example, with leucine, valine, tyrosine, or alanine and most of its derivatives.

If we now compare the atomic groupings which are characteristic of the cell nucleus, and which have already been re-

ferred to as constituents of the nucleic acids (Table II) we see, in the first place, an abundance of nitrogen, and secondly a peculiar grouping of this element between the carbon atoms. This is particularly characteristic in the cyclic complexes which are known as pyrimidine and purine derivatives. In many of these compounds, such as adenine for example, we find a nitrogen atom attached to every carbon atom and the arrangement is such that C and N alternate with each other in the formula.

Similar atomic groupings are found in certain special Bausteine which make up the protein molecule. It is found that those proteins which occur in the cell nucleus are very rich in these groups. This is particularly true of the so-called amidine group which we find in arginine and which exhibits the accumulation of nitrogen shown in the following formula:

$$NH_2 - C = NH - NH - C \cdots\cdots$$

In certain nuclear substances a particularly large amount of histidine is found. This substance belongs to the iminazol group and has the cyclic structure shown in Table III.

These observations compel us to assume that these peculiar linkages of the carbon and nitrogen atoms stand in close relation to the functions of the cell nucleus and especially that concerned with building up new material.

When the proteins of the yolk of insect or hen's egg are converted into young, growing cells, whose function it is to furnish rapidly new tissue, a rearrangement of the atoms takes place in such a way that these peculiar carbon and nitrogen linkages are stored up in the cell nuclei.

The foregoing observations do not exclude the possibility of the same atomic group appearing in other places in the tissues and subserving other physiological functions. Thus for example we find the purine ring in guanine as a constituent of the skin of many organisms in the form of crystals, which apparently influence the color through their optical properties. Or we may find the purine ring among the end products of animal metabolism, since the cyclic grouping is relatively resistant.

Let us now glance once more at the peculiar chemical relations of the cell nucleus. Here we find substances of acid property, the nucleic acids which exist in different forms. These substances have acid properties, and long since I have put forward the view that they are to be considered as polymetaphosphoric acids containing, therefore, a chain of phosphorus and oxygen atoms to which the previously mentioned pyrimidine and purine derivatives as well as carbohydrates are attached.

In the cell nucleus these substances are united only with proteins, and these combinations may be of various kinds. In some cases the combination is quite stable, so that it is impossible to resolve it without destruction of the whole chemical structure. In other cases the nucleic acid is united with the protein in a loose salt-like combination which is readily decomposed under the influence of a stronger acid. This is observed in those cases in which the proteins of the cell nucleus are made up of basic molecules such as the histones. It may be said, therefore, that there are two types of nuclear substances occurring in the different cell nuclei. I may refer to these as the *dissociated* and *non-dissociated* forms. It would seem likely that microscopical differences between the two forms of cell nuclei may be found.

The question presents itself as to whether it is possible to correlate physiological relationships with these two forms of cell nuclei. Up to the present, so far as I know, this has not been possible. In the same organ of one species we find the dissociated, of another species, the non-dissociated forms. For example the nuclei in the heads of the spermatozoa of warm-blooded animals appear to be non-dissociated, so far as my investigations go, while on the other hand they are dissociated in the case of fishes. In the internal organs of higher animals both forms are encountered side by side.

These considerations show us how the methods of biochemical analysis may be utilized for the attainment of a knowledge of living processes.

While the experimental physiologist approaches the living organs with a definite supposition of hypothesis and plans his experiments with reference to this preconceived idea, the histochemist carries on his investigation unhampered by such definite preconceptions, and usually cannot foresee the nature of his results. The descriptive and the experimental method must go hand in hand in the investigation of living function. The ideas derived from the one are carried further by the other.

When nowadays we regard it as necessary to separate the experimental and descriptive sciences, to separate anatomy and physiology, and the chemical and physical methods of investigation, it involves the breaking of a natural continuity. Such separation is only necessary because of the limitations of individual human endeavor, for it is impossible for a single person to master all the methods and to familiarize himself with so vast a wealth of material.

NARCOSIS*

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TWO main reasons induced me to select the subject of narcosis for my lecture before your society. On the one hand, I am following herein the suggestion of your honored President; on the other hand, the problem of narcosis has a personal attraction for me, since with my colleagues at Göttingen, as well as in Bonn, I have devoted a great deal of attention to its investigation. Furthermore, I believe that this theme, the subject of narcosis, possesses an especial interest for medical men, not only from the theoretical but also from the practical side. From the theoretical side, because the processes of narcosis introduce us into the most profound secrets of the mechanism of living matter; from the practical side, because it is incumbent upon the physician to know the actual nature of the condition which he so often induces in man. Practical and theoretical interests have here, once more, the same object. Such union of practical and theoretical interests makes our medical work so fruitful and lends it a special charm among the biological sciences. This is especially manifest in the study of the peculiar phenomena of narcosis, and is also the reason why the subject of narcosis has been so extensively investigated, especially in the latter decades.

The knowledge of the use of narcotic substances, especially those from the vegetable kingdom, is ancient. It extends back to prehistoric times, as we may deduce by analogy with primitive races living to-day. Man has been, from the first, a student of nature. He was forced to adapt himself, at every step, to his environment. This he could do only by very close observation of nature, for there was danger lurking for him

* Delivered October 28, 1911.

wherever, in his wanderings, he was confronted with new conditions. Thus, in his quest for food he had to learn to recognize the peculiar poisonous effects of plants. All primitive races are familiar with them and employ them for various purposes. The use of narcotizing substances, especially for purposes of enchantment, was well known in the Homeric age. Circe mixed narcotic juices with the food of the companions of Odysseus, making them forget their homes; and Hermes knew already an antidote, which he gave to Odysseus as a protection: *μῶλυ δὲ μὶν καλέουσι θεοί.* In Homer we also find, for the first time, although not in connection with poisonous action, the word from which the modern term "narcosis" is derived. The verb *ναρκάω*, "I am paralyzed," appears in Homer as *ἄπαξ εἰρημένον* when he describes how Hector struck Teukros on the shoulder with a sharp stone, so that his hand, paralyzed, let fall the bow (Iliad VIII, 328). This venerable word serves us to-day to distinguish a special group of paralyses, or depressions, which are induced by chemical substances.

The scientific study of narcosis begins, however, only with the time when narcotics came into general use in medical practice for the relief of pain, especially since, in Boston, in 1846, the chemist Jackson and the dentist Morton introduced ether into surgical practice. Soon after this momentous event experiments began for the purpose of explaining the striking action of anæsthetics. Among the numerous explanatory efforts, however, there are only two series of attempts which deserve scientific consideration.

In one series attempts have been made to establish a relation between the depressing action of narcotics and their solubility in certain constituents of the organism. As early as 1847, Bibra and Harless used the fact that cerebral fats are readily soluble in such narcotics as ether and chloroform, as a basis for a hypothesis of the mode of action of narcotics. They assumed that the narcotics act as anæsthetics by extracting the brain fats. Hermann indicated later a similar conception, and

recently Reicher has shown that in deep and long-continued narcosis the fat content of the blood rises indeed quite markedly. While already in these assumptions the relations of solubility between fats and narcotics stand in the foreground, Richet has later on called attention to a second relation in regard to solubility. He noticed that many narcotics were distinguished by a very low degree of solubility in water, and believed that, on the basis of his observations, he could make the general statement that a substance acts the more strongly as a narcotic, the less it is soluble in water. The relations between the solubility of narcotics in fats and water and their depressing action, which in the before-mentioned observations and hypotheses were expressed so incompletely and obscurely, were first made clear and formulated according to definite laws by Overton and by Meyer, independently of one another. Hans Meyer and Overton were able to show that the intensity of the narcotic action of any substance is dependent on the proportion in which it is distributed between water and fat when it is shaken with a mixture of fat and water. The coefficient of distribution, that is, the proportion of solubility of the substance between water and fat, is the greater, the stronger its narcotic action. That is to say, a substance acts the more strongly as a narcotic, the more soluble it is in fats and lipoids and the less soluble it is in water. Meyer and Overton have confirmed this law in the case of a very large number of narcotics. This interesting fact contains apparently a very important requirement for the production of narcotics, although it does not present a "theory of narcotics," as has often been incorrectly stated. It shows us one factor that must be realized if the narcotic is to reach its field of action, but it tells us nothing concerning the mechanism of the narcotizing action itself.

The second series of explanatory attempts ascribes the depressing action in narcosis to a change in the state of aggregation of certain components of the protoplasm under the influence of the narcotic. Claude Bernard, who noticed the

rigidity of muscles which is produced by the influence of chloroform vapor or heat, was the first one to express the view that narcosis consists in a " semicoagulation " of the protoplasm. Binz came to the same conclusion from a microscopic study of ganglion cells and unicellular organisms. He found that the protoplasm of the cells became opaque, granular, and dark under the influence of the narcotic, as is the case in coagulation, and he sees therefore, in narcosis, a depression by coagulation. As a matter of fact, it is easy to observe such changes in unicellular organisms under the influence of large doses of narcotics, but recovery from such a state is no longer possible. In recent times, Höber has expressed similar opinions. Höber makes the hypothesis that the process of excitation is associated with a loosening of the protoplasmic colloids, which consist of lipoids and proteids. In connection with this assumption, Höber offers the further hypothesis that narcotics inhibit this loosening of the colloids, especially in the superficial protoplasmic layers of the cell, so that in consequence the irritability is reduced or abolished.

Thus, we see that widely different hypotheses concerning the nature of narcosis have been expressed, without any of them having as yet achieved general acceptance.

Before we attempt to form a conception of the mechanism of narcosis, it appears to me indispensable that we clearly understand what should be required of any theory of narcosis. Narcosis is a state of living matter, in which, under the influence of certain chemical substances, the physiological processes of the cell are altered in a special way. A scientific study of this state can consist only in seeking to determine, as far as possible, the nature of these changes. The more deeply we analyze them, the clearer becomes the theory of narcosis. In order, however, to comprehend the changes in the physiological processes in living matter, it is requisite that we should first know the normal physiological processes themselves, in all their details. In spite of many important and fundamental researches, we are to-day still far from such knowledge. From

this it is evident that we cannot yet speak of a " final " theory of narcosis. But where in our knowledge do we arrive at final results? Wherever we may look, whatever we may achieve, we are always and again confronted with new problems. Is there, anyway, a finality anywhere? Whoever, impatiently rushing forward, looks for a final word in knowledge will, like Goethe's Faust, only experience grievous disappointment:

" Entbehren sollst Du, sollst entbehren!
Das ist der ewige Gesang,
Der jedem an die Ohren klingt,
Den unser ganzes Leben lang
Uns heiser jede Stunde singt."

On the other hand, whoever is conscious that all things stand in endless coherence will desist from seeking an imaginary goal, and instead will enjoy the inexpressible charm which lies in the unlimited possibilities of finding again and again new links of this coherence. The possibilities of knowledge are endless, because the world is endless. This is true in large as well as in small things, and is true also of our problem. To the extent to which we succeed in discovering new facts which characterize the state of narcosis, to that extent the theory of narcosis develops of itself.

Well, then, what do we know of the changes which living matter undergoes during narcosis? Narcosis is a state of depression. Let us understand what this means. All states of depression in living systems are characterized by the fact that all or single partial processes of the normal metabolism undergo a retardation of their course, which may amount to complete standstill. This shows itself in the following symptom complex. The specific manifestations of life of that system are depressed or extinguished. The irritability to external stimuli is lowered, so that stimuli which are effective in the normal state show no apparent result. At the same time the power of conductivity, that is, the transmission of the excitation from the point of stimulation to some distant place, is correspondingly restricted, for irritability and conductivity

run always and everywhere along parallel lines. This symptom complex occurs in the most diverse living systems and under the influence of manifold agencies. We see it as a result of low temperatures in "frigor depression," or as a result of high temperatures in " heat depression "; we meet it after extreme functional activity, as fatigue; after withdrawal of oxygen, as suffocation; under the influence of chemical substances, as toxic depression; after too low osmotic pressures of the surrounding medium, as " water rigor "; from stoppage of the blood supply to the tissue cells, as asphyxial depression; and under many other conditions.

The question now arises, whether the mechanism of the depressing process is the same under all these widely diverse circumstances. In its generality, we can at once answer this question in the negative. The mechanism of depression in water rigor and in acid intoxication, for instance, is entirely different. Nevertheless, comparative studies of the mechanism of depression under the influence of different factors have shown me that a particular tendency exists toward one etiologic type of depression. In the complex realm of metabolism in all aërobic forms of cell, one part of the many anabolic and catabolic processes is especially sensitive to external influences, and that is the oxygen metabolism. Here is, in a certain sense, the *locus minoris resistentiæ* of the living matter of all aërobic organisms. In fatigue, it is the relative deficiency of oxygen which produces the depression. The increased demand for oxygen, brought about by the increased functional activity, can no longer be satisfied by the amount of oxygen present. The same is true of heat depression. The supply of oxygen cannot keep pace with the accelerated catabolism of the living tissue, induced by the temperature. In the asphyxial depression of the tissue cells which occurs as a result of any stoppage of the blood supply, it is not the withdrawal of the organic nutritive materials in the blood, but only the lack of oxygen, which produces the depression. In prussic-acid poisoning, again, it is the suppression of the oxygen metabolism in the

tissue cells which produces death. Thus we see that oxygenation is the factor, in the metabolism of aërobic cells, which most easily fails under diverse external influences and so forms the starting-point for the development of depression.

The most simple paradigm of this entire group of depressions is therefore suffocation of living cells or tissues in indifferent media free of oxygen. Fortunately we know to a certain extent the working of the mechanism of suffocation.

In normal metabolism during rest the supply of oxygen is always sufficient for the needs of the cells. Molecular oxygen is absorbed by them from the surrounding medium. A certain reserve supply of molecular oxygen, although comparatively small, is always present in the cells themselves, at least in cold-blooded animals not kept at too high a temperature. Many facts force us to this opinion, especially the continuance of normal production of energy and of irritability for a longer or shorter time, under complete exclusion of oxygen supply. The oxygen taken up from the medium is activated by special oxygen carriers and distributed to the oxidizable substances. We know of the existence of such oxygen carriers in the most diverse animal and vegetable cells, and we are accustomed to group them together under the collective name of " oxydases," although their chemical constitution is still completely unknown. The oxygen carriers bring activated oxygen, in the manner of inorganic catalysators, to the oxidizable substances, which by the oxidation are split into carbon dioxide and water. One point here remains still undecided, and that is, whether the oxidation attacks the organic fuel directly, such as, for instance, the carbohydrates, which have been synthetically built up by anabolic processes, or whether only the fragments are oxidized to carbon dioxide and water, while the splitting itself is accomplished by enzymatic processes. It is possible that in different forms of living substances the catabolism takes a different course. At any rate, the principal source of energy in all aërobic organisms is to be found in the oxidative splitting-up processes, and not in the non-oxidative part of the

catabolism. These oxidative splitting-up processes represent the principal source of energy production. That is an important fact. It has a special bearing upon the degree of irritability of living matter, for irritability is measured by the amount of energy production which results from a stimulus.

What changes does this phase of metabolism undergo, when the external supply of oxygen is withdrawn from a living system? No more molecular oxygen enters the living matter from the outside. The molecular oxygen, which at the moment of exclusion of oxygen is still present in the living tissue, will, according to its amount, be used up sooner or later. In the same proportion the extent of the oxidative breakdown will decrease. The catabolism will occur more and more in a non-oxidative manner. As soon as all the oxygen is used up, the destructive process will be entirely non-oxidative. This gradual transition from oxidative to exclusively non-oxidative decomposition corresponds in a characteristic way to the development of the depression. The intensity of the spontaneous vital activities diminishes gradually after the interruption of the external supply of oxygen. Very gradually the irritability for external stimuli decreases. Very gradually also the extension of the excitation from the point of stimulation to adjacent parts becomes restricted. Finally no spontaneous manifestations of life are visible; finally no visible effect is to be obtained from the strongest external stimuli. These are the general consequences which result from an interruption of the oxygen supply and which we observe everywhere in whatever way and at whatever point the oxygen metabolism is disturbed.

I have dwelt in some detail on the relations of the metabolism of oxygen and its disturbances, because our investigations carried out in the laboratories at Göttingen and Bonn have shown that in narcosis, also, there is a similar interference with the oxidation process. The fact that the oxygen metabolism suffers readily under diverse external influences sug-

gested the question whether also, under the influence of narcotics, disturbances of the oxidative processes take place. I had previously studied, by means of an artificial circulation, the rôle of oxygen metabolism in fatigue of the spinal cord of the frog, made especially sensitive by mild strychnine poisoning. It seemed to me, from my experience, that this would be a favorable object for the experimental determination of the question whether the oxidative processes are interfered with during narcosis. This question could be particularly well studied on the fatigued spinal cord, because it was found that the fatigue can be completely removed again only by the supply of oxygen. If the spinal cord is fatigued and oxygen is not supplied, as can easily be arranged with an artificial circulation, and if now the completely fatigued and oxygen-greedy spinal cord is narcotized, it can be determined whether, with a free supply of oxygen, the spinal cord can take it up, and thus recover during narcosis. If the fatigued cord is irrigated during narcosis with arterial ox blood or with an oxygen containing saline solution, and later, while the narcosis still continues, the blood is removed again by oxygen-free salt solution, and if then the narcosis is stopped, it must become manifest whether the centres of the cord have taken up the abundantly supplied oxygen during narcosis, and recovered. Winterstein has performed this experiment at Göttingen, using various narcotics, such as ether, alcohol, chloroform, and carbon dioxide. All the experiments agreed in showing that not the least trace of recuperation occurred; while, after the end of the experiment, the cord was completely restored in a few minutes by perfusion with oxygenated ox blood without narcosis. Herewith the first proof was given that, during narcosis, living tissues are unable to utilize the oxygen offered to them.

Nerves offered a second favorable object for testing our question. We had succeeded, after many vain attempts, in perfecting a method by which it was possible to show that nerves died of suffocation when cut off from all possible supply

of oxygen. This fact, established by H. von Baeyer, placed us in a position to make on the nerve, which proved to be an exceedingly favorable object, experiments on the question of oxygen metabolism during narcosis analogous to those made on the cord. The sciatic nerve of the frog was asphyxiated, and thus made oxygen greedy. When its conductivity was lost and its irritability reduced to a very low level, it was narcotized with ether. Then, during narcosis, oxygen was supplied to it for a long time. After the oxygen had been finally removed by pure nitrogen, the narcosis was stopped. In these experiments, which were first made by myself, afterwards by Fröhlich, and later on by Heaton, there was never any trace of recovery. When the nitrogen was replaced by air, the nerve recovered in one minute and showed normal irritability and restoration of conductivity.

Finally, in a series of experiments which have not yet been published, Ischikawa proved that amœbæ, also, which had been asphyxiated in a gas chamber in pure nitrogen and had become motionless, did not take up oxygen which was supplied to them during narcosis, while after stopping the narcosis and replacing nitrogen by air they rapidly resumed their amœboid motion.

These experiments show unequivocally *that living tissues, even when their demand for oxygen has been raised to an extreme degree by fatigue or asphyxia, cannot, during narcosis, make use of oxygen, even when offered to them abundantly.*

This conclusion caused us to advance one step further. If living tissue, during narcosis, cannot use the oxygen which is supplied to it, this inability might be produced in several ways. Either narcosis depresses the entire phase of catabolism, with all its partial processes, perhaps by paralyzing the first step, or it hinders especially only the oxidation processes. In the former case, we should expect that a narcosis of a certain depth, in which the destructive processes were completely abrogated, could continue for an indefinite time. In the second alternative, that is, if only the oxidation is prevented,

destruction must proceed in non-oxidative form, just as in the absence of external oxygen supply, and the living tissue under narcosis must eventually die of asphyxia, even though sufficient oxygen is constantly at its disposal. We can decide between these two possibilities. On the one hand, experience shows that no narcosis, whatever its depth, can continue indefinitely without the tissue losing its viability. On the other hand, we can demonstrate experimentally that during narcosis catabolism proceeds in non-oxidative manner and that asphyxia gradually supervenes. Here again the nerve proved to be a favorable object for experiment. Heaton has used the two sciatic nerves of the same frog for the following parallel experiment: One nerve was drawn through a gas chamber which contained pure nitrogen; the other was narcotized in a similar gas chamber filled with air. The experiments began simultaneously in the two nerves. In the asphyxiated nerve the irritability sank very gradually lower and lower. When it had fallen to a certain level, the conductivity for an excitation coming from the part of the nerve outside of the gas chamber vanished also. The time at which this degree of depression is reached depends on the length of the asphyxiated portion of the nerve, on the condition of the frog, and on the temperature. At room temperature it requires, on the average, from two to three hours. At the time that the conductivity of the asphyxiated nerve was abolished, the air surrounding the narcotized nerve was replaced by pure nitrogen, and the narcosis interrupted, so that the nerve, after the narcosis was stopped, had no more oxygen at its disposal. If the whole destructive phase of metabolism had been brought to a stop, the nerve should, after stopping the narcosis, be in about the same condition as before it. This was, however, not the case. All the experiments, rather, agreed that during narcosis this nerve was also asphyxiated like the nerve in pure nitrogen, in spite of the fact that the former always had air at its disposal. Its irritability had been greatly reduced and its conductivity was abolished. That it was actually asphyxi-

ated was shown by the control experiment, in which both nerves recovered completely as soon as air was conducted over them. The irritability increased rapidly as the conductivity returned.

Ischikawa has recently performed similar experiments on amœbæ. Amœbæ gradually lose, in nitrogen, their amœboid motions. They regain them only when oxygen is supplied. If amœbæ are narcotized with ether, they are also asphyxiated; for after the narcosis, in the absence of oxygen, they do not regain their amœboid motions. These only return after oxygen is supplied.

It is thus evident that living tissue is asphyxiated during narcosis; that is, that the destructive phase of metabolism proceeds in a non-oxidative manner.

We can add yet another fact. Even during narcosis *the destructive processes can be increased, that is, accelerated, by exciting stimuli.* Heaton has narcotized the two sciatic nerves of a frog in a double chamber under absolutely identical conditions. While one of them remained at rest, the other was continually stimulated by a faradic current applied to the end beyond the chamber. After discontinuing the narcosis in pure nitrogen it was always found that the irritability of the stimulated nerve had fallen to a lower level than that of the other. Placed in air, both recovered to an equal degree. The results of this experiment entirely agree with the phenomena of fatigue, which were found by Thörner in his researches on the fatigue of nerves in nitrogen. On the basis of all these experiments, we may make the following statement: *Living tissue becomes asphyxiated during narcosis. The catabolic phase of metabolism continues in the form of a non-oxidative destruction, just as in asphyxia, and can also, as in asphyxia, be accelerated by exciting stimuli. Recovery from this asphyxia is, as in every asphyxia, only to be attained by supplying oxygen.*

Under these circumstances the idea naturally presents itself, that the entire symptom complex of narcosis is only a manifestation of asphyxia, which the narcotic induces by inhibi-

tion of the oxidative processes. Before we accept this idea, however, we must assure ourselves that there is no fact which stands in the way of its acceptance. It goes without saying, that if asphyxia occurs in narcosis, the general picture of asphyxia must be present. This is actually the case. The cessation of spontaneous evidences of life, the reduction of irritability, the decreased power of conductivity—all the typical symptoms are identical in narcosis and in asphyxia in an oxygen-free medium. In only one point is there a noteworthy difference. *That is in the time relations of the depression symptoms.* In narcosis of nerves, for instance, irritability sinks *in a few minutes* to a point which in pure nitrogen is only reached in *two or three hours.* The question therefore arises, whether we have not here a fact which must inevitably eliminate the idea that narcosis is nothing more than asphyxia. A more careful consideration shows, however, that this is not the case. The experiments which have already been described contain the explanation of this difference in the rapidity of onset of the depression.

The fact that living cells, during narcosis, can make no use of molecular oxygen, even when it is freely offered to them, shows that the narcotic renders the living tissue incapable of undergoing oxidations. It cannot, therefore, utilize for its oxidation processes the oxygen present in itself. The conditions during asphyxia in an oxygen-free medium are, however, quite different, as for instance in asphyxia of nerves in nitrogen. Here the power to carry on oxidations is not interfered with in the least. As long as any trace of molecular oxygen is present, it can be used for oxidation. Now it is of course impossible that, at the moment that the air in a gas chamber is replaced by nitrogen, every trace of oxygen should disappear from the nerve in the chamber. The nerve, therefore, with its small oxygen requirement, can, even in pure nitrogen, carry on its oxidation processes in a more or less decreasing degree, according to the temperature and to the amount of oxygen contained in the nerve itself. Accordingly,

the irritability decreases only gradually, and in proportion to the extent of the decrease of the oxidative processes. *In the depression of nerves in an oxygen-free medium we deal with a slow, while in narcosis we deal with an acute, asphyxia.* That is the factor which produces the difference in time. We have also, therefore, the power of eliminating this difference completely. We may do this, in one way, by those measures which hasten asphyxia in an oxygen-free medium. Such a measure is the increase of the demand for oxygen by raising the temperature. In this case heat depression occurs. Of heat depression we know that it is an asphyxia which results from a relative lack of oxygen, because the supply of oxygen cannot keep pace with the markedly increased demands of the living tissue, just as in fatigue. As H. von Baeyer has shown, complete loss of irritability in nerves may be attained by keeping them for 20 minutes in a gas chamber at a temperature of 42° to 47° C. The lost irritability cannot be restored by reduction of temperature alone; while, after supplying the nerve with fresh air, recovery results in a few minutes. At higher temperatures asphyxia occurs still more rapidly. In the ganglion cells of the cerebral cortex of mammals, asphyxia results in a few seconds when the air supply is cut off. On the other hand, the narcosis of the nerves can be greatly delayed if the narcotic is administered only in small amounts. In short, *the more rapid or slow onset of depression is solely dependent on the rapidity with which the oxidation processes are abolished.* In narcosis this occurs very rapidly, because the narcotic renders the cells incapable of carrying on oxidations; in asphyxia in oxygen-free media, it occurs only very slowly, because the living tissue retains its power to carry on oxidation and continues to do so until the last trace of oxygen present in the tissues is used up. The difference in the time of development of the depression in the two cases is solely dependent on the different way in which the oxidation processes are brought to a standstill. The symptom complex of

narcosis, therefore, not only is comprehensible, but on the basis of the ascertained facts it is inevitable.

It seems to me that, after these considerations, it is no longer possible to doubt, not only that narcosis is accompanied by asphyxia, but that the acute asphyxia is the deciding factor which produces the depression. This does not exclude the possibility that the narcotic may also produce other changes in the living matter, for instance changes in the state of aggregation of certain substances. Whatever other changes may occur, *the factor which produces the characteristic symptom complex of narcosis is under all circumstances the suppression of the power to carry on oxidations.*

The conclusions which may be drawn directly from the facts bring us as far as this; but the problems are by no means finished. At this juncture the new question arises: In what way does the narcotic, by entering the cell, inhibit the power of the latter to carry on oxidations? Here the facts leave us still in the dark. If we wish to answer this question, it can only be done in the form of a hypothesis. I wish to emphasize this point particularly. But "*no true scientist fails to realize that the essential factor of progress lies in a hypothesis which agrees with the facts.*" These words of one of the greatest physiologists, who was also my predecessor in Bonn, shall serve as my excuse if I attempt now, with the assistance of a working hypothesis, to go a step further in the direction indicated.

When we recall the fate of molecular oxygen in the normal metabolism of the cells, from the moment at which it enters the living substance to the moment at which it decomposes the oxidizable materials into carbon dioxide and water, we find that the narcotic, which overflows the cell, could establish its inhibitory action upon the oxidation at various stages of this process.

In the first place we might conceive *that the narcotic, when it has penetrated into the living substance, prevents in some way the entrance of molecular oxygen from the surrounding*

medium into the cell. This assumption, however, may be dismissed at once. If the depression of narcosis were produced by the fact that oxygen could not penetrate into the cells, then we could expect a course of depression with exactly the same time relations as in complete withdrawal of external oxygen; the cell would be in exactly the same position as it is, for instance, in pure nitrogen. The difference in the time relations between the two cases, for instance in the nerves, shows us, however, that this is not the case.

Next we must consider the possibility *that narcotics appropriate the oxygen which enters the cells, and use it for their own oxidation.* The narcotics are, it is true, generally looked upon as chemically indifferent substances, but Bürker has recently published experiments which show that, under certain conditions, narcotics may be oxidized, at least by nascent oxygen. Bürker performed the following interesting experiment: He placed two identical voltameters in the same electric circuit. One of them was filled with acidulated water; the other had in addition a small percentage of ether. Then he decomposed the fluids electrolytically by means of a galvanic current. In the voltameter which contained no ether, the gas collected at the two poles in the usual relation, the volume of hydrogen at the cathode being to the volume of oxygen at the anode as 2 to 1. The relationship was, however, entirely different in the voltameter which contained ether. Here only a very small amount of oxygen collected at the anode; while the analysis of the gas from the anode showed that carbon dioxide, acetaldehyde and acetic acid had also been formed, as oxidation products of ether. Based on this result, Bürker put forward the hypothesis that narcotics had the same effect in living substance as in the voltameter, and that the depression of the oxidation process in narcosis depends on the fact that the narcotic itself appropriates the oxygen. As, in living tissue, oxygen is activated by oxygen carriers, the possibility of oxidation of ether even in the cells is not, indeed, excluded. But under the conditions which obtain in

living tissue, it is doubtful whether it really occurs to such a degree as to reduce the oxidation of respiratory materials to a noticeable extent. For many of the narcotics, oxidation in the cells in very unlikely, and in the case of carbon dioxide it is absolutely excluded.

A third possibility of the interference with oxidation is, *that the narcotic in some way blocks the molecules of oxidizable material, perhaps by a loose chemical fixation, and thus renders them inaccessible to oxidation,* and the oxidation will thus cease. However, this view also has very little likelihood. According to this view, we would have to presuppose that the narcotics, which in themselves present substances with very heterogeneous chemical properties, were also able to block very diversified substances; for in non-oxidative catabolism, such as occurs in narcosis, manifold products arise with very different chemical properties. We would have to assume that all these different substances can be prevented from oxidation by all the different narcotics. We cannot readily have recourse to such an assumption.

Finally, there remains one more possibility to be considered. It might be assumed *that the narcotic renders the oxygen carriers incapable of activating the oxygen, so that the oxidizable materials could no longer be oxidized and decomposition would proceed only in non-oxidative form.* This view seems to me the most probable, as we have inorganic analogies for it. The colloidal solutions of metals, for instance platinum solution, can, as Bredig has shown, be prevented from acting as oxygen carriers by diverse chemical substances, such as corrosive sublimate, hydrogen sulphide, hydrocyanic acid, etc. "Paralyses," or depressions, are produced in this way, which correspond to a great extent with the depressions of living cells. If I therefore form the hypothesis that narcotics, in an analogous way, render the oxygen carriers in living tissues incapable of carrying oxygen, all the facts of narcosis find a simple mechanical explanation.

But still more, the possibility is also given here to combine

the relation between the solubility in lipoids and narcotic action, discovered by Overton and Meyer, with the facts already given concerning the influence of narcotics on oxidation processes. The fact that the lipoid solubility of a substance primarily determines the degree of its narcotic action, shows us that the mechanism which lies at the base of the symptom complex of narcosis must be associated in some way with lipoids. We have seen that this mechanism consists in an inhibition of oxidations, and it is highly probable that this comes about through a paralysis of the oxygen carriers. It is quite natural to assume that the oxygen carriers, whose chemical nature is still entirely unknown to us, stand in some close relation to the lipoids, that they are perhaps themselves of lipoid nature, or that they are attached as specific atom groups to lipoid molecules. By this assumption the relations discovered by Hans Meyer and Overton and the facts shown by us, that narcosis depends on acute asphyxia, would be combined in a natural manner. Both facts would mutually complete each other, and the result would be a further elucidation of the mechanism of narcosis.

However, I wish to emphasize, again, that the conception regarding the nature of inhibition of oxygen metabolism in narcosis is of a purely hypothetical character. It is only an established fact *that narcotics induce an acute asphyxia of the cells. Herein is the essence of narcosis.*

If we are satisfied, for the present, with this knowledge and put the question of the particular mechanism of the asphyxia to one side, the mere fact that narcotics inhibit oxidation processes will in itself guard us from many false conceptions in regard to narcosis. The knowledge of this fact has some significance also for the practical use of narcosis.

Let us ask, first, what we narcotize when we induce narcosis in man by inhalation of ether or chloroform. All tissues of the body are not affected equally by any means. Even if it is assumed that the blood carries the narcotic to all the tissues in nearly the same concentration, the different tis-

sues are influenced to a very different extent by the narcotic. When the ganglion cells are already completely depressed, the nerve fibres and muscles still show no sign of narcosis. The ganglion cells of the brain, and especially those of the cerebral cortex, are most readily affected in their specific functions by narcotics. Thus, if we induce so-called "general" anæsthesia by ether or chloroform narcosis for any operative purpose, we deal in reality only with narcosis of the cerebral cortex. In this lies the great value of narcosis; for we desire in narcosis to eliminate conscious sensation, and the acts of consciousness are, as is well known, due to excitation of the ganglion cells of the cerebral cortex. The ganglion cells of the cerebral cortex, with their functions intact, are the most valuable asset that man possesses. Therefore it is particularly important to us that nothing shall happen which might injure them permanently, and we must therefore know the possible dangers of narcosis, in order to avoid them.

The fact that the ganglion cells of the cerebral cortex lose their specific functional activity, under the influence of narcotics, sooner than any other body cells, must, on the basis of our new data in regard to the relationship of narcosis and asphyxia, naturally give rise to the idea that they are more sensitive to asphyxia than any other body cells. That is actually the fact to a striking extent. Mosso has demonstrated this in a classic way on man, in whom alone direct studies of the conditions of the processes of consciousness can be made. In his experiments on Bertino, he found that a few seconds' interruption of the supply of oxygen sufficed to produce loss of consciousness. Bertino had a large defect in his skull over the frontal lobe, and the cerebral pulsation could be graphically recorded there. The frontal lobe receives its blood supply from branches of the carotid arteries. When Mosso compressed these arteries in the neck, so that the cerebral pulsation ceased, Bertino lost consciousness in five seconds without having had any premonitory disagreeable sensations. After releasing the pressure upon the carotid arteries, con-

sciousness returned at once. This experiment shows how dependent the cells of the cerebral cortex are on their supply of oxygen, and in how short a time unconsciousness occurs after complete interruption of this supply. Here we have an example of a depression rapidly following the withdrawal of oxygen. The associative workings of our ideas and sensations, thoughts and feelings can proceed in an undisturbed manner only when there is complete integrity of the specific irritability of all the ganglion cells concerned. The slightest loss of irritability interrupts the orderly play of excitations and inhibits the activity of consciousness.

From this peculiarity of the cortical cells is the important requirement derived, long known empirically, that in man we should employ a light degree of narcosis, just sufficient to paralyze consciousness. Under such circumstances the depression of the oxidative processes is undoubtedly of very limited extent, and there is no demonstrable danger of permanent injury to the normal brain. When we employ a deeper narcosis, the danger of rapid and complete asphyxia of the ganglion cells increases with the depth of the narcosis. At any rate it ought to be always present in our mind that the deeper the narcosis the more it inhibits oxidation processes, and that the ganglion cells of the cerebral cortex are exceedingly sensitive to lack of oxygen. Here we deal with the most tender and perishable cells of our body.

In this connection I wish, before concluding, to point out an error that has been handed down from olden times, and even at present has not been corrected everywhere. It is the identification of narcosis with sleep.

The origin of this confusion is evident. It is based on the entirely superficial analogy that both states are characterized by loss of consciousness. But not every loss of consciousness is sleep. This confusion, which may have been justified in earlier times, when both conditions were known only by their external symptoms, is to-day, when we have penetrated somewhat more deeply into the inner processes of the cells of the

cerebral cortex, a grave mistake. Closer consideration will show this plainly.

What occurs in the neurons of the cerebral cortex during an act of consciousness? I am far from intending to give here a detailed analysis of these processes. I wish to emphasize only a single general fact. Let us conceive a condition of the cerebral cortex in which the neurons are in metabolic equilibrium; that is, in which the two phases of metabolism, the anabolic and catabolic phases, balance each other. We should have then a state of complete rest, in which no act of consciousness takes place. An act of consciousness ensues only when the metabolic equilibrium in a chain of associated neurons is disturbed by an exciting stimulus which causes a sudden increase of the catabolic phase. Every act of consciousness is the expression of a catabolic disturbance in the cortical neurons. This is not merely an assumption; it is shown, among other things, by the fact that even the simplest conscious process requires the associated co-operation of several ganglion-cell stations, and that on the other hand the nerve fibres which provide for this associated co-operation conduct no other impulses than catabolic excitation processes. On this general basis, for all processes of consciousness there are two possible origins of unconsciousness. Loss of consciousness will occur either because the ganglion cells are depressed, so that the external stimuli produce no excitation, or because exciting stimuli are absent. As we have seen, the first condition prevails in narcosis; the irritability is so much depressed that stimulation is ineffective. In sleep, the second alternative is predominant; the first plays at most the rôle of a predisposing part for the induction of sleep. We sleep, and determine the moment of going to sleep, by limiting as far as possible the sensory stimuli, especially the optical. This state of the utmost exclusion of external stimuli lasts throughout the entire period of sleep. This is supported to a certain extent by fatigue, that is, the decrease of irritability, which the ganglion cells have sustained by the constant action of

sensory stimuli while awake during the day. A comparison of the processes which occur in the ganglion cells of the cerebral cortex during sleep and during narcosis will show us plainly how diametrically opposite these are.

During sleep, restitution occurs. The irritability, which becomes reduced in the course of the day as a result of the fatiguing action of sensory stimuli, gradually rises again. The fatigue of the ganglion cells, which, as we know, depends only on a relative lack of oxygen, becomes completely dispelled. The supply of oxygen, which during constant activity was not quite sufficient to keep irritability at its maximum, is, after the cessation of functional demands, fully sufficient to banish the fatigue. In short, during sleep, restoration occurs principally by the action of oxygen. In the morning the ganglion cells are refreshed and possess their full capacity for work.

How different is narcosis! In narcosis there is, on the contrary, as we have seen, a depression of the oxidation processes. The experiments showed that even with a free supply of oxygen a fatigued ganglion cell did not recover at all during narcosis. There occurs, rather, a gradual asphyxia, and, although this process is only developed to a small extent in light narcosis, still it presents just the reverse of that which sleep brings to the ganglion cells. In the one case, recovery from fatigue by oxidation; in the other, prevention of restitution by inhibition of the oxidation process. There can be no confusion between sleep and narcosis.

If we use narcotics to induce sleep, we must always bear in mind that no true sleep occurs as long as the narcosis of the cortex lasts. We can speak of "hypnotics," or "remedies for sleep" (*Schlafmittel*), only in the sense that, when there is constant excitation of the ganglion cells, they reduce irritability and induce a greater degree of depression, so that true sleep may take place as the narcosis passes off. In that sense a hypnotic may prove beneficial in the hands of the physician, and when used sparingly. The physician must, however, never forget that not the entire period of unconsciousness which fol-

lows the use of the hypnotic is true sleep, but that at first it is, rather, a depression, the injurious effects of which will manifest themselves when the hypnotic is used for a longer period.

Ladies and Gentlemen: I am at the end of my lecture. The facts which I have stated take us, I believe, a step forward in the analysis of narcosis. They show us the general nature of the process, which is merely one of the great group of depressive actions which depend on a disturbance of the oxygen metabolism. They open, however, at the same time, a number of new questions. The previously mentioned hypothesis concerning the method by which narcotics inhibit the process of oxidation shows us the direction in which these questions lie. It may serve us as a guide for the present. The further analysis of the process will principally have to determine the nature of the transmission of oxygen and in what way this is affected by the narcotic. The experiences of modern physical chemistry will be of great help to us in the study of this question. I may, however, take this opportunity of warning against the misuse of physical chemistry in the explanation of biological facts; and this the more, since this misuse, which has grown with the development of that science, is already beginning to arouse in the minds of many biologists a strong distrust of the value of physical chemistry in the analysis of biological processes. It is frequently believed that a biological process is explained when the terminology and certain catchwords, I might almost say the scientific "jargon," of physical chemistry have been applied to biological relations. There has been recently, for example, a great misuse of the word "colloidal process." There is positively nothing gained by it when a biological phenomenon (for instance, excitation or depression) is designated as colloidal process. This is neither correct nor incorrect; it says nothing. That the living tissues contain various colloid substances, and that these colloids undergo alterations in the course of the vital processes, has long been known. We wish, however, to know what it is that happens to the colloids, which of their properties are altered

and how these changes are incorporated into the machinery of the cell. For this purpose patient and careful analysis is required, and not the introduction of mere catch-words. The methods and results of physical chemistry give us very valuable material for such analysis; but it would be very one-sided to consider the methods of physical chemistry only. The methods and results of chemistry, physics, and microscopical research must be employed, as well as those of physical chemistry. In short, every method must be employed which will bring us a step further. That alone can be the general principle of all physiological research, and this principle will also lead up to new knowledge in the investigation of narcosis.

ON FREUD'S PSYCHO-ANALYTIC METHOD AND ITS EVOLUTION*

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THE subject of psycho-analysis, on which your long-honored president has invited me to speak, is one that deals with serious and difficult problems. I shall be glad if I can throw a flashlight on them here and there, and in so doing I shall try to answer some of the questions which have most frequently been asked me concerning the subjects in hand. Do not suppose that I shall pretend to give directions such as could enable any physician to put this method into practice. On the contrary, I beg you to regard it as a matter for congratulation that the leaders in this movement have a strong sense of the need of careful training and high standards on the part of those who desire to join their ranks. I have recently returned from a trip abroad, where I made the personal acquaintance of quite a number of the more prominent psycho-analysts, attended their congress, and was able to learn a great deal about the details of their mode of work. I came away strongly impressed with the fact of the recognition on their part of the importance of their task and that this recognition had had a good effect on the mental attitude of the workers, many of whom are still young and full of promise.

These men seemed to me, for the most part, strikingly eager, earnest, and sincere. "Sie haben gelernt ein Stück Wahrheit zu ertragen," said Freud to some of us when these facts were under comment. I learned to my surprise and interest that the greater number of the investigators had subjected themselves, more or less systematically, to the same sort of searching character-analysis to which their patients

* Delivered November 11, 1911.

were being subjected at their hands. It is fast getting to be felt that an initiation of this sort is an almost indispensable condition of good work; and for this important reason: The main thesis of the supporters of these new doctrines—which are at bottom old doctrines, rearranged and re-emphasized, for psycho-analysis is largely an accentuated phase of education—is that most of the emotional disorders to which we give the name of psychoneuroses arise largely from an instinctive self-concealment, and concealment of one's self from others; that is, from an unwillingness or an inability to see or look at all the facts that should be seen, respecting one's own tendencies and motives, as the basis for the control of feeling, thought, and action. Recognizing this principle, these physicians have seen that so long as their own lives, too, are partially on a false basis, so long as they also are self-concealed, they cannot do justice to their patients, either in the way of appreciation or of criticism. Obviously, a person ridden by prejudices that he does not recognize cannot do justice to another person in a like state; one is reminded of the simile of the " beam " and the " mote." It is, therefore, I repeat, a matter for congratulation that the need of preparation for these tasks is being taken seriously, and the assertion is justifiable that the introduction of this specialty is likely to make better men, in every sense, as well of the physicians who practise it as of the patients whom they treat.

But while no man, however able, can without long study master the details of this method, every man who would be liberal or scientific can and should master its principles and give the movement his generous sympathy and support.

What is psycho-analysis, and what, in general, are its aims? Psycho-analysis is a method of investigating and treating nervous invalidism and (incidentally) faults of character, which owes its strength to the fact that it searches and studies in detail, so far as this is practicable, all the significant experiences through which the patient to be treated has passed, and the motives and impulses which have animated him at psychologic-

ally important moments of his life, even since his earliest childhood. In doing this it discovers, not, indeed, all the causes of the disorder from which he suffers, but a large number of important partial causes, and thus prepares the way for the influences tending toward recovery. This definition is, I think, substantially correct, but it needs some explanation, amplification, and qualification.

First, it is not strictly true to say that the attempt is made, during a psycho-analytic treatment, to pass in review all of the important motives and impulses, or even all of the kinds of motives and impulses, which had animated the mind of the person who subjects himself to this treatment, but, strictly speaking, only a certain class of them,—those, namely, that were originally based on emotions which had been repressed because they were painful or seemed out of harmony with the chosen plan of life, but which, in spite of all repression, had remained as active causes of serious mischief. It does not systematically deal with those motives and impulses which may be designated as aspirations and ideals, derived, as I believe, from the essential endowment of the spiritual nature by which every man is animated and which is to be regarded as an independent, primary, creative force. Psycho-analysis does not, in other words, pretend to take the place of philosophic teaching; but it does help, even without claiming to do so, to give such teaching a better chance to make itself effective.

On the other hand, it is not just to characterize psycho-analysis solely as a therapeutic measure. In proportion as the psycho-analytic movement has developed toward maturity, it has shown itself able to make scientific contributions of great value to psychiatry,[1] psychology, mythology, philology, sociology, as well as to education and to prophylaxis. In other

[1] The value of Jung's argument for ranging Kräpelin's dementia præcox, together with many symptom-complexes classified by Janet as psychasthenia, under the psychological category of the introversions, is now generally conceded.

words, these investigations bring support to every research which deals with the inward and the outward manifestations of human effort and mental evolution, while at the same time they draw important aid from all these inquiries into the psychology of the human race, for the benefit of the single human life.

The practical aim of this method is to enable persons who are hampered by nervous symptoms and faults of character to make themselves more efficient members of society, by teaching them to shake themselves free from the subtle web of delusive, misleading, half-unconscious ideas and feelings by which they are bound and blinded as if through the influence of an evil spell. Such persons—and in some measure the statement is true of all persons—have to learn that they are responsible, not only for the visible, but also for the hidden portions of themselves, and that, hard as the task may be, they should learn to know themselves thoroughly in this sense. For it is the whole of ourselves that acts, and we are responsible for the supervision of the unseen as well as for the obvious factors that are at work. The moon may be only half illuminated and half visible, but the invisible half goes on, none the less, exerting its full share of influence on the motion of the tides and earth.

Some patients may learn to override or sidetrack their troubles and can be helped by various means to do so. These other means are, however, not to be compared, for power of accomplishment or permanency of result, with that of which I now speak to you.

It is difficult to see why any broad-minded person should refuse to recognize, on theoretic grounds at least, the value of the self-knowledge here alluded to, especially when the treatment of the more serious forms of psychoneurotic illnesses is at stake. These more serious forms are very numerous and the causes of enormous suffering. Difficult and doubtful of issue as the treatment of them is, the method here discussed holds out a new and vital hope.

It would obviously be impossible to offer you anything approaching to an adequate account of the means by which it is sought to discover, for each individual case, the particular facts and tendencies from which the particular symptoms [2] that are present may have sprung. It must be enough to assert the fact which Freud established, that each person's memory, if allowed and encouraged to wander, uninhibited by resistances and repressions, may usually be counted upon to furnish the information that is needed. Where this is insufficient, two other plans may be adopted, one of which, indeed, comes largely into play in every case. These two methods are, first, the use of word-associations, the value of which Dr. Jung, of Zurich, has done so much to establish, and, next, the study of dreams.

The significance of the word-association method, stated in briefest terms, is that it serves as a sort of concentrated conversation. The patient, answering at random as he should do, instinctively lets go,[3] for the time being, of the reins which he ordinarily holds tight over his inmost thoughts, and allows glimpses into the mental processes which it is of the utmost importance that he should know yet which constantly tend to elude his attempt to seize them. Further inquiries and associations may, then, if necessary, proceed from such beginnings.

The elucidation of the means by which the interpretation of dreams may be successfully carried on, and a path thereby opened into the inner chambers of the mental life, is one of Freud's contributions which well deserves being designated as a mark of genius. Whatever differences there may be between the conscious lives of different individuals, in our repressed and unconscious lives we are all very much alike—not, indeed,

[2] Such symptoms are not to be regarded as haphazard and unlucky but meaningless signs of breaking down on the part of the nervous system; they are, rather, real and significant *reactions,* dumb expressions of both terms of very deep and vital inner conflicts, but under the form of compromises between instinctive desire or cravings and instinctive denials of these cravings.

[3] If the reins of thought and emotion are not relaxed this fact too will become evident.

in detail, but as regards the principles in accordance with which we are constructed.

Just as we speak the same verbal language, so we speak, at bottom, the same dream language, and can learn to make the meaning of our dreams clear to others and to ourselves. It cannot be too often represented that the disharmony between the conscious and the unconscious portions of our lives, which is sometimes productive of so much misery, ought not to exist. Every one recognizes this after a fashion, and tries, instinctively, but, as a rule, without success, to overcome the disharmony by finding some sort of outlet for the repressed—and usually childish—feelings which his conscious intelligence will not tolerate. But this is not enough. If he would really overcome the disharmony, he must meet the situation face to face, and the study of his dreams, in which his repressed thoughts are represented in caricature and in picture language, is perhaps the best means of obtaining clues to the information which he seeks.

These hidden portions of our lives must be thought of as seeking to make themselves felt in action though not in words. Ordinarily, we keep them, like the evil spirits in Pandora's box, under pretty strong lock and key. At night, however, the locks are loosened, and our repressed emotions succeed in finding their way to the theatre-stage of consciousness. Even then, the thoughts which arise are not allowed to become too evident, but are concealed beneath picturesque symbolisms and disguises.

It is a very interesting fact that, as each new person comes into the world and begins his life of dreams, he adopts forms of symbolism analogous to those which have been in use since even semi-civilized life began. The various animals with which our childhood was familiar come forward to play the rôle of animal-passions; the rapidly moving trains typify our hurrying emotions. And so, too, still or moving water, the rooms or buildings in which we like to place ourselves, the bare or varied landscapes, and many a symbol more, are all

utilized as elements of a picture-language which is almost as well defined as that indicated by the rebuses of the child, or the hieroglyphs of the Egyptians, or the mythology of the ancient Greeks.

So full of meaning are these signs that no dream carries its true, much less its whole, significance on its face; no item, no obvious omission even, is without its bearing; hardly a feature or character is to be found that is not of even multiple value. The general proposition has been laid down—and certainly with good reason—that every dream represents the fulfilment of an unconscious wish. No one would doubt that this statement is true of the day-dreams of childhood, and when for "wishes" we read "partial" or "temporary" wishes, and learn by self-study what these partial wishes are, it is found in the dreams which appear so terrifying, the wish is concealed behind an attempt to repress it, just as the partial wishes of our waking moments are often concealed behind the disguise of fears, a phenomenon very characteristic of the phobias of neurotic patients. Persons unfamiliar with the interpretation of dreams often deny this tendency, and point out that their dreams are nothing but jumbled representations of some trivial happenings of the day before. It is true that every dream takes the happenings of the day before as materials out of which to construct its apparent story. These trivial experiences are utilizable, partly because of their analogical bearings, partly because they are still conveniently available for the memory and yet not fully woven into any other of the various complexes which our emotions tend to manufacture. In utilizing these experiences the dreamer does what any person might do who wished to tell a story while sitting at the dinner-table with his friends. Assuming that he desired to describe a journey he had taken, he might select a salt-cellar to stand for a castle that he had seen, a fork for one road, a spoon for another road, a plate for a pond or lake, etc. But behind these hastily chosen symbols, there would be a connected story; and in the same way, behind

the trivial details which make the outward framework of the dream there is a connected story, which, indeed, reaches, in layer after layer, back into the dreamer's earlier life and even into his childhood. For in every mental act the whole personality of the individual comes into play, although in each act certain elements of the personality are illustrated far more than all the rest. Of course, it need hardly be said that the analogy between the forks and spoons and the apparently trivial incidents of the day previous to the dream-night is by no means a complete one. Unimportant as the real incidents may seem, they are often full of meaning, which, however, only an expert analysis can reveal.[4] Each dream, then, furnishes, to the expert, and to the patient, a path into the inmost recesses of the patient's life, better than any other means could furnish.

As regards the therapeutic value of the psycho-analytic method, it is almost needless to say that there are many cases that baffle every treatment, not excepting that by psycho-analysis, and that this method has its special limitations. The patient, to be treated with success, must be reasonably young, reasonably intelligent, and able to give a large amount of continuous time to the investigation. His outlook as regards conditions of life must be reasonably favorable, or else he must have the capacity for idealization such as will enable him to override outward misfortunes, and to face existing conditions cheerfully. He must want to get well, and not count on his illness as giving him gratifications or advantages which he is unwilling to sacrifice, even for better health. Then,

[4] Perhaps the two most important sets of facts to look for in the interpretation of a dream are: (1) the multiple and multiform special reminiscences suggested or symbolized by each thing, circumstance, or relation; (2) the various "movements" or "tendencies" hinted at. Somebody (the dreamer) is doing or experiencing something or having something done to him. That something is of deeply personal, perhaps infantile significance. Knowledge and keen insight must see through all disguises and determine what that something is. Not infrequently the apparent data must be absolutely reversed in order to be rightly understood.

of course, some sorts of symptoms are less curable than others.

The length of time sometimes required for successful treatments has often been the subject of comment. But in fact it is a great gain to have a method capable, even in a long time, of producing fairly good results. Any one who thinks about the matter must realize that it is extremely difficult to make any considerable change in one's own character or habits. Our good qualities, as well as our faults, are deeply founded. Both have their roots in the experiences of infancy or in the reactions of childhood, and if we would help ourselves to the best purpose we must get back, in knowledge, feeling and imagination, to the conditions under which the deviations from the normal first began. To accomplish this takes time and patience, though the task is full of interest.

It would not be justifiable to assert that the psycho-analytic treatment can accomplish such results as are claimed for it if we could not assert at the same time that the investigations based on psycho-analytic studies have thrown new and important light on the *nature of the disorders* with which the method deals. Without this light, a rational, causal treatment of these affections would be as far out of our reach today as it was in the last century, and we should still be throwing ourselves against the rocks and reefs of this great problem, chipping off a bit of stone here and there, but making no consistent progress.

The splendid insights of Charcot, and the remarkable researches of Pierre Janet with regard to the phenomena of automatism and the mental state of hysterical patients, brought the first real illumination into this obscurity,—an obscurity greater than we then could realize. The lines on which Freud began to work were somewhat parallel to Janet's in that both of these great leaders quickly learned to recognize the importance of the apparently forgotten and seemingly dead experiences of the invalid, and showed that they might still be acting as motive forces in the affairs of the present moment. Freud soon arrived, however, at the important con-

clusion that it is not enough to know single incidents of the past life, let them be never so grave, but that the whole life must be drawn upon and made to yield its entire history, and he proved that when the whole life is exhaustively studied on this plan it is possible to explain the symptoms of illness as largely referable to demonstrable influences operating since birth, and thus to get on without making such large drafts on " inherited tendencies," of which we know so little, as the principal causal factor. Then it gradually became clearer that the gaze of the investigator must be directed with ever greater insistence towards the very earliest years of life as the time when the seeds of mischief are sown—that marvellous period when tendencies are established and paths of least resistance are laid down, which may give a set or bias to all the years to come, and cause the child's mind to become sensitized, as if through a process of anaphylaxis, to special influences which may be brought to bear later, though perhaps not strongly until a much later period. The life-history of the normal child became, naturally, the next object of these ever-widening studies, and then the attention of a special group of investigators was turned upon the childhood-history of the races of men, as described in sagas and in myths. Even the history of criminology and of sexual perversion—already mapped out in part through the studies of many men, but now for the first time made to yield its true lessons—has been largely drawn upon, for the sake of discovering and illustrating the nature of the dangers with which the early years of every child are more or less beset.

One instructive method of getting an idea of what passes in the child's mind, of the difficulties which he encounters and the means that he takes to meet them, is to observe carefully how we ourselves deal with corresponding situations: Every one who is accustomed to scrutinize his own thoughts and conduct must realize that he is often tempted to put out of sight what he does not like to think of; to seek enjoyment

instead of doing work, and, in general terms, to live on a mental plane lower than his best.

Most of the temptations by which we are beset might be classified under one or the other of two headings; namely, the desire for gratifications or undue self-indulgences of a relatively personal sort, and the desire for gratifications implying the approbation, admiration or the attention of others, if only through subserviency or domination. I am not now concerned to prove the prevalence of these temptations or to deny that we may utilize them to our profit, but only to call attention to the fact that a more or less universal and sometimes irresistible tendency exists, which impels us, on the one hand, to secure these gratifications, and, on the other hand, to protect ourselves from self-reproach for so doing. In the interest of these two motives, which are, of course, comparatively rarely conscious motives, we cloak our cravings under forms which tend to make them seem justifiable and even admirable.

Every thoughtful person is more or less aware,—though it is only the well-trained or unusually discriminating observer who can thoroughly appreciate the fact,—that an element of craving for self-gratification may lie hidden under the guise of anger, prejudice, fear, jealousy, depression, desire for self-destruction, " over-conscientiousness," and the wish to inflict or to suffer pain. It is equally true that under the form of restlessness, or that of a sense of incompetency, we symbolize the hidden conflicts which cover our desire to escape from ourselves, or our incapacity to understand or unwillingness to face the full meaning of our emotional desires.

Those of us who call ourselves " well " owe it to those who are forced to call themselves " sick " to study the true nature of these innumerable faults of character. When this is done, it is discovered that these faults deserve the name of " symptoms," and that, like symptoms, they are disguises and com-

promises, concealing painful conflicts that may date back to the experiences of infancy.

It must be remembered that between the period of birth and the later years of childhood each individual recapitulates in a measure the history of civilization. The parent and the community who see in the infant not so much what he is as the promise of what he is to be, make little of those qualities in him which would be considered as intolerable if judged by our adult standards. But these qualities exist, nevertheless, and the growing child to whom they are transmitted must deal with them as he is best able, whether by gradually modifying them for the better, or by shrinking from them in disgust, or by continuing to indulge himself in them in concealed forms. One fact must never be forgotten, namely, that each child comes into the world with one mission which he cannot overlook or delegate and which he shares in common with every living thing,—the mission of preparing to do his part in the perpetuation of his race. For the sake of the establishment of the great function on which this depends, he is provided, in infancy, with a considerable number of capacities in the way of sense-gratification and with ample means of indulging them, which, however, he must eliminate as he grows older or preserve at his risk. But this risk the infant does not see, and before the time comes when he can see it he may have found himself drawn into paths of least resistance, leading both to pleasure and to pain, from which it will be difficult for him to escape. There is, then, no easy course left open for him but to repress his desires for these indulgences, just so far as may be necessary for concealing them from himself, while at the same time he invents substitutes and compromises in which the indulgences are continued under a new form. Yet, unfortunately, the adoption of such compromises is equivalent to laying a foundation for defects of character or for symptoms of obstinate forms of nervous illness, as the case may be.

Clear memories of these earliest years of childhood rarely

are retained. Yet some individuals retain very much more than others, and this fact, taken in connection with the evidence furnished by dreams, by a few careful observations of young children, and by the memories of patients trained under the psycho-analytic treatment, leads to the conclusion that a large part of the apparent forgetting is based really on repression.

From the standpoint of the next later period many of the details of infancy are unpleasant to recall. One is reminded of the Mohammedan cadi who, when asked about the early (Christian) history of his town, replied: "God only knows the amount of dirt and confusion that the infidels may have eaten before the coming of the sword of Islam. It were unprofitable for us to inquire into it."[5]

The period of childhood, though it contains many elements of happiness, which are usually accentuated and continued by the child's delightful power of grief-compensating fancy as exhibited in day-dreams, contains also many elements of suffering. The child's fears—of the dark, of storms, of mystery and power in a thousand forms—have been explained[6] as due to the organic memories of his pre-human ancestry; to the recognition of the contrast between his weakness and the bigness and strength of those about him or (in a religious and philosophic sense) the vastness of his own inexhaustible possibilities. There is nothing to urge against these explanations, but they cannot be regarded as covering the ground. The young child is at least partly like the older child and the adult, and fear, with them, cannot be studied as apart from the desire which so often underlies it. Like Scott's aged harper, we all "wish, yet fear," and frequently the wish becomes gradually repressed, and the fear alone remains. We all "fear" those most whose approbation we most "wish," and fear the tests in which we most long to succeed. The

[5] Cited in James's "Psychology," vol. ii.

[6] *Cf.* Pres. G. Stanley Hall's paper: Study of Fears. Am. Jour. Psychol., January, 1897, vol. viii, pp. 147–249.

child, with his splendid fancy and his intensified training in the symbolism of fairy-tales, loves to play with these fears and wishes. The dark stands for delicious, as well as alarming, mysteries, and beyond these there is also always the longed-for chance of the pleasure of re-discovering himself in his mother's arms.[7]

The strength of the child's tendency to follow pleasurable paths of least resistance may be vastly diminished, or, on the other hand, vastly increased, by the fact that the immense forces of social custom, by prescribing what should be done, help to deprive the child of his own sense of responsibility, while at the same time they seem to relieve the parent from the necessity of seeking to discover what is really passing in the child's mind. We talk of independence, but, in fact, the community is almost fanatic in its demand for conformity. The key to the solution of these difficulties must be sought, not primarily in the education of the younger generation, but in that of the older. It is with the lack of knowledge on the part of the parents, and the disregard by physicians of the need of acquiring and imparting adequate information on these subjects, that the reform must deal. There can be no doubt but that our social and ethical customs, which represent the filtered experience and wisdom of the race, are of immense value. But the ends which they mainly seek and the methods which they follow are not chosen with reference to the needs of the neurotic child. These points are of such importance that an attempt must be made to state them somewhat more fully, even at the risk of exciting misunderstandings.

The family influences under which most healthy-minded children grow up are, of course, eminently beneficial, and this is no place for discussing their shortcomings.

But the fact remains that nervous invalidism is extremely common; that it is closely bound up with social relationships

[7] This pleasure has a philosophic bearing to which I cannot here allude.

of varied sorts; and that the school in which the child gets his first introduction to these relationships is the home.

One cause of unhappiness in married life, for example, is the inability on the part of the husband or the wife to adopt the new duties with a whole heart. This inhibition is often due, in part, to the craving, established in childhood, for an undue continuance of the parental ties, with all that they imply; an unconquerable homesickness, which often cannot be put into words or recognized in its own form, overrules the new interests which ought to be supreme.

These are facts of common knowledge, but under the light of this new movement they have been studied with a thoroughness previously impossible, and have been correlated with others of a kindred sort, with the result of immensely increasing their significance.

It should not be forgotten that father and mother are not only objects of admiration, imitation and veneration to the growing child, but that they stand likewise to him as man and woman, and that, as such, they are in a position of peculiar responsibility and may be centres of peculiar harm.

I am not undertaking here to lay down rules for conduct, nor even to assert that although, on the whole, frankness and a well-guarded, thoroughly wholesome intimacy between parents and children is eminently desirable, it is very undesirable to break down all barriers of restraint between them. The evolution of modesty and of a certain amount of personal reserve needs to be safeguarded, even at some risk.

Real knowledge with respect to these complex matters should be sought, but it is hard to get and its advent is not to be awaited with impatience, or its acquisition as the basis of judgment and conduct assumed on insufficient grounds.

Another point of importance is that the dawning self-consciousness of the infant represents him to himself, not definitely and distinctively as "boy" or "girl," but as a being standing in relations of dependence to other and more powerful beings, whose characteristics he does not differentiate

from the sex-standpoint. The significance of this statement will be understood without difficulty by any one who will consult carefully even his own experience and observation. Every one must be aware that we all have some traits which are commonly designated as masculine, and others designated as feminine, and that the evolution which best marks social progress is based on the working out, in the case of each person, of capacities related to both of these sorts of traits. The attraction which persons of our own sex have for us is of great value as leading to friendships which may become exceedingly warm without ceasing to be eminently desirable. It is, however, well known that such friendships may develop into relationships which are eminently undesirable and a-social, and even, in the case of men, of a kind that would be called criminal. Between these two extremes, tendencies are to be observed, or are to be detected through careful study in a given case, which may lead to hidden conflicts and to distressing nervous symptoms. Good observers have shown it to be true that just as, to a certain degree, many men prefer the society of their fellows at the club to that of their wives and families at home, so, in a much deeper sense, nervous invalids often waver between attractions which would lead them in the direction of the most wholesome and useful relationships, either of marriage or friendship, and those which have an unwholesome tendency. The objectionable forms of these tendencies, if not created, are, at least, accentuated, by the overstrong, or, rather, by the slightly abnormal attachment of the infant to the father on the one hand or to the mother on the other. It is true, at the same time, that there are probably also deeper influences at work, dependent on some tendency which each person brings into the world, but of the exact nature of these latter influences it would be premature to speak. The subtlety of the danger here noted is what gives it its effective power, for what could seem to be freer from danger than parental love? Obviously nothing, when this love is fortified by wisdom and knowledge. In fact, however, it hap-

pens but too often that, either because the child is too immature in his manifestations of affection or because the parents retain too much of their own childishness, that which should be a source of infinite happiness and should lead the child towards independence and self-reliance becomes, instead, an opportunity for the growth of unwise emotion and a weakening tendency to imitation and dependence.

A careful study of the child's personal gratifications has shown that a portion of the earliest and strongest of them, which, for the most part, have to be repressed later, are related, first, to the satisfying of hunger, then to the securing of certain specific pleasures, such as the massive feelings of warm contact (during the diaper period), and those due to the excitation of the orifices of the body, especially the mouth, the urethra and the anus. To the child these sources of gratification stand at first, both morally and from the social standpoint, on an equal footing. He is unaware that he is likely to be subjected to serious temptations with reference to some of them; he does not know that his reaction to them may decide whether he is to become a being capable of recognizing that his best freedom is to be found in a willingness to devote himself to the welfare of the social whole, or whether self-indulgence is to be his ruling motive. The child who continues too long to suck his thumb, or wet his bed, or who finds undue fascination in the emptying of the bladder and the rectum, or detects a mysterious significance in these events, may be acquiring a tendency to prolong bodily indulgences which ought to be outgrown, and laying the foundations for other personal gratifications of more subtle, more distinctively mental, and, socially, of more disastrous sorts. Masturbation, of course, although accused of dangers which do not belong to it, stands high among these over-indulgences of a purely personal, auto-erotic sort.

Freud has been criticised for making too much of the sexual element in these problems; for seeing sexuality where it does not exist. But is this criticism just? The number of

those who think so is growing daily less, as sober judgment and knowledge of the facts come better into play. Think with what inconceivable, with what seemingly unwarrantable tenacity, nature, bent on the perpetuation of the life, both of the individual and the race, has safeguarded the function on which this depends. Many plants if starving will flower all the more abundantly, as if in order that their descendants at least may live. Think how every novel, every drama, is founded on some aspect of the sex problem. Is not the truth rather that these problems are felt to be of such enormous importance that we ought perhaps to shrink from touching them just as we might shrink from handling bombs charged with dynamite of high explosive power? And yet, is this true? Is not the dynamite to a great extent the figment of our imaginations, filled with repressed memories which we have not known how to study, but whose rumblings we have all vaguely felt within us?

This, or something like it, was, at any rate, the feeling which led Professor Freud long ago to enlist for his campaign, and determined him to risk everything for the laying bare of these long-neglected facts. He might have said to himself, whether he did or not, that he would take the great studies of human character, like those by George Eliot, or by Meredith, and would go on where these writers stopped, striving, in the spirit of the novelist turned man of science, to discover the processes of childhood through which the strong, deep tendencies which they describe came into being. Those who oppose this movement out of unwillingness to discuss the sexual life, are not only declining to be scientific and impartial (since to the scientific person nothing is in itself disgusting or unworthy of consideration), but also are rendering it harder for patients to get well, by stamping as indecent their attempts to gain a true knowledge of themselves.

I should like to call your attention to the fact that in the beginning it may be only a slight over-accentuation of an infantile tendency that makes the difference between the promise

of health and the promise of invalidism. But when the lines which enclose the angle of deviation have become extended, as the child grows up to manhood, the actual distance becomes immense. One is reminded, here, of Jean Ingelow's poem, "Divided," and, still more, of George Eliot's great study of Tito, in "Romola." Charming, handsome, kindly, scholarly, Tito seemed, as a youth, to have all possible good qualities, save that he possessed, or was possessed by, an apparently trifling tendency to self-indulgence, or selfishness, of the concealed, insistent, infantile type. This was never very prominent, but it was always present and always irresistible, and it made him in the end a fiend. And yet, from the psycho-analytic standpoint, Tito's was a curable case. At any moment, up to the very last, if he could have been aided to penetrate the history of his own life, and thereby to see at one glance the system of interlocking forces representing his still active tendencies of childhood and their logical outcome in his present acts,—as one looks through a transparent model of the brain-tracts,—he might perhaps have undone the mischief. For a man's emotional and mental past, even if of his infancy, never dies; it is always present and active, and represents a force which is always susceptible, theoretically at least, of modification or neutralization, in the interest of progress.[8]

There are several advantages in classifying, as Freud has been criticised for doing, the many and varied tendencies of which novelists write, as sex-tendencies. But perhaps the most important advantage is the practical one that it enables the physician, on suitable occasions, to point out the direction in which a given act or thought, conceivably innocent in itself, may lead.

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[8] Strictly speaking, we never obliterate the memories of our past experiences, and even to wish to do so would be in accord with the spirit of an Oriental rather than of a Christian philosophy. The new growth to which we should aspire diverges at a certain point from the old but gains a certain richness from the memories of the latter, and these memories cease to be painful, in the old sense at least.

It would be worth while to know whether, when you lay your hand on a man's shoulder, you are to be taken for a friend or arrested for assault and battery. The strongest term which points to the possible practical outcome of your act is oftentimes the best. A bit of self-indulgence, if it represented a force which had its rise in infancy, may not be as harmless as it seems. The child must, at every cross-road, select and accentuate on the one hand, repress on the other. But this power of selection and repression, which stands so high among our attributes, is itself a source of danger. The adoption of this or that *principle* of accentuation or repression may become habitual, and some of them are harmful. The child is like a merchant who cannot oversee all his affairs in detail and so indicates to his subordinates the general trend of his policy and then lets them work it out alone. But let him look out lest he become narrow-visioned and get hoodwinked. The really wise merchant does not often leave his subordinates to work out his plans indefinitely by themselves, whereas the indication of policy made in early childhood is often a decision, in one or another particular, made once for all and for a lifetime. Truly, the child is the father,—indeed, the master,—of the man, to a degree hard to appreciate except for those who have taken the great amount of pains required for following the literature of these researches of which I speak to-night.[9] Not only is the policy of the lifetime often dictated once for all in childhood, but this fact itself is often erased from memory, that is, it is repressed, and the results of an early misjudgment are then accepted as if assumed to be governed by an intelligence cognizant of facts and tendencies of which in reality it knows nothing.

To summarize once more what I have said: Nervous invalidism, in the sense in which I now mean that term, is not

[9] It would be obviously impossible even to indicate here the mischances which often come with the later years of childhood, when curiosity and fantasy become active; still less those which attend the oncoming and course of adolescence.

only a source of suffering: it is also a sign that those who suffer from it cling—unwittingly but under the pressure of strong instincts—to modes of thought and feeling which should be recognized as belonging to childish stages of development. The mode of action of this tendency is subtle, but a crude illustration of the principle indicated is given in the obvious fact that depression and feelings of weakness and incapacity, painful though they are, are often made to serve as self-indulgent and childish self-excuses from effort, and as means of exciting self-pity and the attention from others which almost all children so much crave. The simple recognition of this tendency is, however, not competent to banish it from the mental life of the adult; the whole chain of experiences and shifting emotions which led to the habit must be laid bare and scrutinized. It is, then, found that men sometimes allow themselves even to fall sick, or to suffer pain, or to adopt some species of asceticism or of morbid self-depreciation, for the reason that behind these symptoms and tendencies there lurks often a desire for self-gratification of a childish type the real root of which can usually be revealed in detail, and must be revealed if a radical cure is to be obtained. In the case of neurotic phobias, it is, essentially, himself, not the supposed source of terror, that the patient mainly fears. So, too, morbid introspection is largely a search for emotional excitement, the desire for which only disappears when its true nature is clearly exhibited by the aid of a deep-going introspection of a totally different, a more wholesome and more rational sort, through which we see ourselves, no longer as unfortunate individuals, but as companions in arms in the great march of social progress; as akin, perhaps, with those whom we had called sinners, and had pitied at long range, but akin also with men of devotion and force, whose characteristics we can discover to have been won by conflicts like our own.

Broadly speaking, it may be said that every man has had, theoretically, at his birth, the capacity of developing, under favorable conditions, in such a way that he would have become

possessed of a fairly well-balanced character, and that this capacity was the best element of his birthright. The conditions required for this development may have been such as it would have been extremely hard, even impossible, to secure at the outset, but in the psycho-analytic method we have a means of readjustment, difficult of application, it is true, but through the aid of which at least a certain number of those who have gone seriously astray may be restored to reasonable health. But for this purpose they must teach themselves to review their adolescence, their childhood, and their infancy, and thereby strip off the veils by means of which their ease and pleasure-seeking instincts had sought to conceal them from themselves.

The game is worth the candle, for, in my estimation, no disease from which men suffer causes, in the aggregate, so much misery as the fears, the obsessions, the compulsions, the needless weaknesses, the innumerable faults and vices of character, by which we see ourselves surrounded. All these ills spring virtually from three sources,—inherited tendencies, the failure duly to recognize our spiritual origin and destiny and the obligations which this recognition should impose on us, and the absence, during our development, of the conditions necessary for the successful making of the journey from infancy to adult life.

It is very important to note that the infant starts on his journey of life with a series of instincts, motives and inhibitions which are less strongly unified than are those of the adult. He does not at once feel the intense repression and directive force of public opinion which is to be reflected later by his mother and his nurse. Each sensation, each inclination to seek the renewal of a gratification once felt, he must take at first, at least relatively, in or for itself and at its face value. Until the necessity is felt for the subordination of some impulses and the emphasis of others (those which are necessary for reproduction) as entitled to a relative primacy, the infant's tendencies might be compared to a set of loose threads

of differently colored worsteds, lying side by side or crossing each other more or less at random, but not yet woven into a chosen, much less a beautiful pattern. The accomplishment of this latter task would mean health.

Nervous illnesses and faults of character arise largely as the primary or secondary results of the failure on the part of the forces of civilization, brought to bear on this or that individual child, to set the intricate machinery in action which should weave his threads into a good pattern. We need not now inquire where the fault lies; the main question is as to the effect. Let it be assumed that some special sort of gratification is too strong to be lightly abandoned in the child's mind in favor of the sort of subordination and co-operation offered by the oncoming years; or, to make the facts and argument seem more familiar, let it be assumed that the individual is drawn by some instinct to remain a child, with a child's egotism, longings, whims, propensities, and a child's world of dreams and fancies.

I hardly know, though I might guess, how strongly this audience feels sympathetic to these Freudian doctrines. I do know, however, how I once felt myself. I well remember my own first attempt and failure—perhaps fifteen years ago—to grasp the real thought of Sigmund Freud, then a little-known physician, now deserving to be ranked as a great leader, and honored as we honor such men as Charcot, Hughlings Jackson and Pierre Janet.

I was glancing over a copy of the *Neurologisches Centralblatt* at a friend's house, when my eye was attracted by a bold claim concerning an asserted common origin for all the psychoneuroses. The paragraph stated that these neuroses never arose except on the (partial) basis of some disturbance of the sexual life and that the differences in the character of the symptoms, as, for example, between hysteria and neurasthenia, were determined largely by the period of life at which this or that disorder of the sexual life set in. I was impressed by the boldness and confidence of the statements, but rashly

attributed these qualities to eccentricity and perhaps notoriety-seeking on the part of the writer, and laid the paper down with a distinct feeling of disgust: the reasoning, I thought, could not be correct.

How different are my sentiments at present, now that through three years' hard work I have learned what these statements really mean; have made the personal acquaintance of the author of them and his supporters, and have discovered what a treasure-house of facts respecting the deep currents of human life they have amassed. I have come to believe that if we had the power and the will to turn inward the searchlight of self-knowledge on a large scale, there would be far less prejudice and cruelty in the world than there is at present; far less envy, jealousy and suspicion; far less terror, disappointment, depression of spirits and suicide; far less disorders of the nervous system; far less inability to realize our best destinies. The whole great drama of life is played—in embryo as one might say—within the mind and heart of each and every individual, before he sees it played,—for the first time as he thinks,—on the larger stage of the social world around him; and this fact is worth our knowing.

To bring about an advance in these directions, an advance in the prophylactic education of the child, an advance in the better understanding and treatment of neurotic invalids, would be well worth all the vast labor expended, or to be expended, on these investigations. It is not for the purpose of humbling ourselves that we need to scrutinize our repressed thoughts. There is little need of final judgments, but much need of freeing ourselves through wider knowledge from the unseen chains that restrain the freedom of the reason and the will.

ILLUMINATING GAS AND THE PUBLIC HEALTH *

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IN the days of William Harvey there was no such thing as illuminating gas. One of the most striking passages in the "Intellectual Development of Europe," by Dr. John W. Draper—a New York medical man, who was also a brilliant historical writer—contrasts unfavorably the unlighted streets of Harvey's London with those of Moorish Cordova, which, six hundred years earlier, were well illuminated: "Cordova [about the tenth century] boasted of more than two hundred thousand houses and more than a million of inhabitants. After sunset a man might walk through it in a straight line for ten miles by the light of the public lamps. Seven hundred years after this time there was not so much as one public lamp in London."

Illuminating gas derived from the distillation of bituminous coal was first used in a few private houses and factories at the end of the eighteenth century and for cities early in the nineteenth century. A centennial celebration of this latter event was held in Philadelphia in March, 1912. In the cities of the United States gas did not become a common illuminant until about 1850, but by 1855, according to Dr. Samuel Eliot, the father of President Eliot, there were several hundred gas companies in successful operation in America. The revolution wrought by the substitution of gas for oil for lighting purposes and the reluctance of some to exchange gas for electricity are pleasantly touched upon by Stevenson in his well-known sketch in "*Virginibus Puerisque*" entitled "A Plea for Gas Lamps."

* Delivered November 25, 1911.

From the beginning until about 1880 there was only one principal kind of illuminating gas for cities and towns, namely, that made by distilling bituminous coal and hence properly called "coal-gas." But about 1880 a new kind, known as "water-gas," was invented, which has since, to a large extent, displaced coal-gas for illuminating purposes.

Water-gas is not made from bituminous but from anthracite coal, and not by distillation, but by passing steam (the vapor of water) upward through retorts filled with glowing coal (carbon). The hot carbon (C) decomposes the water (H_2O) and combines with its oxygen (O), setting free its hydrogen. But since there is an excess of carbon in the retort and a limited supply of oxygen in the water vapor much carbonic monoxide (CO) and but little carbonic dioxide or carbonic acid (CO_2) results. The gaseous output of the retort is thus largely hydrogen and carbonic monoxide, a mixture of gases excellent for fuel, but burning with a blue flame poor for illuminating purposes. This "water"-gas must therefore be "enriched" with other gases, and for this purpose such gases are added to it by further treatment of no special interest to sanitarians. The end result is a gas of fair illuminating and heating quality, containing a large percentage of the well-known and highly poisonous carbonic monoxide (CO). At least three times as much of this deadly poison is usually present in the water-gas as in the coal-gas sold in Massachusetts, but there is reason to believe that the water-gas is far more than three times as dangerous as the coal-gas—very much as a grain of morphine is far more dangerous than a third of a grain.

As soon as the new water-gas began to be introduced, in the early 80's, long-established and prosperous gas companies in Massachusetts, threatened by the innovation and looking about for weapons of defence, seized upon and exploited the fact that water-gas was rich in poisonous gases and hence dangerous to the public health; and from that time forward, for this and other reasons, the illuminating gas question has become a public health question.

In 1885 an article bearing the same title as the present paper appeared in the *Annual Report of the State Board of Health, Lunacy, and Charity of Massachusetts.* It was carefully prepared by the able Secretary of the Board, the late Dr. Samuel W. Abbott, and the reason for its appearance at that time was the recent perfection of a simple and convenient patented process for the manufacture of the new kind of illuminating gas, then and since known as "water"-gas. This was placing upon the market an illuminating gas easier and often somewhat cheaper to make, and ranking higher in candle power, than the ordinary coal-gas derived by the distillation of bituminous coal, but a gas also much more heavily charged with carbonic oxide (CO). Promoters of the new process naturally urged its adoption upon the old and established gas companies, which in some cases began to make use of it, especially for supplementary supplies, but in other cases, particularly if they were already prosperous, refused to have anything to do with it. Advantage was also taken of the water-gas process to form new and competing companies, charters being sought on the promise of lower prices and higher candle power for gas. Attempts were likewise made to buy out at low prices long-established and prosperous companies occupying inviting territory, by threats of invasion and competition with gas of lower price and higher candle power.

In Massachusetts, a comparatively thickly settled and therefore attractive territory for the manufacture and sale of gas, there were in the early 80's many and prosperous gas companies, and these for the most part, under the leadership of the largest—the Boston Gas Company—refused to adopt the new process or to be frightened by threats of competition into selling out at low prices. But when the water-gas interests undertook to obtain charters in Massachusetts for new and competing companies, they encountered a formidable obstacle in a statute (enacted in 1880) forbidding the distribution and sale of illuminating gas containing 10 per cent. or more of

CO. This law it was therefore necessary to have annulled before the new process could be introduced into that State.

A battle royal for the repeal of the law now began between the older coal-gas companies on the one side, who did not care to pay for or use the new process, or did not desire to sell out to the new companies, or did not want competition, and those newer companies which for one reason or another wished to enter Massachusetts territory and sell and distribute water-gas containing more than 10 and often as much as 30 per cent. of carbonic oxide. Popular attention was drawn by the old gas companies to the sanitary aspects of the question, and the battle before long raged fiercely around the question of the public health. Meantime the State Board of Health, Lunacy, and Charity referred the mooted question of the relative poisonous properties of the two gases, coal-gas and water-gas, for investigation to two professors of the Massachusetts Institute of Technology—one, the eminent sanitary chemist, the late William Ripley Nichols, and the other, then a physiologist, the present author. These investigators soon after made a report, based upon extensive experiments upon animals, showing, as might have been expected, that much greater danger exists in water-gas than in the ordinary coal-gas (*Report of Massachusetts State Board of Health, Lunacy, and Charity, for 1885,* p. 275). In the same report Dr. S. W. Abbott, then Secretary of the Board and an excellent statistician, published the paper already referred to above, in which he showed that for the preceding 20 years there had been but four deaths from gas poisoning in Massachusetts and predicted many more if the 10 per cent. limit should be abandoned.

Victory in the Legislature rested for a time with the older companies. But in 1888 the Gas Commissioners (who had been created in 1885) were empowered to license certain companies to make and sell water-gas for illuminating purposes; and in 1890 the 10 per cent. statute was repealed, because meantime the opposition of the older companies was for one reason or another relaxed, while the State Board of Health (as it was

now and had since 1886 been called) made no effective objection. Commercial conditions had changed, and many of the coal-gas companies now wanted the privilege of making water-gas if it suited their convenience. Moreover, water-gas was being widely used in other States without public protest, and when the commissioners recommended the change it was speedily made by the Legislature—with what obviously disastrous consequences to the public health we shall learn in the present paper. Of the unobserved and perhaps imperceptible consequences, such as diminution of vital resistance and increased susceptibility to disease either constitutional or infectious, we have, and in the nature of the case can have, no exact knowledge. There is reason to believe, however, that here also the consequences, if less disastrous, have been no less real.

MORTALITY FROM ILLUMINATING GAS POISONING IN MASSACHUSETTS: MORE THAN 1200 DEATHS IN THE LAST 20 YEARS

It was predicted by the investigators employed by the State Board in 1884 and reaffirmed by Dr. Abbott in 1885, that if water-gas should replace coal-gas in Massachusetts the consequences to the public health would probably be dangerous if not disastrous. Other experts of equal or greater eminence took precisely the opposite ground and even ridiculed the possibility of any such consequences. Among these were Professor C. F. Chandler, of Columbia University, and the distinguished English chemist, Dr. E. Frankland, who stated in a letter read during these hearings: "I have no hesitation in saying that it (water-gas) may be used with safety both in public buildings and private houses. I should be delighted to substitute this pure and powerful illuminating agent for the gas with which my house in London is at present supplied, although it is used in all the bedrooms."

More than a quarter of a century has since gone by and there are now available for study the results of a considerable, though by no means total, replacement of coal-gas by water-

gas during a period of about 20 years (1890-1909). The author of the present paper and one of his associates, Mr. Franz Schneider, Jr., have accordingly undertaken a careful inquiry to see how far the predictions referred to have come true. The problem is of course complicated by the fact that in spite of the legislative permission to manufacture and distribute water-gas, this has by no means wholly displaced coal-gas. The results at hand, originally published in the *Journal of Infectious Diseases,* vol. ix, No. 3, 1911, are therefore not such as we might have obtained if the replacement had been complete. Since 1890 some companies have made only water-gas; others, only coal-gas; many have made a mixture of the two, and some have made each intermittently. Still, the broad fact remains that an increasingly larger amount of the poisonous gas, CO, has been distributed since 1890 than before that date and not only absolutely but relatively to the population. The matter is further complicated by the use of illuminating gas for suicide, a subject which requires, and in the present paper will receive, special consideration and discussion.

One good result of the long and active agitation in Massachusetts was that a State Gas Commission had been provided for in 1885. Another was that in 1888 the Gas Commissioners were required to investigate, keep a record of, and report all deaths (or injuries to health) from gas poisoning within the State. From 1888 onward, therefore, we have for Massachusetts a fairly complete report of fatalities and other consequences of gas poisoning, and one probably far better than any possessed by any other State. It is perhaps the only record of the kind existing anywhere. Fortunately we have also, for the same period, the returns of the Medical Examiners concerning deaths from illuminating gas—a body of experts whose opinions possess expert value.

We have taken for study the *fatalities,* only, from gas poisoning. Of the numerous injuries which do not result fatally we have, and can have, no complete record. Some are

reported by the Gas Commissioners, but many are never reported at all and many less striking and seemingly transient effects, such as headache or malaise, are neither heard nor even thought of as due to gas poisoning.

As stated above, we have obtained the records of death from gas poisoning in Massachusetts from two sources, namely,

TABLE A.

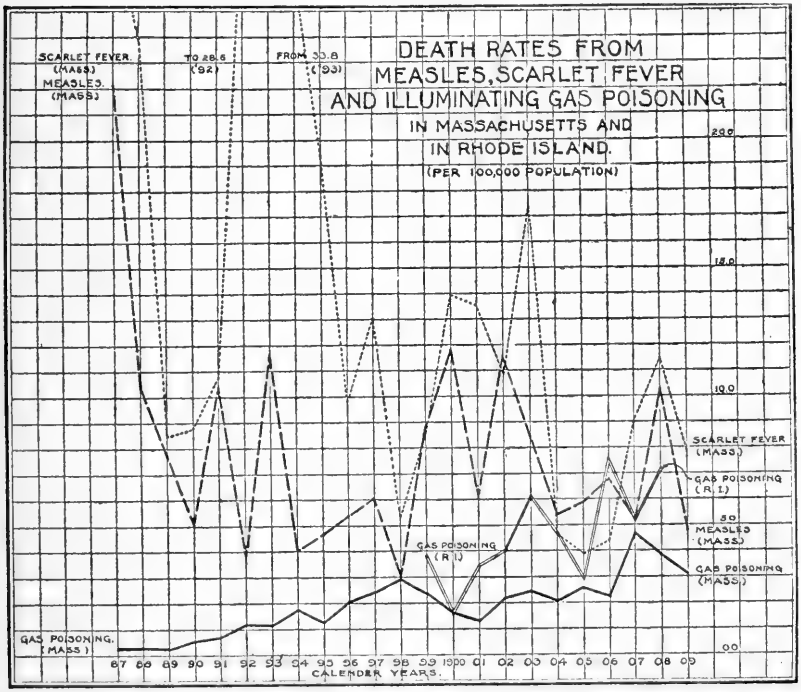
DEATHS FROM ILLUMINATING GAS POISONING IN MASSACHUSETTS. (1886–1909.)

Years Ending Dec. 31.	Medical Examiners' Returns.	Gas Commissioners' Returns.
1886	5	0
1887	6	0
1888	6	0
1889	5	2
1890	12	10
1891	16	14
1892	28	18
1893	27	25
1894	43	33
1895	31	26
1896	52	51
1897	63	58
1898	78	77
1899	65	65
1900	45	46
1901	37	37
1902	63	62
1903	71	72
1904	61	59
1905	77	72
1906	68	71
1907	147	145
1908	123	115
1909	102	99
Totals	1,231	1,157

the reports of the Gas Commissioners, and the returns of the Medical Examiners. The former are published in the Commissioners' *Annual Reports,* the latter in the *State Registration Reports.* The Gas Commissioners' records we owe to a provision of the law already referred to, permitting the use of water-gas, but at the same time requiring all gas companies to

return to the Commissioners a written report of any death or injury due to gas distributed by the company in question. On the whole this arrangement has worked out fairly well, although in the early years the Commissioners complained with reason that some deaths were not reported. The Commissioners' records begin with the year 1886 and it is interesting to note that poisoning by illuminating gas did not earn itself

CHART I.



a separate place in the classification of deaths reported by the Medical Examiners until that same year. The figures of the latter are also available, therefore, since 1886. For data previous to 1886 we have only Dr. Abbott's valuable paper of 1885.

The table now given (Table A) shows side by side the figures derived from the two independent sources mentioned.

These data are for the *calendar* year indicated, and include only deaths from poisoning by illuminating coal-gas and water-gas. Deaths from oil gas or acetylene gas and deaths caused by gas explosions, or from burning by gas, have been excluded.

The table shows substantial agreement in the two sets of data, especially in the later years. The Medical Examiners' figures are probably the more accurate.

Some of the salient features of this table are the sharp rise beginning in 1890 from a very low previous level and continuing to a high maximum in 1898, with a fall to a lower level in 1901, followed by a rebound which in 1907 reached the highest point in the entire table. From five or six deaths each year before 1890, the number rose to 147 deaths from poisoning by illuminating gas in 1907. Previous to 1885, according to Dr. Abbott, there had been only four deaths during 20 years.

The same fluctuations which appear in this table may be seen in more graphic form, but as death *rates,* in the lowest curve—the heavy black line marked "Gas Poisoning, Mass."—on Chart I.

Variations corresponding more closely to those in Table A may also be seen upon Chart II in the heavy black line marked "Deaths by Gas Poisoning." It should be noted, however, that the correspondence of these data is not exact in all cases, since the figures in the table above and the curve on Chart I represent *calendar* years and rates, while the heavy black line on Chart II represents actual deaths and years ending *June* 30. The highest point of the line on Chart II thus falls in 1908 and not as on Table A and Chart I, in 1907.

SOME DEATH RATES FROM SCARLET FEVER, FROM MEASLES AND FROM ILLUMINATING GAS IN MASSACHUSETTS AND IN RHODE ISLAND

We can best realize the growing importance of illuminating gas as a cause of death by comparing its mortality rate for a period of years with the death rates from such familiar dis-

eases as scarlet fever and measles in States having trustworthy vital statistics. For this purpose we have computed the following statistics for two such States, namely, Massachusetts and Rhode Island:

TABLE 1.

DEATH RATES FROM SCARLET FEVER, FROM MEASLES AND FROM ILLUMINATING GAS IN MASSACHUSETTS AND IN RHODE ISLAND.

(Per 100,000.)

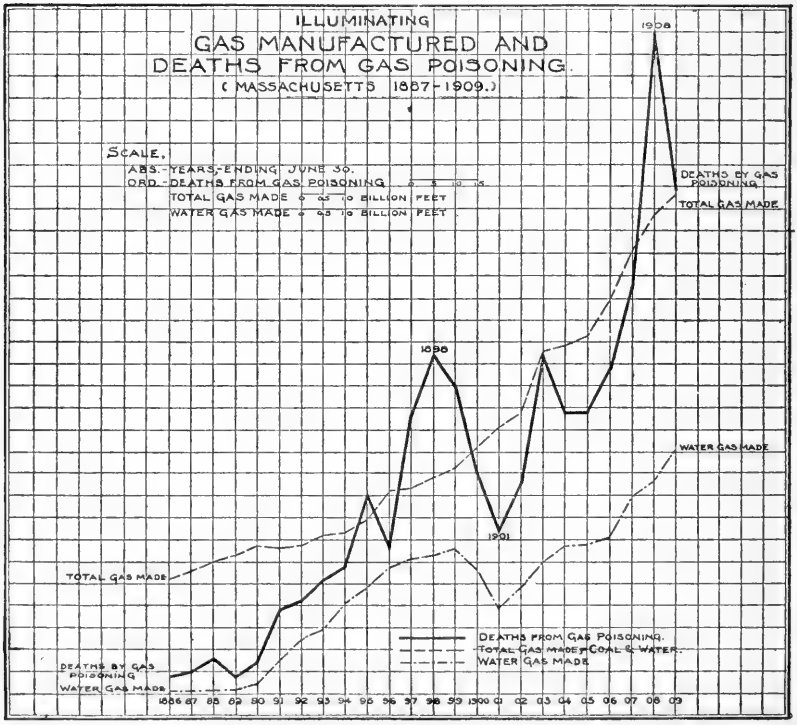
Calendar Years.	Scarlet Fever (Mass.)	Measles (Mass.)	Illuminating Gas (Mass.)	Illuminating Gas (R. I.)
1887	28.80	22.08	0.29	
1888	23.78	10.33	0.29	
1889	8.49	7.85	0.23	
1890	8.76	5.09	0.54	
1891	10.74	10.31	0.70	
1892	28.56	3.76	1.19	
1893	33.80	11.52	1.13	
1894	26.51	4.00	1.76	
1895	19.31	4.63	1.24	
1896	9.73	5.35	2.03	
1897	13.05	6.03	2.40	
1898	5.25	2.05	2.91	
1899	8.56	8.78	2.37	
1900	13.94	11.77	1.60	1.63
1901	13.52	6.03	1.30	3.42
1902	10.84	11.53	2.18	4.01
1903	17.42	8.44	2.43	6.10
1904	4.65	5.39	2.06	4.69
1905	3.90	5.89	2.56	1.92
1906	4.39	6.76	2.21	7.50
1907	9.04	5.18	4.67	5.15
1908	11.46	10.27	3.82	7.15
1909	7.86	4.77	3.10	

Table 1 shows strikingly how important poisoning by illuminating gas has recently become as a cause of death in Massachusetts and in Rhode Island; and the same facts are displayed graphically by the diagrams on Chart I (p. 107). The death rate from the two contagious diseases (scarlet fever and measles) has evidently greatly declined, while that from illu-

minating gas poisoning has greatly increased, so much so that the latter bids fair soon to exceed the former.

The death rate from poisoning by illuminating gas was higher in Massachusetts in 1907 than from scarlet fever in 1905 and 1906, while in Rhode Island the death rate from illuminating gas from 1903 to 1907 was at times higher than

CHART II.



that in Massachusetts from either scarlet fever or measles. Poisoning by illuminating gas has evidently become in Massachusetts and in Rhode Island a cause of death nearly as effective as is scarlet fever or measles. It has of late years claimed as many victims as has typhoid fever in some American and many German cities.

AMOUNTS AND KINDS OF ILLUMINATING GAS MANUFACTURED IN MASSACHUSETTS (1886–1909)

The following table (Table 2), the main features of which appear also on Chart II, p. 110, shows the amounts of total illuminating gas (coal-gas and water-gas) and of water-gas manufactured in each year in Massachusetts. The data are derived from the Annual Reports of the Gas Commissioners.

TABLE 2.

AMOUNTS OF ILLUMINATING GAS MADE AND OF WATER-GAS, AND DEATHS FROM ILLUMINATING GAS IN MASSACHUSETTS.

(1886–1909.)

Years Ending June 30.	Total Coal- and Water-Gas Made (Million Cu. Ft.)	Water-Gas Made (Million Cu. Ft.)	Deaths from Illuminating Gas.
1886	2,625	12	...
1887	2,765	28	5
1888	3,010	47	8
1889	3,156	78	4
1890	3,346	212	7
1891	3,300	777	19
1892	3,370	1,231	21
1893	3,594	1,467	26
1894	3,671	2,022	29
1895	3,955	2,413	45
1896	4,639	2,876	33
1897	4,731	3,090	63
1898	4,901	3,167	77
1899	5,120	3,265	70
1900	5,608	2,881	50
1901	6,059	1,961	37
1902	6,372	2,400	48
1903	7,776	2,989	78
1904	7,882	3,335	64
1905	8,126	3,373	64
1906	8,902	3,536	74
1907	9,998	4,471	92
1908	10,902	4,862	148
1909	11,360	5,518	114

The same facts are depicted graphically upon Chart II, which deserves and will repay careful study. The apparent discrepancy between these data of deaths and those given on other tables is due to the fact that the " years " end here on June 30, and not as in the other cases on December 31.

A COMPARISON OF MORTALITY FROM ILLUMINATING GAS IN MASSACHUSETTS WITH AMOUNTS AND KINDS OF GAS MANUFACTURED

From Table 2 and Chart II it appears that the total quantity of illuminating gas made in Massachusetts has, on the whole, increased rather steadily, year by year, since 1886. Once only has there been a slight decrease (in 1891) and at times (as in 1896, 1903, 1906, 1907, and 1908) the increase has been very rapid. The curve on Chart II shows also on the whole a much more rapid annual increase of output in the later than in the earlier years.

The total quantity of water-gas made shows likewise, on the whole, a great increase since its distribution for illuminating purposes became legally possible in 1890. But the water-gas curve, though approximately parallel to the total gas curve for the years since 1901, was not so before that time. On the contrary, from 1890 to 1896 it was rising much more rapidly; from 1899 it was nearly parallel; and from 1899 to 1901 it declined sharply, whereas the total gas production increased more rapidly than before.

The third line on Chart II, the heavy black line, shows the deaths, year by year, from illuminating gas in Massachusetts, and, like the other two lines, it shows on the whole a great increase since 1890. It is, however, much less regular in form, and the increase which it shows is much greater than that shown by the other two lines. To the line of total gas production it shows only the most general relation of rapid increase, and that only with numerous and striking exceptions of departure, as in 1896, 1899, 1900, 1901, 1904, 1905, and 1909. If the number of deaths had merely increased *pari passu* with the total amount of gas manufactured, we must have supposed that the poisonous quality of the gas had remained constant and the habits of the consumers unchanged. But this is clearly not the case. The deaths increased very much more rapidly from 1890 to 1898 and from 1901 to 1908 than did the total amount of gas made, while from 1898 to 1901 and from 1903 to 1906 deaths actually decreased while total gas production

increased. We are therefore driven to seek some other explanation for the great increase of deaths from illuminating gas than the mere expansion of the industry and the increasing use of gas.

For an explanation we need not look far. If, instead of comparing the death curve with the curve of total illuminating gas, we compare it with that of water-gas made, we find a remarkable, though not a perfect, general correspondence. Except in 1896, 1899, 1904, and 1909, this general correspondence is close and striking, both curves rising and falling together, though often at different rates. The general increase in deaths, barring the exceptional years noted, may therefore be readily explained by the general increase in the amount of water-gas made.

From 1898 to 1908 the amount of total gas made had doubled, while the fatalities had not quite done likewise. But while the quantity of total gas made increased about fivefold from 1886 to 1908, the fatalities increased nearly thirty fold. At the same time we find the variations in the amount of water-gas manufactured coinciding much more nearly with the fluctuations in the number of deaths. The remarkable increase of such deaths in 1891 corresponds with the first appearance of any large amount of water-gas. And when the deaths reached a maximum in 1897–99 water-gas had reached a percentage proportion of the total output which it has never equaled either before or since.

In 1900 the New England Gas and Coke Company installed a large coal-gas plant in Everett, and the effect of the introduction of their product into the illuminating gas of the Metropolitan District was to produce an actual decrease for three or four years in the total amount of water-gas manufactured in the State. It is noteworthy and significant that this decrease corresponds closely with the low phase of 1901 in the curve of deaths by gas poisoning. But, as indicated by the diagram, the natural growth of the gas industry soon called for more gas. The check to the production of water-gas in

1901 was only temporary, and the increased output since 1901 has been attended by a corresponding increase in deaths from gas poisoning.

In consideration of all these facts we are warranted in concluding that the amount of water-gas produced stands in some close relation to the number of deaths by illuminating

TABLE 3.

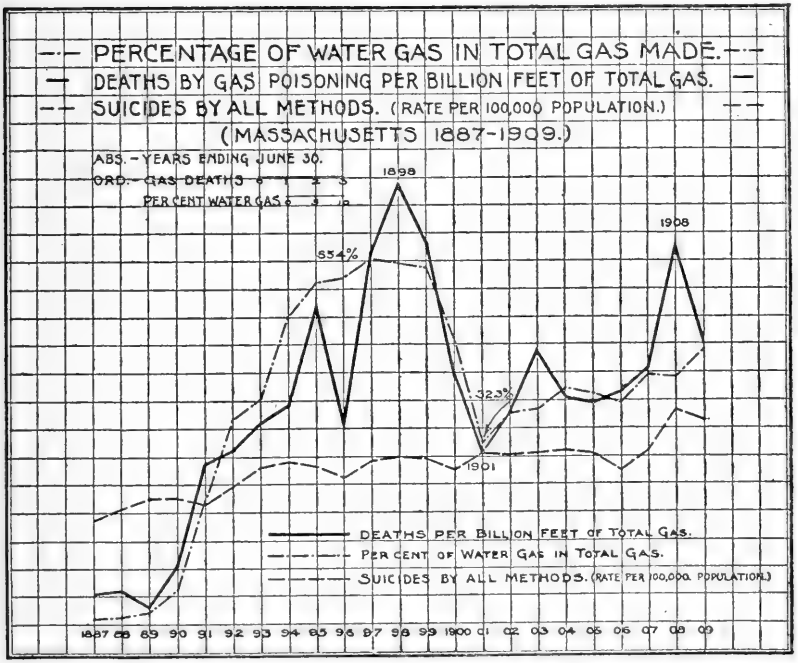
PERCENTAGE WHICH WATER-GAS MADE WAS OF TOTAL ILLUMINATING GAS MADE, AND DEATHS PER BILLION CUBIC FEET OF TOTAL ILLUMINATING GAS MADE (MASSACHUSETTS, 1887–1909).

Years Ending June 30.	Percentage of Water-Gas Made to Total Gas Made	Deaths per Billion Cubic Feet of Total Gas Made
1887	1.01	1.09
1888	1.56	1.17
1889	2.43	0.64
1890	6.34	2.10
1891	22.20	5.76
1892	36.60	6.24
1893	40.80	7.24
1894	55.00	7.90
1895	61.00	11.39
1896	62.00	7.12
1897	65.40	13.31
1898	64.60	15.70
1899	63.80	13.67
1900	51.40	8.92
1901	32.30	6.11
1902	37.70	7.54
1903	38.40	9.78
1904	42.30	8.12
1905	41.30	7.88
1906	39.70	8.31
1907	44.70	9.20
1908	44.50	13.57
1909	48.60	10.05

gas. This conclusion is justified and confirmed by a comparison of the percentage which water-gas formed of the total gas manufactured, with the deaths per billion feet of total gas produced. If the water-gas is really to blame, the larger the percentage of water-gas the more dangerous should be each unit of the resultant product. On the other hand,

by dividing the deaths from gas poisoning by the total amount of gas made, we should obtain a measure of the poisonous effect of a unit of the total gas. In other words, if the theory that water-gas has been the primary cause of the deaths by gas poisoning is true, we should expect to find some general agreement between the percentage of water-gas to total gas made, and deaths by gas poisoning for each unit, such as a

CHART III.



billion feet, of total gas made. That such agreement actually exists appears from Table 3 and its corresponding chart (Chart III).

Table 3, and especially Chart III, shows a remarkable concordance between the percentage of water-gas manufactured year by year and the corresponding death rate (ratio) from illuminating gas per billion feet of total gas made. In spite

of some differences (as, for example, 1896, 1904, 1906, 1908, 1909), it is difficult to avoid the conclusion that the water-gas curve and the death curve stand in the relation of cause and effect.

The agreement between the variations in the percentage of water-gas made and the number of deaths year by year is obviously not absolute, but when we reflect upon the actual conditions under which water-gas is made and distributed, we may well be surprised that the agreement is as close as it is. For illuminating gas is sold in Massachusetts by many companies and under a great variety of conditions. Some companies distribute only coal-gas and some only water-gas, but most distribute a mixture of the two. And this mixture may vary widely from time to time in the percentage of the two gases. Again, there is, as we shall learn below, a marked seasonal variation in the deaths from illuminating gas, and there is good reason to believe that the mildness or severity of Massachusetts winters may cause annual as well as seasonal variations in the mortality from gas poisoning. These various factors naturally forbid any absolute correspondence between the amount of water-gas made and the deaths from gas poisoning. When we consider this great variety of circumstances, the wonder is, not that the two curves occasionally differ, but that they run so nearly parallel.

THE USE OF ILLUMINATING GAS IN MASSACHUSETTS FOR PURPOSES OF SUICIDE

Since 1890 illuminating gas has been gradually discovered by the public to be a convenient and effective means of suicide. Whereas before that time it was very difficult to commit suicide by the use of illuminating gas, and probably very few would-be suicides resorted to its use, it has come of late years to be one of the easiest and surest agents of self-destruction. The reports of the Medical Examiners contain ample evidence of this fact.

Table B, prepared by us from the returns of the Medical

Examiners, shows not only the use, but the increasing use, of illuminating gas for purposes of suicide. At the same time this table is a sufficient answer to those who have the assur-

TABLE B.

DEATHS FROM ILLUMINATING GAS POISONING (MASSACHUSETTS, 1886–1909). (Medical Examiners' Returns.)

Years Ending June 30	Accidental Deaths	Suicidal Deaths	Total Deaths
1886*	1	1	2
1887	4	1	5
1888	7	1	8
1889	2	2	4
1890	5	2	7
1891	18	1	19
1892	9	12	21
1893	7	9	26
1894	14	15	29
1895	28	17	45
1896	20	13	33
1897	47	16	63
1898	48	29	77
1899	35	35	70
1900	35	15	50
1901	11	26	37
1902	9	39	48
1903	47	30	77
1904	29	35	64
1905	41	23	64
1906	35	39	74
1907	41	51	92
1908	55	93	148
1909	43	71	114
1909†	23	31	54
Totals	624	607	1,231

*First six months. †Second six months.

ance to proclaim that, excepting as it is used by suicides, water-gas is no more dangerous to life than is coal-gas.

Of the 1231 deaths by gas poisoning reported by the Medical examiners in the years 1886–1909, 607, or 49.4 per cent., were reported by them to be suicides and the remainder acci-

dental deaths. Table B gives these data in detail for the separate years.

We have also computed, for the same period, the death *rates* from illuminating gas and those by illuminating gas from accidental sources and from suicidal sources, as reported by the

TABLE 4.

DEATH RATES FROM POISONING BY ILLUMINATING GAS AND FROM ACCIDENTAL AND FROM SUICIDAL POISONING BY ILLUMINATING GAS (MASSACHUSETTS, 1887–1909).

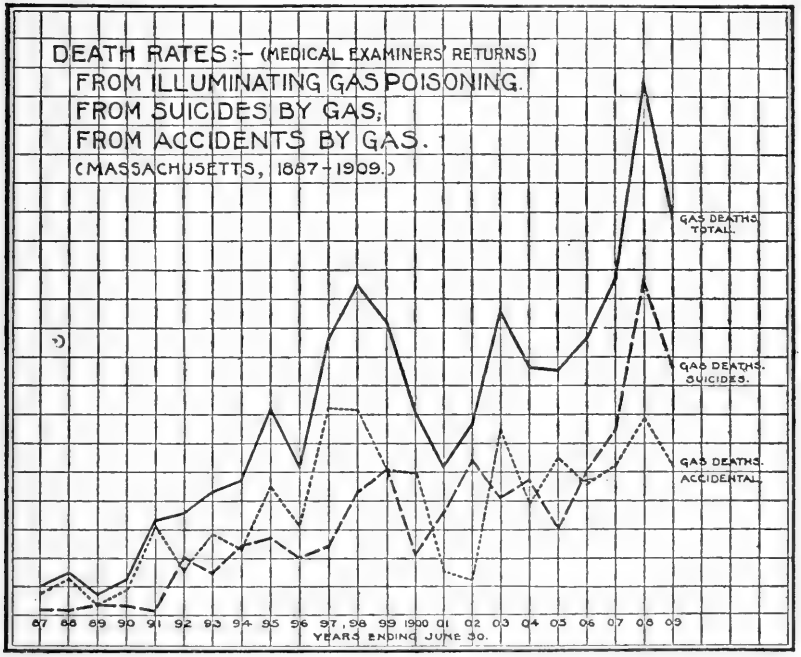
(Medical Examiners' Returns.)

Years Ending June 30	Gas Deaths (Totals)	Gas Accidents	Gas Suicides
1887	0.251	0.19	0.5
1888	0.381	0.33	0.05
1889	0.180	0.09	0.09
1890	0.31	0.22	0.09
1891	0.831	0.79	0.04
1892	0.690	0.33	0.51
1893	1.034	0.71	0.38
1894	1.184	0.57	0.61
1895	1.804	1.12	0.68
1896	1.129	0.78	0.51
1897	2.40	1.79	1.61
1898	2.87	1.79	1.08
1899	2.55	1.82	1.27
1900	1.78	1.25	0.54
1901	1.30	0.39	0.91
1902	1.66	0.31	1.35
1903	2.63	1.61	1.03
1904	2.16	0.98	1.18
1905	2.13	1.36	0.77
1906	2.41	1.14	1.27
1907	2.92	1.30	1.62
1908	4.60	1.71	2.89
1909	3.46	1.31	2.16

Medical Examiners (Table 4 and Chart 4). It is hardly necessary to repeat that these, while obviously open to the objection that they represent merely the opinion of the Medical Examiners, are the best data we have and are probably on the whole not far wrong.

It may, of course, be urged that it is often difficult even for expert medical examiners to discover whether or not a particular death was suicidal or accidental. But even if this be granted and if some deaths reported as accidents were really suicides, the reverse may likewise be true, and there is no good reason to doubt that in a large percentage of cases the Medical

CHART IV.



Examiners' returns are correct. If any reasonable doubt could exist as to the fact that many accidental deaths do occur from poisoning by illuminating gas it would be dissipated by an examination of the data shown on the following table (Table 5) and its corresponding chart (Chart V), on pp. 120–121.

This table and its corresponding plate show how sudden was the increase in 1891 of deaths from illuminating gas, an increase much more reasonably explained by increase in accidents than by increase in suicidal use of the new and as yet

generally unknown poison, especially when we observe that this increase was accompanied by a decrease in the whole number of suicides for the year. Again, in 1895, with no increase in the whole number of suicides, there was a very large increase in the number of deaths from poisoning by illuminating

TABLE 5.

DEATHS FROM SUICIDE BY ALL METHODS, DEATHS FROM ILLUMINATING GAS, AND POPULATION (MASSACHUSETTS, 1887–1909).

(Medical Examiners' Returns.)

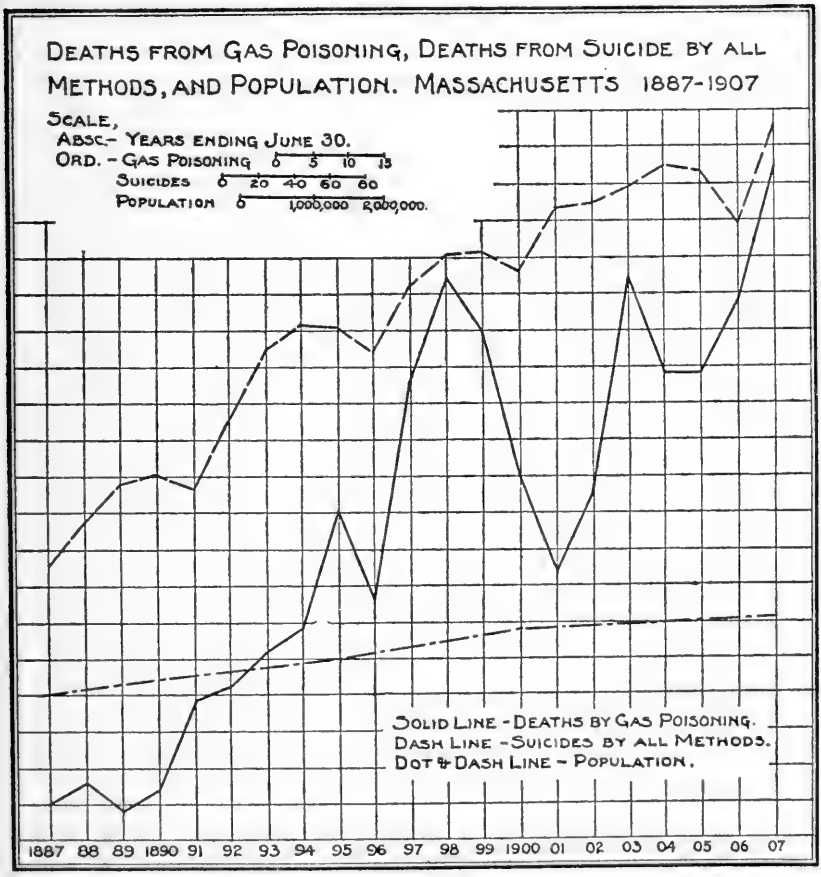
Years Ending June 30	Suicides by All Methods	Deaths from Illuminating Gas	Population of the State
1887	152	5	
1888	175	8	
1889	196	4	
1890	202	7	2,238,943
1891	194	19	
1892	231	21	
1893	270	26	
1894	284	29	
1895	282	45	2,500,183
1896	269	33	
1897	304	63	
1898	321	77	
1899	323	70	
1900	312	50	2,805,343
1901	347	37	
1902	350	48	
1903	358	77	
1904	369	64	
1905	366	64	3,003,680
1906	338	74	
1907	390	92	
1908	494	148	
1909	476	114	

gas; in 1904, while the whole number of suicides was increasing, deaths from illuminating gas decreased; while in 1906 the reverse was the case. Undoubtedly, there is on the whole a striking correspondence in the forms of the two curves, such as ought to exist when we remember that (as shown in Table B) about one-half of all the deaths in the lower line are an important factor in the upper.

A STUDY OF THE SEASONAL DISTRIBUTION OF DEATHS FROM ILLUMINATING GAS IN MASSACHUSETTS

We had not been studying the general subject of illuminating gas poisoning very long before it became plain that such poisoning bears a close relation to the seasons. And this re-

CHART V.



lation proved to be almost precisely what might have been anticipated. Deaths from illuminating gas are comparatively few in summer and comparatively many in winter, as is shown

by the first column in the following table, and by the heavy black line on the corresponding chart (Chart VI) based upon it. The reason is, of course, because in summer, with open windows, short nights, and outdoor life, people in Massachusetts are much less exposed to gas poisoning than in winter, when they are housed most of the time, often in apartments piped for gas and having little or no ventilation. Similar considerations probably make gas poisoning also largely a matter of latitude—northern cities suffering more from gas poisoning than southern cities—and likewise produce annual variations according as the winters are mild or severe.

TABLE 6.

Seasonal Distribution of Deaths from Illuminating Gas, of Deaths by Accident from Illuminating Gas, of Deaths by Suicide from Illuminating Gas, and of Suicides by All Methods (Massachusetts, 1886–1909).

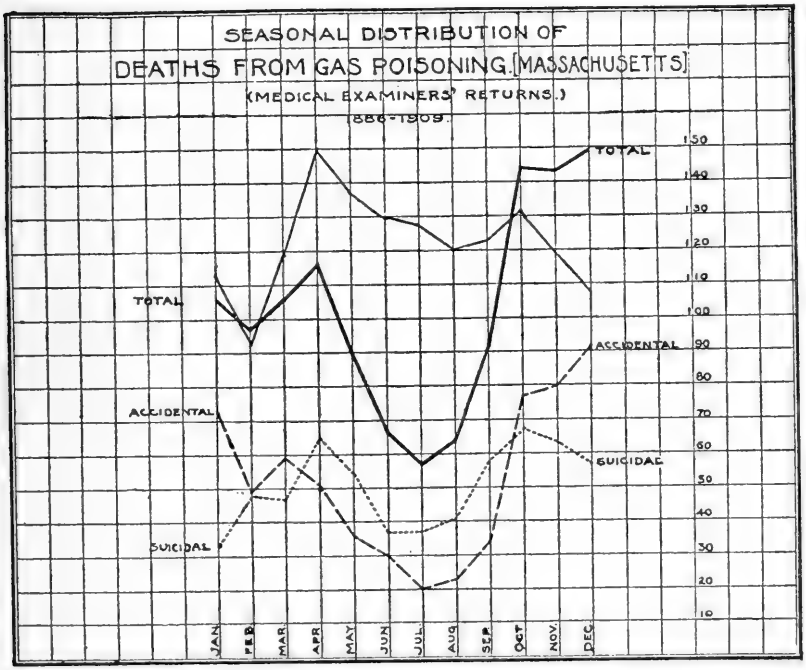
(Medical Examiners' Returns.)

Month	Total Deaths from Illuminating Gas	Accidental Deaths from Illuminating Gas	Suicidal Deaths from Illuminating Gas	Suicides by All Methods
January.....	106	73	33	568
February.....	97	49	48	462
March.....	106	59	47	597
April.....	116	51	65	749
May.....	90	36	54	686
June.....	67	30	37	647
July.....	57	20	37	634
August.....	64	23	41	603
September....	92	34	58	611
October.....	144	77	67	655
November.....	143	80	63	594
December.....	149	92	57	541

This table and the corresponding chart (Chart VI) disclose many interesting and important details. December stands out as the month of most deaths, and December is one of the months of shortest days and longest nights as well as of lowest average temperature. It is therefore one of the times of greatest use of gas, of most indoor life, and of least ventilation by open doors and windows. It is not surprising that these condi-

tions are correlated with the highest mortality from poisoning by illuminating gas. What is remarkable is that the deaths from this source were almost equally numerous in October and November, although the days are then longer, the average temperature considerably higher, and the possibility of comfortable sleeping with more open windows is much greater;

CHART VI.



while January, which in length of day and temperature closely resembles December, shows fewer deaths than does December from illuminating gas.

July, as might be expected, shows the smallest number of deaths (57), June (67) and August (64) more, and each about the same number, while September yields an increase of more than 40 per cent. over June and over August. These facts are not surprising when we reflect upon the cooler and longer

nights of June and August over those of July, and the much cooler nights—often with frosts—of September over those of June and of August. But beginning with October there is no great difference in the deaths by months until we come to January, when in spite of very cold weather and very short days we find a marked decrease of deaths from poisoning by illuminating gas, the deaths for January, February, March, April, and May differing astonishingly little.

We are aided in explaining these various figures by the fact that April and October are the months of most numerous suicides, not only by all methods (as shown by the last column in Table 6 and by the corresponding thin, solid line, without legend, on Chart VI), but also by illuminating gas; so that the curve of total deaths by illuminating gas is necessarily quite different from what it would be if it represented only those deaths due to accident, and if accidents were solely due to considerations correlated with the movement of the seasons—such as temperature and length of days—and effective ventilation. We find here, readily enough, a satisfactory explanation of the large number of total deaths in October (144) and November (143) as compared with December (149) when the deaths from suicide (both by all methods and by gas) were passing during these months from a maximum to a much lower level. The fact appears to be that while the accidental gas deaths were increasing during this quarter (as appears in Table 6 and Chart VI and as would be required by theory) the suicidal gas deaths were declining almost *pari passu;* so that a remarkably even and high total of deaths from illuminating gas was maintained during this last quarter of the year.

In the next quarter (January–March) the gas suicides were considerably fewer, as were also the deaths from accidental gas poisoning, and very likely the same explanation holds good of both these causes of death; namely, that conditions had now become comparatively endurable, those that were absolutely intolerable having already destroyed their victims or having been changed for the better. The high number of

total deaths in April appears to be chiefly due to the excess of suicides in general characteristic of that month, as does also the lower but still large number in May, when, as required by theory, the seasonal conditions do not greatly favor accidental gas poisonings and when, in fact—as shown by our figures—such poisonings are comparatively few.

It is also interesting to note, in passing, that upon Table 6, and excepting in the first quarter, a close correspondence is shown between the frequency of suicides by all methods and those by illuminating gas.

THE RELATION OF CERTAIN COMBUSTION PRODUCTS OF ILLUMINATING GAS TO THE PUBLIC HEALTH

The principal combustion products of illuminating gas are carbonic acid (CO_2), water (H_2O), light, and heat. Small, but not insignificant amounts of ammonia, sulphurous acid, soot, and other substances are also produced.

Carbonic acid, an inevitable product of all complete combustion of carbon compounds, while not a desirable addition to the atmosphere of a dwelling, a store, or a workshop, is probably, unless present in very large quantities, of but little consequence from the stand-point of health or comfort.

Water vapor, which is also copiously and inevitably produced in the ordinary combustion of illuminating gas, is probably of more importance than is carbonic acid to health and comfort. Evidence of its abundant presence may often be seen in the water upon the windows of shops, of stores, or of living rooms, upon which it condenses freely and runs down, sometimes almost in streams. The high humidity to which this testifies is often prejudicial to the comfort, and probably also to the health or working capacity, of the inmates.

The light produced by illuminating gas varies widely in amount and composition. The old-fashioned coal-gas gave an agreeable and apparently powerful yellowish light, and when those who were accustomed to it began to be served with water-gas, many found the latter bluish and less efficiently luminous. Much here depends, no doubt, upon the special

form of burner, or " tip " employed, but after all is said and done there are many—of whom the author is one—who, having lived with both kinds of gas (and with many kinds of mixtures of the two) would gladly go back to the old-fashioned coal-gas at double the present cost of gas, not only because of its greater safety, but also because of its greater and more agreeable illuminating effects.

As to the question of heat produced by combustion—a question of great economic importance for those using gas as a source of power, or for cooking or heating purposes, and of much hygienic significance for persons occupying rooms lighted by gas, it should be said that water-gas is not greatly superior to coal-gas, while, since much heat is produced by the combustion of either gas, their hygienic effects in this particular are probably not very different. Electric lighting (although open to other objections) is vastly preferable to gas lighting on the score of heat production and that of objectionable chemical products.

Among the less abundant products of the combustion of illuminating gas is sulphurous acid. Most coals used in the manufacture of gas—and hence known as " gas coals "—contain a small percentage of sulphur, some of which appears in illuminating gas as hydrogen sulphide and some as bisulphide of carbon, or other sulphur compounds. These, when burned, formed sulphurous acid, an irritating and poisonous gas. Most of the sulphur compounds in illuminating gas are, however, removed by processes of purification during manufacture, but owing to the difficulty of complete removal, 20 grains of sulphur in every hundred cubic feet have generally been allowed by law to remain in the gas distributed to the public. The 20-grain limit has prevailed in Great Britain for about half a century, and was apparently copied into American statutes when legal regulation of the quality of illuminating gas was first undertaken—in Massachusetts, for example, in 1861. And until quite recently no objection to this legal limit has been raised by the gas manufacturers or

by anyone else. A few years ago, however, the London gas companies sought to have this sulphur regulation removed, claiming that because the best gas coals are now scarce, it is much more difficult than formerly to procure coals low in sulphur, so that processes for the removal of sulphur have become more costly and really burdensome to the industry of gas manufacture. And after protracted hearings with the taking of much testimony the sulphur restrictions were, in fact, removed in England. A little later gas manufacturers in the United States and in Canada came forward with a similar demand, and in Massachusetts the legal limit for sulphur has now been raised from 20 grains to 30 grains per 100 cubic feet of gas. A complete discussion of the whole subject of the relation of the combustion products of sulphur compounds in illuminating gas to the public health would require a monograph. Suffice it to say that the testimony taken by the British Commission having the matter in charge, and by the Gas Commissioners of Massachusetts (not to mention other authorities) was voluminous, instructive, and important, and deserving of careful attention. It is the opinion of the author of the present paper that the British authorities were not sufficiently considerate of the public health aspects of the subject when they allowed all restrictions upon the sulphur content of illuminating gas to be removed, and that the Massachusetts Gas and Electric Light Commissioners acted more wisely when they declined to follow the British example, and merely relaxed somewhat the severity of the legal requirements regarding sulphur.

Illuminating gas is required by law in Massachusetts (and in many other places) to be free from ammonia as well as from sulphuretted hydrogen, but this is more because of injury to fixtures than because of danger to health.

THE PREVENTION OF POISONING BY ILLUMINATING GAS

The question naturally arises, What can be done for the protection of the public health against poisoning by illuminating gas, which as a cause of sickness and death now almost

equals in Massachusetts and Rhode Island some of the dreaded infectious and contagious diseases? We must admit at the outset that about one-half of the recorded deaths from this source are voluntary or suicidal, but while recognizing this fact we have no right to dismiss it as irrelevant to the present discussion. The State seeks, as far as possible, to prevent suicide, by laws, for example, regulating the sale of other poisons and of firearms, and may well regard with concern the general distribution to the public of a dangerous gas readily available for self-destruction.

Even more serious are the public consequences of the widespread distribution to sick and well for industrial and domestic purposes of a dangerous and highly poisonous substance, insidious in its mode of operation, quickly harmful in its effects, and delivered under such pressure that leaks are frequent. Those who have read and reflected upon the facts given in the preceding sections will hardly need to be told how prejudicial to the public health even small leaks of illuminating gas must be, especially if long continued, while the leakage or escape of larger amounts is well known to be often fatal to those exposed. The simplest and most natural remedy for these evils would be, of course, to return to the former practice of making and distributing only coal-gas instead of water-gas or a mixture of the two. But here, as so often in public health problems, a balance must be struck between industrial advantages accruing to the public in less cost, and some saving of life and health. If the industrial, economic, or efficiency gain is very great, it may justify some increase of danger to life and health. But if it is not very great, then life and health have the prior claim. In the present case it is not claimed that water-gas in Massachusetts or Rhode Island is, as a rule, much if any cheaper to manufacture than is coal-gas, but that it is very convenient to produce because more quickly made when needed. The claims of the advocates of water-gas in 1884 that this gas would furnish 24 candles of light against the 16 candles of the old-fashioned coal-gas do

not appear to have been substantiated, since most of the gas now distributed in Massachusetts equals—according to the State Inspector—only about 18 candles. The price of gas to the consumer has, however, fallen greatly since 1884, and this decrease in cost, as far as it is due to the use of water-gas, must be balanced against the damage done to the public health by the loss of more than 1200 lives and an unknown amount of less obvious injury to life and health.

Undoubtedly a mixture of coal-gas and water-gas, such as is often distributed to-day, is less dangerous than is water-gas alone, but this appears to be merely because the dangerous constituent, carbonic oxide, so abundant in water-gas, is diluted by the process of mixture; and up to a certain point, the greater the dilution, the less the danger. We know from experience that when carbonic oxide forms only about 6 per cent. of illuminating gas very little danger exists. We also know from experience that 20–30 per cent. of carbonic oxide means danger. But whether 10 per cent. or perhaps 12 per cent. might be allowed without much danger, we do not yet know. It should, however, be possible to determine by experiment the minimum amount safely allowable.

Meantime, in view of the appalling loss of more than 1200 lives which has occurred in Massachusetts since the 10 per cent. restriction upon carbonic monoxide was removed, it seems not unfair or unreasonable to demand a return to the 10 per cent. limit until such time as evidence shall be forthcoming that a higher percentage will properly safeguard the public health.

A CONSIDERATION OF THE NATURE OF HUNGER*

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"WHY do we eat?" This question, presented to a group of educated people, is likely to bring forth the answer, "We eat to compensate for body waste, or to supply the body with fuel for its labors." Although the body is in fact losing weight continuously and drawing continuously on its store of energy, and although the body must periodically be supplied with fresh material and energy in order to keep a more or less even balance between the income and the outgo, this maintenance of weight and strength is not the motive for taking food.

Primitive man, and the lower animals, may be regarded as quite unacquainted with notions of the equilibrium of matter and energy in the body, and yet they take food and have an efficient existence, in spite of this ignorance. In nature, generally, important processes, such as the preservation of the individual and the continuance of the race, are not left to be determined by intellectual considerations, but are provided for in automatic devices. Natural desires and impulses arise in consciousness, driving us to action; and only by analysis do we learn their origin or divine their significance. Thus our primary reasons for eating are to be found, not in convictions about metabolism, but in the experiences of appetite and hunger.

APPETITE AND HUNGER

The sensations of appetite and hunger are so complex and so intimately interrelated that any discussion is sure to go

* Delivered December 16, 1911. The results here stated were published in the American Journal of Physiology, 1912, xxix, 441–454.

astray unless at the start there is clear understanding of the meanings of the terms. The view has been propounded that appetite is the first degree of hunger, the mild and pleasant stage, agreeable in character; and that hunger itself is a more advanced condition, disagreeable and even painful—the unpleasant result of not satisfying the appetite.[1] On this basis appetite and hunger would differ only quantitatively. Another view, which seems more justifiable, is that the two experiences are fundamentally different.

Careful observation indicates that appetite is related to previous sensations of taste and smell of food. Delightful or disgusting tastes and odors, associated with this or that edible substance, determine the appetite. It has therefore important psychic elements in its composition, as the studies by Pawlow and his collaborators have so clearly shown. Thus, by taking thought, we can anticipate the odor of a delicious beefsteak or the taste of peaches and cream, and in that imagination we can find pleasure. In the realization, direct effects in the senses of taste and smell give still further delight. We now know from observations on experimental animals and on human beings, that the pleasures of both anticipation and realization, by stimulating the flow of saliva and gastric juice, play a highly significant rôle in the initiation of digestive processes.[2]

Among prosperous people, supplied with abundance of food, the appetite seems sufficient to ensure for bodily needs a proper supply of nutriment. We eat because dinner is announced, because by eating we avoid unpleasant consequences, and because food is placed before us in delectable form and with tempting tastes and odors. Under less easy circumtances, however, the body needs are supplied through the much stronger and more insistent demands of hunger.

The sensation of hunger is difficult to describe, but almost every one from childhood has felt at times that dull ache or gnawing pain referred to the lower mid-chest region and the epigastrium, which may take imperious control of human actions. As Sternberg has pointed out, hunger may be sufficiently insistent to force the taking of food which is so dis-

tasteful that it not only fails to rouse appetite, but may even produce nausea. The hungry being gulps his food with a rush. The pleasures of appetite are not for him—he wants quantity rather than quality, and he wants it at once.

Hunger and appetite are, therefore, widely different—in physiological basis, in localization, and in psychic elements. Hunger may be satisfied while the appetite still calls. Who is still hungry when the tempting dessert is served, and yet are there any who refuse it, pleading they no longer need it? On the other hand, appetite may be in abeyance while hunger is goading.[3] What ravenous boy is critical of his food? Do we not all know that "hunger is the best sauce"? Although the two sensations may thus exist separately, they nevertheless have the same function of leading to the intake of food, and they usually appear together. Indeed the co-operation of hunger and appetite is probably the reason for their being so frequently confused.

THE SENSATION OF HUNGER

In the present paper we shall deal only with hunger. The sensation may be described as having a central core and certain more or less variable accessories. The peculiar dull ache of hungriness, referred to the epigastrium, is usually the organism's first strong demand for food; and when the initial order is not obeyed, the sensation is likely to grow into a highly uncomfortable pang or gnawing, less definitely localized as it becomes more intense. This may be regarded as the essential feature of hunger. Besides the dull ache, however, lassitude and drowsiness may appear, or faintness, or violent headache, or irritability and restlessness such that continuous effort in ordinary affairs becomes increasingly difficult. That these states differ much with individuals—headache in one, and faintness in another, for example—indicates that they do not constitute the central fact of hunger, but are more or less inconstant accompaniments, and need not for the present engage our attention. The "feeling of emptiness," which has been mentioned as an important element of the experience,[4] is an

inference rather than a distinct datum of consciousness, and can likewise be eliminated from further consideration. The dull pressing sensation is left, therefore, as the constant characteristic, the central fact, to be examined in detail.

Hunger can evidently be regarded from the psychological point of view, and discussed solely on the basis of introspection; or it can be studied with reference to its antecedents and to the physiological conditions which accompany it—a consideration which requires the use of both objective methods and subjective observation. This psychophysiological treatment of the subject will be deferred till the last. Certain theories which have been advanced with regard to hunger and which have been given more or less credit must first be examined.

Two main theories have been advocated. The first is supported by evidence that hunger is a general sensation, arising at no special region of the body, but having a local reference. This theory has been more widely credited by physiologists and psychologists than the other. The other is supported by evidence that hunger has a local source and therefore a local reference. In the course of our examination of these views we shall have opportunity to consider some pertinent new observations.

THE THEORY THAT HUNGER IS A GENERAL SENSATION

The conception that hunger arises from a general condition of the body rests in turn on the notion that, as the body uses up material, the blood becomes impoverished. Schiff advocated this notion, and suggested that poverty of the blood in food substance affects the tissues in such manner that they demand a new supply. The nerve-cells of the brain share in this general shortage of provisions, and because of internal changes give rise to the sensation.[5] Thus is hunger explained as an experience dependent on the body as a whole.

Three classes of evidence are cited in support of this view:

1. *"Hunger Increases as Time Passes"—A Partial Statement.*—The development of hunger as time passes is a common observation which quite accords with the assumption that the

condition of the body and the state of the blood are becoming constantly worse, so long as the need, once established, is not satisfied.

While it is true that with the lapse of time hunger increases as the supply of body nutriment decreases, this concomitance is not proof that the sensation arises directly from a serious encroachment on the store of food materials. If this argument were valid we should expect hunger to become more and more distressing until death. There is abundant evidence that the sensation is not thus intensified; on the contrary, during continued fasting hunger wholly disappears after the first few days. Luciani, who carefully recorded the experience of the faster Succi, states that after a certain time the hunger feelings vanish and do not return.[6]. And he tells of two dogs that showed no signs of hunger after the third or fourth day of fasting; thereafter they remained quite passive in the presence of food. Tigerstedt, who also has studied the metabolism of starvation, declares that although the desire to eat is very great during the first day of the ordeal, the unpleasant sensations disappear early, and at the end of the fast the subject may have to force himself to take nourishment.[7] The subject, "J. A.," studied by Tigerstedt and his co-workers, reported that after the fourth day of fasting, he had no disagreeable feelings.[8] Carrington, after examining many persons who, to better their health, abstained from eating for different periods, records that "habit-hunger" usually lasts only two or three days and, if plenty of water is drunk, does not last longer than three days.[9] Viterbi, a Corsician lawyer, condemned to death for political causes, determined to escape execution by depriving his body of food and drink. During the eighteen days that he lived, he kept careful notes. On the third day the sensation of hunger departed, and although thereafter thirst came and went, hunger never returned.[10] Still further evidence of the same character could be cited, but enough has already been given to show that, after the first few days of fasting, the hunger-feelings cease. On the theory that hunger is a manifestation of bodily need, are we to suppose that, in the

course of starvation, the body is mysteriously not in need after the third day, and that therefore the sensation of hunger disappears? The absurdity of such a view is obvious.

2. *"Hunger May be Felt Though the Stomach be Full"—A Selected Alternative.*—Instances of duodenal fistula in man have been carefully studied, which have shown that a modified sensation of hunger may be felt when the stomach is full. A famous case described by Busch has been repeatedly used as evidence. His patient, who lost nutriment through the fistula, was hungry soon after eating, and felt satisfied only when the chyme was restored to the intestine through the distal fistulous opening.[11] As food is absorbed mainly through the intestinal wall, the inference is direct that the general bodily state, and not the local conditions of the alimentary canal, must account for the patient's feelings.

A full consideration of the evidence from cases of duodenal fistula cannot so effectively be presented now as later. That in Busch's case hunger disappeared while food was being taken is, as we shall see, quite significant. It may be that the restoration of chyme to the intestine quieted hunger, not because nutriment was thus introduced into the body, but because the presence of material altered the nature of intestinal activity. The basis for this suggestion will be given in due course.

3. *"Animals May Eat Eagerly After Section of Their Vagus and Splanchnic Nerves"—A Fallacious Argument.*—The third support for the view that hunger has a general origin in the body is derived from observations on experimental animals. By severance of the vagus and splanchnic nerves, the lower œsophagus, the stomach, and the small intestine can be wholly separated from the central nervous system. Animals thus operated upon nevertheless eat food placed before them, and may indeed manifest some eagerness for it.[12] How is this behavior to be accounted for—when the possibility of local peripheral stimulation has been eliminated—save by assuming a central origin of the impulse to eat?

The fallacy of this evidence, though repeatedly overlooked, is easily shown. We have already seen that appetite as well as

hunger may lead to the taking of food. Indeed the animal with all gastro-intestinal nerves cut may have the same incentive to eat that a well-fed man may have, who delights in the pleasurable taste and smell of food and knows nothing of hunger pangs. Even when the nerves of taste are cut, as in Longet's experiments,[13] sensations of smell are still possible, as well as agreeable associations which can be roused by sight. More than fifty years ago Ludwig pointed out that, even if all the nerves were severed, psychic reasons could be given for the taking of food,[14] and yet because animals eat after one or another set of nerves is eliminated, the conclusion has been drawn by various writers that the nerves in question are thereby proved to be not concerned in the sensation of hunger. Evidently since hunger is not required for eating, the fact that an animal eats is no testimony whatever that the animal is hungry, and therefore, after nerves have been severed, is no proof that hunger is of central origin.

Weakness of the Assumptions Underlying the Theory that Hunger is a General Sensation.—The evidence thus far examined has been shown to afford only shaky support for the theory that hunger is a general sensation. The theory furthermore is weak in its fundamental assumptions. There is no clear indication, for example, that the blood undergoes, or has undergone, any marked change, chemical or physical, when the first stages of hunger appear. There is no evidence of any direct chemical stimulation of the gray matter of the cerebral cortex. Indeed attempts to excite the gray matter artificially by chemical agents have been without results;[15] and even electrical stimulation, which is effective, must, in order to produce movements, be so powerful that the movements have been attributed to excitation of underlying white matter rather than cells in the gray. This insensitivity of cortical cells to direct stimulation is not at all favorable to the notion that they are sentinels set to warn against too great diminution of bodily supplies.

Body Need May Exist Without Hunger.—Still further evidence opposed to the theory that hunger results directly

from the using up of organic stores is found in patients suffering from fever. Metabolism in fever patients is augmented, body substance is destroyed to such a degree that the weight of the patient may be greatly reduced, and yet the sensation of hunger under these conditions of increased need is wholly lacking.

Again if a person is hungry and takes food, the sensation is suppressed soon afterward, long before any considerable amount of nutriment could be digested and absorbed, and therefore long before the blood and the general bodily condition, if previously altered, could be restored to normal.

Furthermore, persons exposed to privation have testified that hunger can be temporarily suppressed by swallowing indigestible materials. Certainly scraps of leather and bits of moss, not to mention clay eaten by the Otomacs, would not materially compensate for large organic losses. In rebuttal to this argument the comment has been made that central states as a rule can be readily overwhelmed by peripheral stimulation, and just as sleep, for example, can be abolished by bathing the temples, so hunger can be abolished by irritating the gastric walls.[16] That comment is beside the point, for it meets the issue by merely assuming as true the condition under discussion. The absence of hunger during the ravages of fever, and its quick abolition after food or even indigestible stuff is swallowed, still further weakens the argument, therefore, that the sensation arises directly from lack of nutriment in the body.

The Theory that Hunger is of General Origin Does Not Explain the Quick Onset and the Periodicity of the Sensation. —Many persons have noted that hunger has a sharp onset. A person may be tramping in the woods or working in the fields, where fixed attention is not demanded, and without premonition may feel the abrupt arrival of the characteristic ache. The expression "grub-struck" is a picturesque description of this experience. If this sudden arrival of the sensation corresponds to the general bodily state, the change in the general bodily state must occur with like suddenness or have a critical point at which the sensation is instantly precipitated. There

is no evidence whatever that either of these conditions occurs in the course of metabolism.

Another peculiarity of hunger which I have noticed in my own person, is its intermittency. It may come and go several times in the course of a few hours. Furthermore, while the sensation is prevailing, its intensity is not uniform, but marked by ups and downs. In some instances the ups and downs change to a periodic presence and absence without change of rate. In making the above statements I do not depend on my own introspection alone; psychologists trained in this method of observation have reported that in their experience the temporal course of the sensation is distinctly intermittent.* In my own experience the hunger pangs came and went on one occasion as follows:

Came	Went
12–37–20	38–30
40–45	41–10
41–45	42–25
43–20	43–35
44–40	45–55
46–15	46–30

and so on, for ten minutes longer. Again in this relation, the intermittent and periodic character of hunger would require, on the theory under examination, that the bodily supplies be intermittently and periodically insufficient. During one moment the absence of hunger would imply an abundance of nutriment in the organism, ten seconds later the presence of hunger would imply that the stores had been suddenly reduced, ten seconds later still the absence of hunger would imply a sudden renewal of plenty. Such zig-zag shifts of the general bodily state may not be impossible, but from all that is known of the course of metabolism, such quick changes are highly improbable. The periodicity of hunger, therefore, is further evidence against the theory that the sensation has a general basis in the body.

* I am indebted to Professor J. W. Baird, of Clark University, and his collaborators, for this corroborative testimony.

The Theory that Hunger is of General Origin Does Not Explain the Local Reference.—The last objection to this theory is that it does not account for the most common feature of hunger, namely, the reference of the sensation to the region of the stomach. Schiff and others who have supported the theory[17] have met this objection by two contentions: First they have pointed out that the sensation is not always referred to the stomach. Schiff interrogated ignorant soldiers regarding the local reference; several indicated the neck or chest, 23 the sternum, 4 were uncertain of any region, and 2 only designated the stomach. In other words the stomach region was most rarely mentioned.

The second contention against the importance of local reference is that such evidence is fallacious. An armless man may feel tinglings which seem to arise in fingers which have long since ceased to be a portion of his body. The fact that he experiences such tinglings and ascribes them to dissevered parts does not prove that the sensation originates in those parts. And similarly the assignment of the ache of hunger to any special region of the body does not demonstrate that the ache arises from that region. Such are the arguments against a local origin of hunger.

Concerning these arguments we may recall, first, Schiff's admission that the soldiers he questioned were too few to give conclusive evidence. Further, the testimony of most of them that hunger seemed to originate in the chest or region of the sternum cannot be claimed as unfavorable to a peripheral source of the sensation. The description of feelings which develop from disturbances within the body is almost always indefinite. As Head and others have shown, conditions in a viscus which give rise to sensation are likely not to be attributed to the viscus, but to related skin areas.[18] Under such circumstances we do not dismiss the testimony as worthless merely because it may not point precisely to the source of the trouble. On the contrary, we use such testimony constantly as a basis for judging internal disorders.

With regard to the contention that reference to the peri-

phery is not proof of the peripheral origin of a sensation, we may answer that the force of that contention depends on the amount of accessory evidence which is available. Thus if we see an object come into contact with a finger, we are justified in assuming that the simultaneous sensation of touch which we refer to that finger has resulted from the contact, and is not a purely central experience accidently attributed to an outlying member. Similarly in the case of hunger—all that we need as support for the peripheral reference of the sensation is proof that conditions occur there, simultaneously with hunger pangs, which might reasonably be regarded as giving rise to those pangs.

OBJECTIONS TO SOME THEORIES THAT HUNGER IS OF LOCAL ORIGIN

With the requirement in mind that peripheral conditions be adequate, let us examine the state of the fasting stomach to see whether indeed conditions may be present in times of hunger which would sustain the theory that hunger has a local outlying source.

Hunger Not Due to Emptiness of the Stomach.—Among the suggestions which have been offered to account for a peripheral origin of the sensation is that of attributing it to emptiness of the stomach. By use of the stomach tube Nicholai found that when his subjects had their first intimation of hunger the stomach was quite empty. But, in other instances, after lavage of the stomach, the sensation did not appear for intervals varying between one and a half and three and a half hours.[19] During these intervals the stomach must have been empty, and yet no sensation was experienced. The same testimony was given long before by Beaumont, who, from his observations on Alexis St. Martin, declared that hunger arises some time after the stomach is normally evacuated.[20] Mere emptiness of the organ, therefore, does not explain the phenomenon.

Hunger not Due to Hydrochloric Acid in the Empty Stomach.—A second theory, apparently suggested by observations on cases of hyperacidity, is that the ache or pang is due to hydrochloric acid secreted into the stomach while empty. Again

the facts are hostile. Nicolai reported that the gastric wash-water from his hungry subjects was neutral or only slightly acid.[21] This testimony confirms Beaumont's statement, and is in complete agreement with the results of gastric examination of fasting animals reported by numerous experimenters. There is no secretion into the empty stomach during the first days of starvation. Furthermore, persons suffering from absence of hydrochloric acid (achylia gastrica) declare that they have normal feelings of hunger. Hydrochloric acid cannot therefore be called upon to account for the sensation.

Hunger Not Due to Turgescence of the Gastric Mucosa.—Another theory, which was first advanced by Beaumont, is that hunger arises from turgescence of the gastric glands.[22] The disappearance of the pangs as fasting continues has been accounted for by supposing that the gastric glands share in the general depletion of the body, and that thus the turgescence is relieved.* This turgescence theory has commended itself to several recent writers. Thus Luciani has accepted it, and by adding the idea that nerves distributed to the mucosa are specially sensitive to deprivation of food he accounts for the hunger pangs.† Also Valenti declared two years ago that the turgescence theory of Beaumont is the only one with a semblance of truth in it.[23] The experimental work reported by these two investigators, however, does not necessarily sustain the turgescence theory. Luciani severed the previously exposed vagi after cocainizing them, and Valenti merely cocainized the nerves; the fasting dogs, eager to eat a few minutes previous to this operation, now ran about as before, but when offered food, licked and smelled it, but did not take it. This total neglect of the food lasted varying periods up to two

*A better explanation perhaps is afforded by Boldireff's discovery that at the end of two or three days the stomachs of fasting dogs begin to secrete gastric juice and continue the secretion indefinitely. (Boldireff: Archives biologiques de St. Petersburg, 1905, xi, p. 98.)

† Luciani: Archivio di fisiologia, 1906, iii, p. 54. Tiedemann long ago suggested that gastric nerves become increasingly sensitive as fasting progresses. (Physiologie des Menschen. Darmstadt, 1836, iii, p. 22.)

hours. The vagus nerves seem, indeed, to convey impulses which affect the procedure of eating, but there is no clear evidence that those impulses arise from distention of the gland cells. The turgescence theory, moreover, does not explain the effect of taking indigestible material into the stomach. According to Pawlow, and to others who have observed human beings, the chewing and swallowing of unappetizing stuff does not cause any secretion of gastric juice.[24] Yet such stuff when swallowed will cause the disappearance of hunger, and Nicholai found that the sensation could be abolished by simply introducing a stomach sound. It is highly improbable that the turgescence of the gastric glands can be reduced by either of these procedures. The turgescence theory, furthermore, does not explain the quick onset of hunger, or its intermittent and periodic character. That the cells are repeatedly swollen and contracted within periods a few seconds in duration is almost inconceivable. For these reasons, therefore, the theory that hunger results from turgescence of the gastric mucosa can reasonably be rejected.

HUNGER THE RESULT OF CONTRACTIONS

There remain to be considered, as a possible cause of hunger-pangs, contractions of the stomach and other parts of the alimentary canal. This suggestion is not new. Sixty-six years ago Weber declared his belief that "strong contraction of the muscle fibers of the wholly empty stomach, whereby its cavity disappears, makes a part of the sensation which we call hunger.[25] Vierordt drew the same inference twenty-five years later (in 1871),[26] and since then Ewald, Knapp, and Hertz have declared their adherence to this view. These writers have not brought forward any direct evidence for their conclusion, though Hertz has cited Boldireff's observations on fasting dogs as probably accounting for what he terms "the gastric constituent of the sensation."[27]

The Empty Stomach and Intestine Contract.—The argument commonly used against the gastric contraction theory is that the stomach is not energetically active when empty. Thus Schiff

stated "the movements of the empty stomach are rare and much less energetic than during digestion."[28] Luciani expressed his disbelief by asserting that gastric movements are much more active during gastric digestion than at other times, and cease almost entirely when the stomach has discharged its contents.[29] And Valenti stated only year before last, "we know very well that gastric movements are exaggerated while digestion is proceeding in the stomach, but when the organ is empty they are more rare and much less pronounced," and therefore they cannot account for hunger.[30]

Evidence opposed to these suppositions has been in existence for many years. In 1899, Bettmann called attention to the contracted condition of the stomach after several days' fast.[31] In 1902, Wolff reported that after forty-eight hours without food the stomach of the cat may be so small as to look like a slightly enlarged duodenum.[32] In a similar circumstance I have noticed the same extraordinary smallness of the organ, especially in the pyloric half. The anatomist His also recorded his observation of the phenomenon.[33] Six years ago Boldireff demonstrated that the whole gastro-intestinal tract has a periodic activity while not digesting.[34] Each period of activity lasts from 20 to 30 minutes, and is characterized in the stomach by rhythmic contractions 10 to 20 in number. These contractions, Boldireff reports, may be stronger than during digestion, and his published records clearly support this statement. The intervals of repose between periodic recurrences of the contractions lasted from one and a half to two and a half hours. Especially noteworthy is Boldireff's observation that if fasting in continued for two or three days, the groups of contractions appear at gradually longer intervals and last for gradually shorter periods, and thereupon, as the gastric glands begin continuous secretion, all movements cease.

Observations Suggesting a Relation Between Contractions and Hunger.—When Boldireff's paper first appeared I was studying auscultation of abdominal sounds. Repeatedly there was occasion to note that the sensation of hunger was, as already stated, not constant but recurrent, and that its momen-

tary disappearance was often associated with a rather loud gurgling sound, as heard through the stethoscope. That contractions of the alimentary canal on a gaseous content might explain the hunger pangs seemed probable at that time, especially in the light of Boldireff's observations. Indeed Boldireff himself had considered hunger in relation to the activities he described, but solely with the idea that hunger might *provoke* them; and since the activities dwindled in force and frequence as time passed, whereas, in his belief they should have become more pronounced, he abandoned the notion of any relation between the phenomena.[35] Did not Boldireff misinterpret his own observations? When he was considering whether hunger might cause the contractions, did he not overlook the possibility that the contractions might cause hunger? A number of experiences have led to the conviction that Boldireff did, indeed, fail to perceive part of the significance of his results. For example, I have noticed the disappearance of a hunger pang as gas was heard gurgling upward through the cardia. That the gas was rising rather than being forced downward was proved by its regurgitation immediately after the sound was heard. In all probability the pressure that forced the gas from the stomach was the cause of the preceding sensasion of hunger. Again the sensation can be momentarily abolished a few seconds after swallowing a small accumulation of saliva or a teaspoonful of water. If the stomach is in strong contraction in hunger, this result can be accounted for as due to the inhibition of the contraction by swallowing.[36] Thus also could be explained the prompt vanishing of the ache soon after we begin to eat, for repeated swallowing results in continued inhibition.* Furthermore, Ducceschi's discovery that hydrochloric acid diminishes the tonus of the pyloric portion of the stomach[37] may have its application here; the acid would be secreted as food is taken and would then cause relaxation of the very region which is most strongly contracted.

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* The absence of hunger in Busch's patient while food was being eaten (see p. 135) can also be accounted for in this manner.

The Concomitance of Contractions and Hunger in Man.—Although the evidence above outlined had led me to the conviction that hunger results from contractions of the alimentary canal, direct proof was still lacking. In order to learn whether such proof might be secured, one of my students, Mr. A. L. Washburn, determined to become accustomed to the presence of a rubber tube in the œsophagus.* Almost every day for several weeks Mr. Washburn introduced as far as the stomach a small tube, to the lower end of which was attached a soft rubber balloon about 8 cm. in diameter. The tube was thus carried about each time for two or three hours. After this preliminary experience the introduction of the tube and its presence in the gullet and stomach were not at all disturbing. When a record was to be taken, the balloon, placed just below the cardia, was moderately distended with air, and was connected with a water manometer ending in a cylindrical chamber 3.5 cm. wide. A float recorder resting on the water in the chamber permitted registering any contractions of the fundus of the stomach. On the days of observation Mr. Washburn would abstain from breakfast, or eat sparingly; and without taking any luncheon would appear in the laboratory about two o'clock. The recording apparatus was arranged as above described. In order to avoid the possibility of an artifact, a pneumograph, fastened below the ribs, was made to record the movements of the abdominal wall. Between the records of gastric pressure and abdominal movement, time was marked in minutes, and an electromagnetic signal traced a line which could be altered by pressing a key. All these recording arrangements were out of Mr. Washburn's sight; he sat with one hand at the key, ready whenever the sensation of hunger was experienced to make the current which moved the signal.

Sometimes the observations were started before any hunger was noted; at other times the sensation, after running a course, gave way to a feeling of fatigue. Under either of these cir-

* Nicolai (loc. cit.) reported that although the introduction of a stomach tube at first abolished hunger in his subjects, with repeated use the effects became insignificant.

cumstances there were no contractions of the stomach. When Mr. Washburn stated that he was hungry, however, powerful contractions of the stomach were invariably being registered. As in the experience of the psychologists, the sensations were characterized by periodic recurrences with free intervals, or by periodic accesses of an uninterrupted ache. The record of Mr. Washburn's introspection of his hunger pangs agreed closely with the record of his gastric contractions. Almost

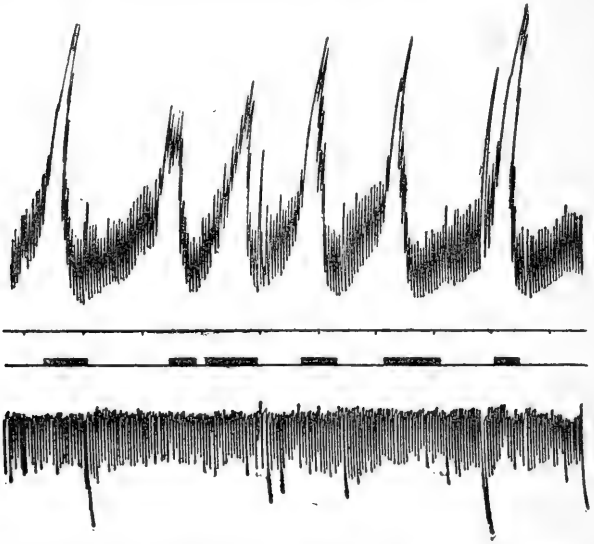

FIG. 1. One-half the original size. The top record represents intragastric pressure (the small oscillations due to respiration, the large to contractions of the stomach); the second record is time in minutes (ten seconds); the third record is Mr. Washburn's report of hunger pangs; the lowest record is respiration registered by means of a pneumograph about the abdomen.

invariably, however, the contraction nearly reached its maximum before the record of the sensation was started (see Fig. 1). This fact may be regarded as evidence that the contraction precedes the sensation, and not *vice versa,* as Boldireff considered it. The contractions were about a half minute in duration and the intervals between varied from 30 to 90 seconds, with an average of about one minute. The augmentations of intragastric pressure in Mr. Washburn ranged between 11 and 13 in

twenty minutes; I had previously counted in myself eleven hunger pangs in the same time. The rate in each of us was, therefore, approximately the same. This rate is slightly slower than that found in dogs by Boldireff; the difference is perhaps correlated with the slower rhythm of gastric peristalsis in man compared with that in the dog.[38]

Before hunger was experienced by Mr. Washburn the recording apparatus revealed no signs of gastric activity. Sometimes a rather tedious period of waiting had to be endured before contractions occurred. And after they began they continued for a while, then ceased (see Fig. 2). The feeling of hunger, which was reported while the contractions were recur-

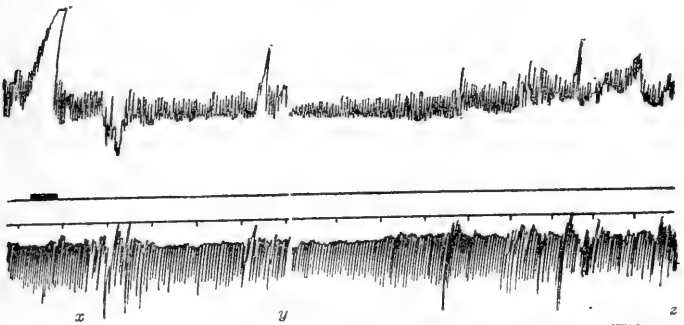

FIG. 2. One-half the original size. The same conditions as in Fig. 1. (Fifteen minutes.) There was a long wait for hunger to disappear. After *x*, Mr. Washburn reported himself "tired but not hungry." The record from *y* to *z* was the continuance on a second drum of *x* to *y*.

ring, disappeared as the waves stopped. The inability of the subject to control the contractions eliminated the possibility of their being artifacts, perhaps induced by suggestion. The close concomitance of the contractions with hunger pangs, therefore, clearly indicates that they are the real source of those pangs.

Boldireff's studies proved that when the empty stomach is manifesting periodic contractions, the intestines also are active. Conceivably all parts of the alimentary canal composed of smooth muscle share in these movements. The lower œsophagus in man is provided with smooth muscle. It was possible to

determine whether this region in Mr. Washburn was active during hunger.

To the œsophageal tube a thin rubber finger-cot (2 cm. in length) was attached and lowered into the stomach. The little rubber bag was distended with air, and the tube, pinched to keep the bag inflated, was gently withdrawn until resistance was felt. The air was now released from the bag, and the tube further withdrawn about 3 cm. The bag was again distended

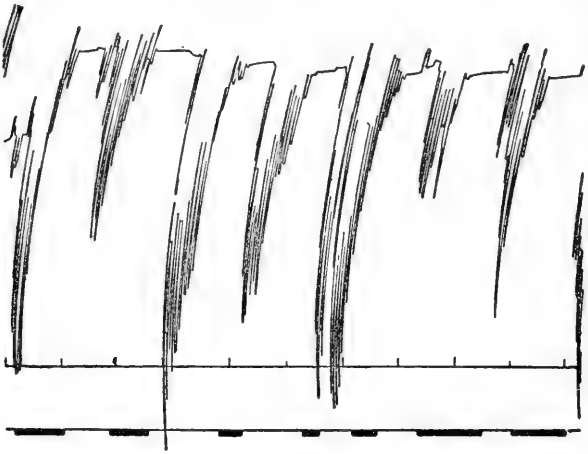

FIG. 3. One-half the original size. The top record represents compression of a thin rubber bag in the lower œsophagus. The pressure in the bag varied between 9 and 13 cm. of water, The cylinder of the recorder was of smaller diameter than that used in the gastric records. The œsophageal contractions compressed the bag so completely that, at the summits of the large oscillations, the respirations were not registered. When the oscillations dropped to the time line, the bag was about half inflated. The middle line registers time in minutes (ten seconds). The bottom record is Mr. Washburn's report of hunger pangs.

with air at a manometric pressure of 10 cm. of water. Inspiration now caused the writing lever, which recorded the pressure changes, to rise; and a slightly further withdrawal of the tube changed the rise, on inspiration, to a fall. The former position of the tube, therefore, was above the gastric cavity and below the diaphragm. In this position the bag, attached to a float-recorder (with chamber 2.3 cm. in diameter), registered the periodic oscillations shown in Fig. 3. Though individually more prolonged than those of the stomach, these contractions, it will be noted, occur at about the same rate. It is probable that the

periodic activity of the two regions is simultaneous, for otherwise the stomach would force its gaseous content into the œsophagus with the rise of intragastric pressure.

What causes the contractions to occur has not been determined. From evidence already given they do not seem to be directly related to bodily need. Habit no doubt plays an important rôle. For present considerations, however, it is enough that they do occur, and that they are abolished when food, which satisfies bodily need, is taken into the stomach. By such indirection, as already stated, are performed some of the most fundamental of the bodily functions.

Peculiarities of Hunger Explained by Contractions.—If these contractions are admitted as the cause of hunger, most of the difficulties confronting other explanations are readily obviated. Thus the occurrence of hunger at meal times is most natural, for, as the regularity of defecation indicates, the alimentary canal has habits. Activity returns at the usual meal time as the result of custom. By taking food regularly at a definite hour in the evening for several days, a new hunger period can be established. Since at these times the œsophagus and the empty stomach strongly contract, hunger is aroused.

The contractions furthermore explain the sudden onset of hunger and its peculiar periodicity—phenomena which no other explanation of hunger can account for. The quick development of the sensation after taking a cold drink is possibly associated with the well-known power of cold to induce contraction in smooth muscle.

The great intensity of hunger during the first day of starvation, and its gradual disappearance till it vanishes on the third or fourth day, are made quite clear, for Boldireff observed that the gastric contractions in his fasting dogs went through precisely such alterations of intensity, and were not seen after the third day.

In fever, when bodily material is being most rapidly used, hunger is absent. Its absence is understood from an observation reported four years ago, that infection, with systemic involvement, is accompanied by a total cessation of all move-

ments of the alimentary canal.[39] Boldireff observed that when his dogs were fatigued the rhythmic contractions failed to appear. Being "too tired to eat" is thereby given a rational explanation.

Another pathological form of the sensation—the inordinate hunger (bulimia) of certain neurotics—is in accordance with the well-known disturbances of the tonic innervation of the alimentary canal in such individuals.

Since the lower end of the œsophagus, as well as the stomach, contracts periodically in hunger, the reference of the sensation to the sternum by the ignorant persons questioned by Schiff was wholly natural. The activity of the lower œsophagus also explains why, after the stomach has been removed, or in some cases when the stomach is distended with food, hunger can still be experienced. Conceivably the intestines also originate vague sensations by their contractions. Indeed the final banishment of the modified hunger sensation in the patient with duodenal fistula, described by Busch, may have been due to the lessened activity of the intestines when chyme was injected into them.

The observations recorded in this paper have, as already noted, numerous points of similarity to Boldireff's observations on the periodic activity of the alimentary canal in fasting dogs. Each period of activity, he found, comprised not only widespread contractions of the digestive canal, but also the pouring out of bile, and of pancreatic and intestinal juices rich in ferments. Gastric juice was not secreted at these times; when it was secreted and reached the intestine, the periodic activity ceased.[40] What is the significance of this extensive disturbance? Recently evidence has been presented that gastric peristalsis is dependent on the stretching of gastric muscle when tonically contracted.[41] The evidence that the stomach is in fact strongly contracted in hunger—*i.e.*, in a state of high tone —has been presented above.* Thus the very condition which

* The "empty" stomach and œsophagus contain gas (see Hertz: Quarterly Journal of Medicine, 1910, iii, p. 378; Mikulicz: Mittheilungen aus dem Grenzgebieten der Medicin und Chirurgie, 1903, xii, p. 596). They would naturally manifest rhythmic contractions on shortening tonically on their content.

causes hunger and leads to the taking of food is the condition, when the swallowed food stretches the shortened muscles, for immediate starting of gastric peristalsis. In this connection the recent observations of Haudek and Stigler are probably significant. They found that the stomach discharges its contents more rapidly if food is eaten in hunger than if not so eaten.[42] Hunger, in other words, is normally the signal that the stomach is contracted for action; the unpleasantness of hunger leads to eating; eating starts gastric secretion, distends the contracted organ, initiates the movements of gastric digestion, and abolishes the sensation. Meanwhile pancreatic and intestinal juices, as well as bile, have been prepared in the duodenum to receive the oncoming chyme. The periodic activity of the alimentary canal in fasting, therefore, is not solely the source of hunger pangs, but is at the same time an exhibition in the digestive organs of readiness for prompt attack on the food swallowed by the hungry animal.

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[27] Knapp: American Medicine, 1905, x, p. 358. Hertz: loc. cit., p. 37.
[28] Schiff: loc. cit., p. 33.
[29] Luciani: loc. cit., p. 542.
[30] Valenti: loc. cit., p. 95.
[31] Bettmann: Philadelphia Monthly Medical Journal, 1899, i, p. 133.
[32] Wolff: Dissertation, Giessen, 1902, p. 9.
[33] His: Archiv für Anatomie, 1903, p. 345.
[34] Boldireff: loc. cit., p. 1.
[35] Boldireff: loc. cit., p. 96.
[36] Cannon and Lieb: American Journal of Physiology, 1911, xxix, p. 267.
[37] Ducceschi: Archivio per le Scienze Mediche, 1897, xxi, p. 154.
[38] Cannon: American Journal of Physiology, 1903, viii, p. xxi; 1905, xiv, p. 344.
[39] Cannon and Murphy: Journal of the American Medical Association, 1907, xlix, p. 840.
[40] Boldireff: loc. cit., pp. 108–111.
[41] Cannon: American Journal of Physiology, 1911, xxix, p. 250.
[42] Handek and Stigler: Archiv für die gesammte Physiologie, 1910, cxxxiii, p. 159.

THE CONTINUOUS ORIGIN OF CERTAIN UNIT CHARACTERS AS OBSERVED BY A PALEONTOLOGIST*

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ONE method of ascertaining the height of a mountain is with a single instrument, the barometer; another method is by triangulation with several instruments. Thus we may differ from Johannsen in his remark that morphology as a science of great collections in museums is of no value in genetics. The brilliant progress in heredity of the last nine years, beginning in 1903 with the rediscovery of Mendel's law, should not blind us to the four broad inductions from Paleontology,[1] that transformation is a matter of thousands or hundreds of thousands of years, that to the living observer all living things may be delusively stationary, that invisible tides of genetic change may be setting in one direction or another and yet observable only over very long periods of time, that discontinuous mutations or saltations may be mere ripples on the surface of these tides.

Whatever the truth as to these reflections, by a strange paradox it is certain that some stationary characters, some apparently dead things in the eyes of the zoologist and botanist, become movable and alive in the eyes of the paleontologist.

Thus a paleontologist comes before the Harvey Society of Physiologists and Physicians with the conviction that his vision is of a different angle from that of the experimentalist, and that by the triangulation of experiment, of anatomy and of paleontology the truth may at least be more nearly approached.

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* Delivered January 20, 1912.

[1] Osborn, Henry F., Darwin and Palæontology. One of the addresses in Fifty Years of Darwinism. 8vo. Henry Holt & Co., New York, May 1, 1909.

The origin and history of "characters" is our quest, and now that attention is concentrated all along the line of observation in plants and animals, living and fossil, on the genesis and behavior of single characters, we have laid the train of substantial progress. A vast gain is that which relegates the problem of species to a side issue, or rather to an incidental result of the accumulation and modification of a greater or less number of units.

Among mammals a "character" may be racial shape of head or length of limb, it may be a cusplet on a grinding tooth, color of hair, or a sportive white lock of hair, it may be the brown or blue color of the eye, it may be the speed of a horse, or the obstinacy of a mule, in short, any structure or function, simple or extremely complex, which is stable and distinct in heredity. A "new character" is something which is unknown before, it may be a new unit, like the horns of cattle, it may be a new form or proportion of such a unit. "I understand by the term unit character," observes Morgan, "any particular structure or function that may appear in heredity independent of other characters. Such unit characters may in themselves be extremely complex and include the possibility of further splitting up." The point where Mendelism bears on the problem is, therefore, in its bearing on the continuous or discontinuous origin of the thousands of characters which display this more or less complete discontinuity in heredity.

Is there more evidence of discontinuity and of lawlessness, or of continuity and of law, in the origin of such new characters? Perhaps no more appropriate question could be chosen as the subject of a lecture in memory of William Harvey, the author of the doctrine of epigenesis, for the essence of this doctrine is that of "successive differentiation of a relatively homogeneous rudiment into the parts and structures which are characteristic of the adult." Paleontology is at one with embryology in the belief that differentiation is in the main gradual and continuous.

Yet, to our question, the answer prevailing among experimentalists and Mendelians at the present time is that

there is little evidence either for continuity or for law; this despite the fact that a large part of the evidence for discontinuity in the origin of characters is most unsound.

In fact, our first purpose in this Harvey Lecture is to show how surprisingly unsound this evidence is when we consider that discontinuity has become practically a dogma among a very large number of zoologists and botanists.

It will appear that the evidence for discontinuity in the *heredity* of characters is as convincing as that for discontinuity in the origin of characters is most unsound.

Our second purpose in this Harvey Lecture is to show that the evidence for continuity in the genesis of certain characters in man and other mammals is very strong indeed, further, that some of these characters, while apparently continuous in origin, certainly become discontinuous in heredity; from which it follows that discontinuity in heredity constitutes no proof of discontinuity in origin.

How then do these manifold characters of which the body is made up arise, continuously or discontinuously? A conservative opinion from what may be gathered in the whole field of observation at the present time is that while the greater part of evolution is continuous, especially in the origins of certain parts and in the development of certain proportions, there must also be a discontinuity, especially in numerical or meristic structures, such as vertebræ and teeth, and in chemical components and reactions which are essentially antithetic or discontinuous. In other words, there is both continuity and discontinuity, and one problem is to distinguish what is continuous from what is discontinuous.

I. EVIDENCES FOR DISCONTINUITY

Darwin has been widely misunderstood of late as believing in continuity,[2] whereas he chiefly believed in discontinuity.[3]

[3] Cf. Poulton, E. B.: Darwin and the "Origin," 1909, pp. 49–50. "His observation and study of nature led him to the conviction that large variations, although abundant, were rarely selected, but that evolution proceeded gradually and by small steps,—that it was 'con-

In his original (1859) and final (1872) opinion evolution is due chiefly to the selection of heritable "individual differences"; these have been understood by some as "fluctuations." His true meaning as to these *individual differences* is to be found in the cases he cited, which may be collected from hundreds of observations in the "Origin of Species" and "Variation of Animals and Plants under Domestication," to the effect that such individual differences or *new characters* were in the nature of *minor saltations,* structural or functional, and always hereditary. If we note some of the observations which he assembled in commenting on the genesis of the race horse and the greyhound, breeds which he used by way of illustration of the genesis of new forms in nature, we find they include such suddenly appearing new characters as horn rudiments, taillessness, curliness of the hair, characters which are discontinuous in Bateson's sense, or mutations in that of De Vries;[4] intermingled with these new characters he cited others which are obviously reversional. That he believed in the adding up of minor saltations there can be no question; but on the admirable ground that no evidence had been adduced in nature of evolution by *major saltations,* he rejected St. Hilaire's hypothesis of the natural appearance of entirely new types of animals and plants, or of new or profoundly modified organs; there was no evidence in 1872 and there is none to-day of the sudden appearance in nature of such a breed as the short-legged Ancon sheep. Morgan remarks,[5] "Darwin undoubtedly supposed that by the continuous selection of minor saltations a character could be slowly shifted in the direction of Selection.

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tinuous' and not 'discontinuous.'" In answer to this opinion of the most eminent British exponent of pure Darwinism it may be said that *small steps are discontinuities.* (H. F. O.)

[3] Osborn, H. F.: Darwin's Theory of Evolution by the Selection of Minor Saltations, Amer. Naturalist, vol. xlvi, No. 542, 1912, pp. 76–82.

[4] In 1909 L. Plate showed clearly that the "mutations" of De Vries are practically identical with the "individual differences" of Darwin. See Darwinismus und Landwirthschaft, Berlin, 1909.

[5] Morgan, T. H.: Letter, January 11, 1912.

This also appears to be the opinion of the conservative mutationists of the present day."

Aside from his chief emphasis on the selection of "individual differences" Darwin also undoubtedly believed in the selection of *heritable fluctuations of proportion* as illustrated in his classic rebuttal of Lamarck in respect to the long neck of the giraffe:

> So under nature with the nascent giraffe, the individuals which were the highest browsers, and were able during dearths to reach even an inch or two above the others will often have been preserved; for they will have roamed over the whole country in search of food. These slight proportional differences will favor survival and will be transmitted to offspring.

If, however, unusual length of neck in the giraffe, as in man, is a saltatory and heritable fluctuation, there is no reason why this classic case also may not strengthen the opinion that Darwin was essentially a mutationist. Fluctuations of proportion, the transmission of which is now in dispute, however, formed a small part of Darwin's scheme, nor was fluctuating variability especially connected by him with the process of evolution.

A very critical re-examination of Darwin's works leads us, therefore, to largely dissent from the influential opinion of De Vries [6] that there was always a doubt in Darwin's mind as to whether "the selection of mutations" or "the selection of extreme variants" played the greater part in the origin of species. As above noted, the actual cases which Darwin cited and his repeated emphasis shows that minor saltations of the De Vries type were chiefly in his mind.

It is obvious that Darwin could not draw such sharp distinctions either in language or in definition as we may to-day, profiting by forty years of experiment and of analysis.

Let us therefore closely examine the kinds of saltation or discontinuity in mammals which have been recorded during the last fifty years by Darwin, Bateson, and others and see what they signify.

[6] De Vries, Hugo: Die Mutationstheorie, Leipzig, 1901, p. 24.

1. *Major and Minor Saltations in Mammals as Supposed Material for Selection*[7]

The above exposition of Darwin has a very direct bearing on the problem of continuity and discontinuity because the saltations which he believed to be among the possible materials

TABLE I

Comparative Table of Saltations.

	1	2	3	4	5	6	7	8	9	10	11
	Man	Horses	Cattle	Sheep	Deer	Pigs	Dogs	Cats	Rabbits	Guinea Pigs	Mice
1. Proöpic brachycephaly, abbreviation of face			×				×				
2. Sudden development of horns on hornless races		×							×		
3. Absence of both horns on horned races			×	×							
4. Supernumerary horns on horned races				×							
5. Absence of 1 horn on horned races					×						
6. Jaw appendages	×			×		×					
7. Taillessness, absence of caudals	×	×		×				×		×	
8. Earlessness, absence of the external ear.											
9. Single ears, loss of one ear									×		
10. Short-leggedness, or limb abbreviation			×	×			×				
11. Consolidation of paired hoofs, syndactylism			×			×					
12. Polydactylism	×	×	×	×	×	×	×	×		×	
13. Epidermal thickenings	×										×
14. Mottled skin markings	×	×	×			×					
15. Excessive hairiness, or length of hair	×	×	×	×			×	×	×	×	
16. Hairlessness, entire absence of hair		×	×				×				×
17. Excessively fine or silky hair	×		×	×				×	×		×
18. Reversed hairs			×							×	
19. White hair locks											
20. Curled-hair	×	×		×			×				
3*a*. Duplication of horns (transverse)				×							

of natural selection and of evolution were chiefly drawn from the very same sources of evidence, namely, hybridization and artificial conditions of environment, which are now drawn upon

[7] The writer is greatly indebted to Dr. Charles B. Davenport, of the Carnegie Institution Station for Experimental Evolution, and to Professor T. H. Morgan, of Columbia University, for criticism and suggestion on this section.

by the adherents of discontinuity; the only difference is one of degree, not of kind. The great saltatory characters of Darwin cited below (Table I) in mammals are no more profound than those cited by De Vries as composing the supposed "elementary" species of *Œnothera.* It is therefore interesting to compare twenty distinct types or forms of *major and minor* saltation in eleven different types of mammals. Our authorities are Allen, Azara, Bateson, Brinkerhoff, Castle, Darwin, Davenport, Haecker, Percival, Poulton, Ridgeway, Root, Seton, Sutton, Twining. The accompanying table presents at once the very impressive result obtained by this comparison.

The very uniformity of the result makes us suspicious as to the significance of saltations, major or minor, in evolution. In eleven different kinds of mammals, namely, man, horses, cattle, sheep, deer, pigs, dogs, cats, rabbits, guinea pigs, mice, we observe that saltations exactly or closely similar repeatedly occur. These saltations are of the same kind, in fact, they partly include those which were regarded by Darwin as possibly part of the evolution process through selection, namely, as stable in inheritance and as under certain circumstances favoring the animals which possessed them.

We evidently have to do with abnormal disturbances of the germinal factors or determiners. Some of these saltations are very stable in heredity and certain of them become widespread; some are prepotent and dominant, others are recessive (*e.g.,* angora, or "long coat" in rabbits, Castle); some (*e.g.,* bent tail in certain mice, Plate) follow neither the Mendelian law nor the principle of blended inheritance.

On the unit-character doctrine we imagine that one of three things may be happening in the germ plasm.

First, a "determiner" may drop out and we see a race of mammals springing up without tails, or color, or hair. In cattle the determiner for horns is dominant, therefore something is added.

Second, a "determiner" may be suddenly lost or modified, and we see excessive hair, curly hair, silky hair, dwarfed or short limbs, brachydactylism.

Third, and even more inexplicable, there occurs the appearance of a new "determiner" or the removal of an "inhibitor" and we observe horns suddenly arising on hornless races like horses and rabbits.

That fancy breeds can be established through the abnormal behavior and selection of these "determiners" there is no question. That nature works through the sudden appearance of new and favorable "determiners" is as yet unproved; it is absolutely disproved in the case of horns, for through paleontology we know that horns arise in a continuous manner. The only mammal known to us at present in which it would appear that a duplicate horn may have sprung into existence through saltation is *Tetraceros,* the four-horned antelope of India. Saltation is possibly of significance in the case of the sudden alteration of hair character because we know of a very considerable number of curly-haired horses in Mexico and South America, which are, however, eliminated by breeders for the reason that correlated with curliness of the hair are apt to arise certain other characters in the hoofs and limbs which are unfavorable.

Under wild or natural conditions in mammals we have as yet secured no direct evidence of such origins or establishment of saltations either major or minor. There is reason to believe that peculiar or anomalous mammals if they do arise are driven away from the herds.

It would appear that the obvious abnormality of the majority of these characters throws the remainder, as well as saltatory new characters in general, under suspicion of abnormality.

Paleontology, however, furnishes the most direct evidence of the abnormality of saltations in such of the hard parts as are enumerated in Table I by presenting counter evidence that such profound changes as abbreviation of the face (proöpic brachycephaly), development or loss of horns, reduction or absence of caudal vertebræ, abbreviation or elongation of limbs, syndactylism or consolidation of separate metapodials have all been established, wherever we know their history, through continuity and not through discontinuity.

2. *Bateson's Evidence (1894) for Discontinuity*

Bateson in 1894 [8] was the first to advance clearly the discontinuity hypothesis in its modern form as a mode of origin of species. At the time his work appeared it suffered a searching review from Scott.[9] Mutationists,[10] however, still refer to it as laying the foundations for the discontinuity hypothesis. In order to test the "*Materials for the Study of Variation*" critically in the light of the subsequent advance in paleontology, Dr. W. D. Matthew, who is without bias in the question, was requested to examine all the cases of discontinuity in mammals cited by Bateson with reference to the question whether or not these cases have any real significance in evolution. He reports:

> Of the 320 cases of discontinuity cited in mammals the greater part are obviously teratological and have no direct significance in relation to paleontologic evolution except for a very few instances such as the supernumerary or fourth molar teeth of *Otocyon*. While not significant [in evolution] these teratological cases are interesting because they show the prevalence of homœosis, and indicate that many of the remaining cases which might [otherwise] be considered normal saltations or reversions may actually be teratologic, but disguised by homœosis; all of the possibly significant cases (such as the supernumerary molars) are thereby placed under suspicion. Setting aside this suspicion the minority of the "significant" cases in teeth and feet may be said to afford evidence of the meristic variability of vestigial and rudimentary structures. Bateson's statement that such variability is related not to non-functionalism but to terminal position in a series appears to me directly in conflict with his [Bateson's] own evidence, as it certainly is with all my experience. This accords with commonly observed data in paleontology, for no paleontologist would question that vestigial teeth or bones are apt to [finally] disappear by "discontinuous" evolution. *As to the appearance by saltatory evolution of new and primarily functional parts in teeth or feet, I know of no ade-*

[8] Bateson, Wm.: Materials for the Study of Variation Treated with Especial Regard to Discontinuity in the Origin of Species, Macmillan & Co., London, 1894.

[9] Scott, W. B.: On Variations and Mutations, Amer. Jour. Science (3), vol. xlviii, 1894, pp. 355–374.

[10] Darbishire, A. D.: Breeding and the Mendelian Discovery, 8vo, Cassell & Co., London, 1911.

quate paleontologic evidence in its favor. It is either demonstrably false or decidedly improbable. In the cases of supernumerary teeth (*Otocyon myrmecobius,* Cetacea, etc.) saltatory evolution may be regarded as reasonable in default of any paleontologic evidence to the contrary. Meristic or numerical evolution in fully functional vertebræ is intrinsically probable as the only method of evolutionary change.

The fact that so many cases of supernumerary teeth are associated with asymmetry throws doubt on the significance of all such cases; asymmetric variations and those occurring only in upper or only in lower teeth have no analogy in paleontology; such cases as occur abnormally are recognized as of a different and non-significant class than normal evolutionary changes.

A summary of Matthew's report is as follows:

Bateson cites 323 cases of discontinuity in vertebræ, teeth and skull. Of these 286 are abnormal, or teratological, or reversional, and have absolutely no significance in evolution; ten cases of supernumerary (or fourth molar) teeth are possibly significant because among the mammals there are a few genera with fourth molars which may possibly have arisen by saltation. There remain only thirty-seven cases which may be ranked as "probably significant," and these are the meristic additions or reductions of vertebræ in the spinal column, significant because of the well-known numerical variations in the vertebral formulæ of different mammals, and secondly because vertebræ can be added or subtracted only discontinuously.

Summary of Bateson's 323 Cases

		Non-Significant	Possibly Significant	Variations Vestigial or Reversional
I.	Vertebræ	17 (asymmetry)	27*	
II.	Teeth	83	10†	67
III.	Feet	110		
		210	37	67

* Numerical variations of cervical, dorsal and lumbar vertebræ.
† Additional molars, cf. *Octocyon, Myrmecobius, Cetacea.* Six cases insufficiently described.

The fact that the vast majority of germinal anomalies examined in the above review of Darwin and of Bateson have no significance in evolution in a state of nature, throws all germinal anomalies under suspicion as natural processes, important as they may be in artificial breeding and hybridizing. Yet some of these anomalies in mammals are less profoundly discontinuous than those which De Vries has cited in plants under the designation of "mutations." The most important of these De Vries' mutations may now be considered.

3. *Evidence for De Vries' Mutation Theory*

In 1901 the biological world was aroused, as it had not been since 1859, by the publication of De Vries' hypothesis.[11]

Here was a new and apparently sure foundation for discontinuity in the supposed sudden appearance of *elementary species* or "mutants" arising with the acquisition of entirely new characters, new forms of plants or animals quite free from their ancestors and not linked to them by intermediates. The influence and vitality of this great work is shown in a citation from Darbishire (1911, *op. cit.*, p. 5):

> The view that species have originated by mutation is based on Prof. de Vries' observations on the Evening Primrose (*Œnothera Lamarckiana*) (Fig. 1). Working with this form, he was able to witness, for the first time, the actual process of the origin of new species.

Critical analysis during the past two years by Davis and by Gates[12] of the very species *Œnothera Lamarckiana* on which De Vries chiefly based his monumental work, tends to show that *O. Lamarckiana* is possibly a hybrid of *O. biennis* and *O. grandiflora* and not a natural species. Thus the "elementary species" which are springing from it in various

[11] De Vries, Hugo: Die Mutationstheorie, Leipzig, 1901, p. 24.

[12] Davis, Bradley Moore: Genetical Studies on Œnothera. II. Some Hybrids of *Œnothera biennis and O. grandiflora* that resemble *O. Lamarckiana*, Amer. Naturalist, vol. xlv, April, 1911, pp. 193–233. Gates, R. R.: The Mutation Theory. The American Naturalist, vol. xlv, No. 538, April, 1911, pp. 254–256. Mutation in Œnothera, Amer. Naturalist, vol. xlv, No. 538, October, 1911, pp. 577–606.

gardens may prove to be comparable to the familiar results of hybridization in mammals and birds.

Davis, on the basis of his prolonged experimental researches, says (p. 193):

> Indeed, the theory of De Vries may fairly be said to rest chiefly upon the behavior of this interesting plant, the account of which forms so large a part of his work "Die Mutationstheorie" (2 vols., Leipzig, (1901) . . . .

Gates makes the following statement (pp. 255–296):

> In a reperusal of the work one is struck by the optimism of its author and the brilliancy and breadth of his exposition of the views set forth. . . . The analysis of the data amassed by Darwin, in which it is shown that Darwin's *single variations* are the same as De Vries' mutations, seems to the reviewer particularly effective. . . . Probably the time will soon come when nearly all biologists will be ready to admit that mutation, or the sudden appearance of new forms, has been an important factor at least, in species formation of plants and animals. Admitting this, it remains to be discovered what relation these sudden appearances bear to *the general trends of evolution which are apparent in so many phylogenies* [italics our own] . . . For, granting the facts of mutation, we have only accounted for micro-evolution, and it is still to be shown that the larger tendencies can be sufficiently accounted for by the same means, without the intervention of other factors. . . .

The skepticism of both these botanists is striking. Their opinions as to the existence of larger evolutionary trends are exactly in accord with those of paleontologists.

4. *Evidence for Discontinuity from Mendelian Heredity and Experimental Selection*

The newest bulwark of the discontinuity hypothesis is that erected since 1903 by the revival of the great discovery of Mendel (1865) and by the negative results of experiments on fluctuating or quantitative variation.

From the prevalence of discontinuity in heredity, the separateness of "unit characters" as they appear in the body and the equally sharp separableness of their complex of "factors," "determiners" or "genes" in the germ has arisen the *purely theoretical assumption of the discontinuity of origin of*

all characters in the germ. We shall attempt to show that this assumption is a *non-sequitur.*

First, however, the truly marvellous and epoch-making Mendelian discoveries require our special examination in their bearing on the problem of continuity and discontinuity. We have reviewed[13] the contributions of Allen, Bateson, Castle, Cannon, Cuénot, Darbishire, Davenport, Durham, Farrabee, v. Guita, Haacke, Hagedoorn, Harmon, Hurst, Laughlin, Morgan, Pearson, Plate, Punnett, and Rosenoff. This review covers unit characters only as observed in mammals, to which none the less the principles discovered by Mendel in the common garden pea (*Pisum sativum*) apply with striking uniformity.

The prevailing field of the researches of these talented investigators in mammals has been in color characters, chemical in essence, in various species of rodents, chiefly mice and guinea pigs, also in Ungulates, such as horses and cattle, the latter studied less by experiment than from stud books. Hair form in rodents and in man and skin pigment have also been exactly investigated. The most striking general result is the principle of antithesis of characters which mutually exclude each other, as typified by the antithesis of Mendel's "tallness" and "shortness" in peas.

The second great result is that when these antithetic characters meet in the germ cells, one dominates over the other; this dominance is a sort of perpetual prepotency. "Prepotency," observes Darbishire, "is an attribute of individuals and capricious in its appearance. . . . Whatever be the nature of this power . . . it is clear that it has nothing to do with dominance . . . dominance is an invariable attribute of particular characteristics."[14] Plate (1910), on the contrary, observes, "But a variety of facts seem to indicate that a reversal of dominance may occur under certain circumstances and a domi-

[13] With the aid of Miss Mary M. Sturgess, now attached to the Carnegie Institution Station for Experimental Evolutions at Cold Spring Harbor, L. I.

[14] Darbishire: op. cit., p. 96.

nant character may become recessive, and *vice versa.*"[15] Such reversal of dominance would appear to be the case in a comparison of the mule (cross between ass ♂ and horse ♀) and the hinny (cross between the horse ♂ and the ass ♀).

When antithetic characters or functions meet in heredity, there is either "prepotency," or "dominance," or "recession" (*i.e.,* latency), or "inhibition," a something which indirectly prevents the appearance of characters, or "imperfect dominance," of "blending." In brief, there are *degrees of separableness and antithesis.*

Dominance, Conservative or Progressive.—It will be seen at once that progressive evolution through discontinuity would depend on the *dominance of racially new characters and types.*

The experimental evidence is conflicting, it does not show that new characters are necessarily dominant.

There are many instances of dominance of wild species (older type) over domesticated species (newer type); thus De Vries suggested (1902) that the dominant characters are those which are racially older. One case among the mammals is that the wild gray color in mice dominates over grades below it, black, brown, and white (Plate, 1910).

Examples of dominance in single characters are that more intense dominate over less intense colors (Plate, 1910, Davenport, 1907); in the eyes, brown over gray, gray over blue; in the skin, brunettes over blondes (Davenport, 1909), piebalds over pure albinos (Plate, 1910); in the hair, wavy or spiral forms dominate over straight (Davenport, 1908). These facts of *experiment* are directly opposed to the *natural* fading out of color in desert races like the quagga, which lost all the stripes of its intensely colored relative the zebra.

The idea that the positive or present character dominates over the negative, latent or absent character has become a prevailing one.

It seems highly probable, observes Davenport (1910), that the future will show that many more advanced or progressive conditions are really due to one or more unit-characters not present in the less ad-

[15] Plate.

vanced condition. In that case it will appear that there is a perfect accord in the two statements that the progressive and the "present" factor are dominant (pp. 89–90) . . . the specific characteristics are mostly those that appear late in ontogeny (p. 86) . . . the potency of a character may be defined as the capacity of its germinal determiner to complete its entire ontogeny. If we think of every character as being represented in the germ by a determiner, *then we must recognize the fact that this determiner may sometimes develop fully, sometimes imperfectly and sometimes not at all* [italics our own]. . . . When such a failure occurs in such a normal strain a sport results. . . . Potency is variable. Even in a pure strain a determiner does not always develop fully and this is an important cause of individual variability (Davenport, 1910, p. 92).

Plate similarly favors the hypothesis of dominance of newer or progressive characters. He observes (1910):

The [Mendelian] laws of inheritance favor progressive evolution in two ways, for . . . higher, more complicated characters are generally dominant to the lower, and . . . qualitative characters usually follow the Mendelian principle in the case of closely related forms (races, varieties), while in the crossing of species they follow intermediate [or blended] inheritance as a rule. In the latter case there is the possibility that the crossing may have a swamping effect, but this can play no large rôle on account of the infrequency of hybrids between species (Plate, 1910, p. 606).

Plate is of the opinion that phyletic evolution is discontinuous as regards the transformations of the determinants [determiners], but in most cases is continuous in their visible outward workings. He thus maintains that while germinal transformations are discontinuous there may be no real antithesis between continuous and discontinuous somatic variation.

Mendelians appear to agree, *first*, that there are *grades of continuity and discontinuity*, that there are antithetic characters which are sharply discontinuous, others which are partly continuous, blended or intermediate. *Second*, some new characters are dominant, others are recessive. *Third*, it would appear that complete discontinuity or entire dominance or recession are qualities in heredity *which may gradually evolve*. Many characters show imperfect dominance (Castle, 1905); gametic purity is not absolute (Castle, 1906); selection is of importance

in the improvement of races (Castle, 1907). There are a number of truly blending characters, such as lop-earedness in rabbits (Castle, 1909); cross blends of long and short hairs (Castle, 1906), cross blends between short- and lopeared rabbits which are permanent (Castle, 1909), blends in weight inheritance and in skeletal proportion (Castle, 1909).

Recent work has led to the opinion (Hatai, 1911)[16] that blended inheritance may be considered to be a limited case of alternative inheritance where dominance is imperfect; Mendel's law of alternative inheritance may be considered as the standard in all the cases referred to it (Hatai, 1911, p. 106). Certain characters which were considered formerly to blend are now regarded as showing a certain kind of segregation or unit inheritance. Thus Davenport (1909) observes:

> Skin pigment does not show thorough blending inheritance, but segregation (sometimes imperfect), a more pigmented being imperfectly dominant over a less.[17] . . . The reason, the same author observes (1909), for the blending of hair and skin color in man is the non-development of distinct color unit-determiners owing to the fact that in man for a long period there has been no selection for intensity of color, whereas in the lower mammals definite color determiners have long been maintained by selection.

Thus the prevalent recent opinion or hypothesis among Mendelian observers is *that there is a real discontinuity between the germinal or blastic characters and what the paleontologist or morphologist generally observes, is only an apparent continuity between somatic characters.*

Since, however, the behavior of visible or somatic characters forms our only means of knowing whether the determiners are continuous or discontinuous, it is obvious that this opinion or rather this ingenious hypothesis requires further examination and experiment.

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[16] Hatai, Shinkishi: The Mendelian Ratio and Blended Inheritance, Amer. Naturalist, vol. xlv, No. 530, February, 1911, pp. 99–106.

[17] Pigmentation of the skin seems to depend in man on a series of color intensity units, possibly one or a few large units, more probably a number of small units so close together as to be almost continuous (Davenport, 1910).

5. *Johannsen's Pure Line Theory*[18]

The hypothetical contrast between a real discontinuity of the blastic determiners and a delusive continuity of visible or somatic form is pushed to its extreme in the "pure-line" conception which marks the latest development in heredity, an advance upon Weismann's germ-plasm theory and Mendel's unit-character law. Through experiments on successive generations of self-fertilizing plants (the garden bean), Johannsen has reached a standpoint which may be briefly stated as follows:

A "pure line" is composed of the descendants of one pure strain or homozygotic organism exclusively propagated by self fertilization; such pure lines demonstrate the stability of hereditary constitution in successive generations where undisturbed by cross breeding or mingling with other strains, showing that the only real changes in organisms are those due to the sudden appearance of new determiners in the germ.

To replace the word *determiner* the term *gene* is proposed. The *genotype* represents the sum total of all the genes in the fertilized germ cell, gamete or zygote; we do not know a genotype, but we are able in experiment to demonstrate "genotypical differences." The *biotype* is a group of similar genotypes or pure strain individuals.

Gene, genotype, and biotype are not seen; they are the smaller and larger units of heredity.

The phenotype is what we see; it is the developing organism. Morphology supported by the huge collections of the museums has operated with "phenotypes" in phylogenetic speculation. It is thus a science of phenotypes and is not of value in genetics because phenotype description is inadequate as the starting point for genetic inquiries. The adaptation of phenotypes through the direct influence of environment [Buffon's factor] or of use and disuse [Lamarck's factor] is not of genetic importance. Ontogenesis is a function of the genotype, but the genotype is not a function of ontogenesis. The idea of evolution by continuous transitions from one type to another has imposed itself upon zoologists and botanists, who are examining chiefly shifting phenotypes in very fine gradations. There is such a continuity in phenotypes but not in the genotypes from which they spring. All degrees of continuity between phenotypes may be found, but real genetic transitions must be distinguished from the transitions which we find in museums.

[18] Johannsen, W.: The Genotype Conception of Heredity, Amer. Naturalist, vol. xlv, No. 531, March, 1911, pp. 129–159.

Genotypes, it is true, can only be examined by the qualities and reactions of the phenotypes.

Such examination shows that within pure lines—if no new mutations or other disturbances have been at work—there are no genotypical differences in the characters under examination. The only real discontinuity is that between different genotypes. The mutations observed in nature have shown themselves as considerable discontinuous saltations. There is no evidence for the view that mutations are practically identical with continuous evolution. In pure lines no influence of special ancestry can be traced; all series of progeny keep the genotype unchanged through long generations. Discontinuity between genotypes and constant differences between the genes show a beautiful harmony between Mendelism and pure line work.

Selection will have no hereditary influence in changing genotypes. Even the selection of fluctuations in pure lines is ineffective to produce a new genotype.

Heredity may thus be defined as the presence of identical genes in ancestors and descendants, or heredity stands for those properties of the germ cells that find expression in the developing and developed phenotype.

Jennings observes:

What distinguishes the different genotypes, then, is *a different method of responding to the environment.* And this is a type of what heredity is; *an organism's heredity is its method of responding to the evironmental conditions* [p. 84]. . . . It appeared clear, and still appears clear, that a very large share of the apparent progressive action of Selection has really consisted in the sorting over of preexisting types, so that it has by no means the theoretical significance that had been given to it [p. 88]. . . . I had hoped to accomplish this myself, but after strenuous, long-continued and hopeful efforts, I have not yet succeeded in seeing Selection effective in producing a new genotype. This failure to discover Selection resulting in progress came to me as a painful surprise, for like Pearson I find it impossible to construct for myself a "philosophical scheme of evolution," without the results of Selection, and I would like to see what I believe must occur [pp. 88–89]. . . . It would seem that the diverse genotypes must have arisen from one, in some way, and when we find out how this happens, then such Selection between genotypes will be all the Selection that we require for our evolutionary progress [p. 89].

Johannsen's general conception of the origin of progressive or retrogressive new characters is that "it is sufficient to state that the essential point in evolution is the alteration, loss or

gain of the genes or constituents of the genotypes . . . all evidences as to 'mutations' point *to the discontinuity of the changes in question.*"

6. *Negative Results of Experiments on Quantitative Variation*

We agree with Johannsen that an *appearance* of continuity might arise through the selection of degrees of hereditary fluctuation in structure or function, for example, of tallness or shortness of stature, of intensity or faintness of color. This brings up the problem of fluctuation in the germinal determiners. Some Mendelians discard fluctuations altogether as non-hereditary; thus Punnett (1911, p. 138)[19] observes: "At the present time we have no valid reason for supposing that they [fluctuations] are ever inherited."

The problem, however, is not as to quantitative ontogenic variations caused by favorable or unfavorable environment or by changes or habit, but as to *heritable fluctuations springing from the germ plasm.* Experiments have been directed to the point whether variations in size, in proportion, etc., of hereditary unit characters are transmitted and accumulated by selection.

Davenport also has reached negative results; he observes (1910):

> In the last few decades the view has been widespread that characters can be built up from perhaps nothing at all by *selecting in each generation the merely quantitative variation that goes farthest in the desired direction.* The conclusion upon which De Vries laid the greatest stress, that quantitative and qualitative characters differ fundamentally in their heritability, is supported by our experiments (p. 96). I have made two tests of this view using the plumage color of poultry (p. 94). . . . After three years of selection of the reddest offspring no appreciable increase of the red was observed except in one case, which looks like a sport (p. 96). These fluctuating quantitative conditions depend on variations in the point at which the ontogeny of the character is stopped; and the *stopping point* is in turn often if not usually determined by external conditions which favor or restrict the ontogeny. Thus the selection of redness of comb, of polydactylism, of syndactylism, have not proven the inheritance of quantitative variations. Apparently, within limits, these quantitative

[19] Punnett, R. C.: Mendelism, Macmillan Co., 1911 (3d edition).

variations have so exclusively an ontogenic signification that they are not reproduced so long, at least, as environmental conditions are not allowed to vary widely.

Similarly Love [20] from experiments on the yielding power of plants remarks:

Unless further studies produce different results we can say from the facts at hand that there is no evidence to show that a basis exists for cumulative selection.

Similar conclusions have been reached by Pearl (1909) [21] in the breeding of fowls for laying purposes.

All the above results are negative.

Even the positive or affirmative results obtained by Cuénot and later by Castle, wherein quantitative characters may be shifted in one direction or the other by selection, are now given a new interpretation by certain Mendelians.

On the other side Cuénot showed by continued selection of lighter colored mice that the coat became paler; and Castle has shown that in rats the coat through selection may be made darker. Castle remarks (1911): [22]

I prefer to think with Darwin that selection . . . can heap up quantitative variations until they reach a sum total otherwise unattainable, and that it thus becomes creative.

He cites cumulative results in the development of a fourth toe in the hind foot of guinea-pigs and in the modification of the dorsal striping of hooded rats.

Morgan's remarks (1912) on these positive experiments are as follows:

Castle has been very guarded in regard to the *interpretation* of the results of selection in this case. It is probable that extreme selection

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[20] Love, Harry H.: Are Fluctuations Inherited? Contr. VI, Lab. Experim. Plant-Breeding, Cornell Univ., Amer. Naturalist, vol. xliv, No. 523, July, 1910, pp. 412–423.

[21] Pearl, Raymond: Is there a Cumulative Effect of Selection Abstammungs und Verebungslehre, 2, 1909, H. 4.

[22] Castle, W. E.: The Nature of Unit Characters, The Harvey Lectures, delivered under the Auspices of the Harvey Society of New York, 8vo, J. B. Lippincott Co., pp. 90–101.

is necessary to maintain the higher stage reached. It does not breed true and slips back easily. If this is correct it suggests: first, that nothing permanent has been effected in the germ-cells; and second, that the result is due to the discovery of more extreme cases of fluctuating variations than ordinarily occur.

The general import of these experiments and opinions *is that fluctuations in the determiners, or genes, can be utilized to establish a new quantitative mean.* It is obvious that what have been measured by biometricians as hereditary "fluctuations" might be regarded as "saltations" of all degrees, but such saltations do not represent *new* determiners in the Mendelian or Johannsen sense; they are mere fluctuations in existing determiners. Pure Mendelians would allege that tallness in man or other mammals can only be accumulated through the saltatory origin of "tall" determiners which are not connected continuously through intermediate forms with the antithetic "short" determiners. As to stature Brownlee observes (1911, p. 255): [23]

> I think that I have shown that there is nothing necessarily antagonistic between the evidence advanced by the biometricians and the Mendelian theory. . . . (1) If the inheritance of stature depends upon a Mendelian mechanism, then the distribution of the population as regards height will be that which is actually found, namely, a distribution closely represented by the normal curve.

6. *Summary as to Discontinuity and Mendelism*

Genetics is the most positive, permanent and triumphant branch of modern biology. Its contributions to heredity are epoch-making. But heredity is the conservative aspect of biology, and experimental genetics thus far chiefly reveals the laws of conservation rather than of natural progression.

Genetics has not yet brought us one single step nearer the solution of the problem of the progressive origin of new char-

[23] Brownlee, J.: The Inheritance of Complex Growth Forms, such as Stature, on Mendel's Theory, Proc. Roy. Soc. Edinburgh, vol. xxxi, Pt. II, 1911, pp. 251–256.

acters in mammals. The very independence, multiplicity and discontinuity of the units leave us farther afield. In place of what used to be regarded as the instability of the organisms, as a whole, we now have to conceive of the instability of thousands, nay hundreds of thousands of units.

As shown in our analysis of the saltations cited by Darwin and Bateson, Mendelism has revealed the fact that the majority of saltations simply reflect failures in the germinal mechanism. The inference is natural that the remaining minority also represent anomalies, or lawless conditions. Over a half century of anatomical research among mammals in a state of nature has failed to demonstrate the sudden origin of a single new progressive character which has become fixed in the race.

Nor have Mendelism and experimentalism released us from the hard confines of examination of the germ through the soma; behavior of unit characters in the soma is the sole means of knowing the behavior of the "determiners" in the germ. If the unit characters in the soma behave discontinuously we are forced to the conclusion that their determiners behave discontinuously; if, on the contrary, these unit characters behave continuously, are we not forced to the conclusion that there is a continuity in the behavior of the corresponding determiners?

Let us therefore proceed to consider the value of some of the evidence for continuous behavior in the germinal origin of certain new somatic characters, again repeating our opinion that certain other characters are essentially antithetic, without intermediates, and consequently discontinuous both in heredity and in origin.

II. EVIDENCES FOR CONTINUITY

Abandoning the historical background, we come to our own subject, *the origin and establishment in continuity of certain characters which when established exhibit many of the distinctive features of unit characters, namely, segregation, stability, pure heredity, and possibly, although this has not yet been demonstrated, dominance and recession in successive generations.*

1. *Rectigradations and Allometrons.*

In fifteen previous papers by the writer beginning in 1889[24] the observation is repeatedly made that all absolutely new characters which we have traced to their very beginnings in fossil mammals arise gradually and continuously. One by one these characters, which are independently changing in many parts of the organism, at the same time accumulate until they build up a degree of change which paleontologists designate as a "mutation" in the sense of Waagen, who proposed this inter-specific term in 1869; finally these new characters attain a sufficiently important phase to designate the stage as a species.[25]

These new characters were first (1891) termed "definite variations"; subsequently (1907)[26] the term "rectigradations" was applied to them.

Rectigradation is merely a designation for the earliest discernible stages of certain absolutely new characters; it involves no opinion nor hypothesis as to genesis; it is a simple matter of observation. Referring to the figure (p. 200) of the upper grinding teeth of the horse, the majority of the fourteen characters have been observed to arise as rectigradations.

Quite different is the *allometron*. This is a new designation for the continuous change of proportion in an existing character which may be expressed in differences of measurement. Since 1902 and especially during the past year the behavior

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[24] Osborn, H. F.: The Paleontological Evidence for the Transmission of Acquired Characters, Amer. Naturalist, vol. xxiii, No. 271, July, 1899, pp. 561–566.

[25] This sentence may be contrasted with that of Punnett (op. cit., p. 15): "Speaking generally, species do not grade gradually from one to the other, but the differences between them are sharp and specific. Whence comes this prevalence of discontinuity if the process by which they have arisen is one of accumulation of minute and almost imperceptible differences? Why are not intermediates of all sorts more abundantly produced in nature than is actually known to be the case?"

[26] Osborn, H. F.: Evolution of Mammalian Molar Teeth to and from the Triangular Type, 8vo, Macmillan Company, September, 1907.

of allometrons has been very carefully investigated by myself and by my colleague, Dr. W. K. Gregory.

RECTIGRADATION = a qualitative change, the genesis of a new character in an adaptive direction.

ALLOMETRON = a quantitative change, the genesis of new proportions in an existing character.

The distinction between a rectigradation and an allometron is readily grasped: when the shadowy rudiment of a cusp or of a horn first appears it is a rectigradation; when it takes on a rounded, oval or flattened form this change is an allometron. In mammals rectigradations are comparatively few and infrequent, while allometrons comprise the vast number of changes in the hard parts. In the origin of cusp and horn rudiments rectigradations are parallel or convergent (see Fig. 3), in the changing proportions of a skull allometrons are divergent (Figs. 1, 3).

Granting, without at present considering the evidence,[27] that these rectigradations and allometrons arise continuously through entirely unknown laws, also that they are blastic or germinal characters, the question arises, Do they become separable as unit or alternating characters in heredity?

In general, paleontology furnishes quite as strong proof as Mendelism or experimental zoology *as to the individuality, separableness, and integrity of single characters in evolution.* But, whether both rectigradations and allometrons are separable in heredity can only be demonstrated through experiments on cross breeding or hybridizing.

The special object of this Harvey Lecture is to show that certain at least of the rectigradations and allometrons observed in mammals are separable in heredity, that they split up into larger and smaller groups or units, some into partially blend-

[27] This evidence is for the first time fully presented in the writer's monograph on the "Titanotheres," in preparation for the U. S. Geological Survey.

ing units, others into absolutely distinct or non-blending units; finally that at least in the first cross they exhibit dominance.

The very important remaining question whether, like the quality of "tallness" or "shortness" in Mendel's classic experiments on the pea, these allometrons continue to split into dominants and recessives in later crosses, has not been investigated, but is probably capable of investigation in mammals which do not become sterile in the first hybrid generation.

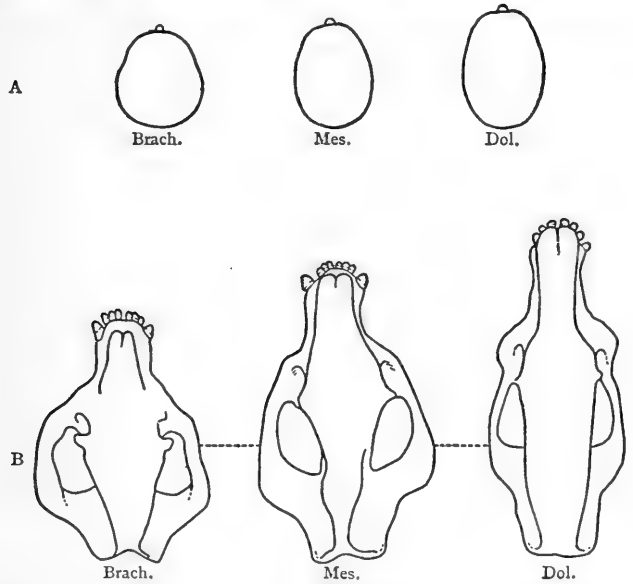

FIG. 1. CONTINUOUS ORIGIN OF ALLOMETRIC "UNIT CHARACTERS" IN THE CRANIUM (*A*) AND SKULL (*B*) OF MAN AND TITANOTHERES.

A, Man	Brachycephaly	Mesaticephaly	Dolichocephaly
B, Titanotheres	Brachycephaly (*Palæosyops*)	Mesaticephaly (*Manteoceras*)	Dolichocephaly (*Dolichorhinus*)

Five examples of the continuous evolution of rectigradations and allometrons may be cited, namely:

1. Skull and horns of titanotheres (Figs. 1, 3, 4).
2. The horns of cattle (Fig. 2).
3. The cranium of man (Fig. 1).
4. The skull of horses (Figs. 4, 5, 6, 7).
5. Teeth (Fig. 8).

One of the most salient examples of the genesis of unit characters through continuity is that of the evolution of horns, *i.e.*, of the osseous prominences on the skull. Horns are now known definitely to be "unit characters," first through their sudden and complete disappearance in the niata and polled breeds of cattle; second, because they conform to the laws of sex-limited inheritance. The pertinent question is, Do horns originate continuously or discontinuously?

2. *Horns of Titanotheres*

The titanotheres are an extinct family of quadrupeds distantly related to the horses, tapirs and rhinoceroses, to the evolution of which the author has devoted twelve years of investigation, assisted by Dr. W. K. Gregory. As set forth in an earlier contribution [28] the genesis of horns as rectigradations has been observed in four or five distinct phyla of titanotheres. These phyla descend independently from a single ancestor of remote geologic age. Both in respect to new cusps on the teeth and new horn rudiments on the skull there is observed what in our ignorance may be called *an ancestral predisposition to the genesis of similar rectigradations.* This predisposition betrays the existence of *law* in the origin of certain new characters; it recalls a sagacious remark of Darwin:

> . . . The principle formerly alluded to under the term of *analogical variation* has probably in these cases often come into play; that is, the members of the same class, although only distantly allied, have inherited so much in common in their constitution, that they are apt to vary under similar exciting causes in a similar manner; and this would obviously aid in the acquirement through natural selection of parts or organs, strikingly like each other, independently of their direct inheritance from a common progenitor.[29]

Briefly, the history of the origin of the titanothere horns

[28] The Four Inseparable Factors of Evolution. Theory of Their Distinct and Combined Action in the Transformation of the Titanotheres, an Extinct Family of Hoofed Animals in the Order Perissodactyla, Science, N. S., vol. xxvii, No. 682, January 24, 1908, pp. 148–150.

[29] Origin of Species, vol. ii, p. 221.

is as follows: (*a*) from excessively rudimentary beginnings, *i.e.*, rectigradations, which can hardly be detected on the surface of the skull; (*b*) there is some predetermining law or similarity of potential which governs their first existence, because (*c*) the rudiments arise independently on the same part of the skull in different phyla at different periods of geologic time; (*d*) the horn rudiments evolve continuously, and they gradually change in form (*i. e.*, allometrons); (*e*) they finally become the dominating characters of the skull, showing marked variations of form in the two sexes; (*f*) they first appear in late or adult stages of ontogeny, but are pushed forward gradually into earlier and earlier ontogenic stages until they appear to arise prenatally.

In the titanotheres (Fig. 3) the bony swelling is seen at the junction of the nasals and frontals (black shading), in dolichocephalic skulls it appears chiefly on the nasals, in brachycephalic skulls chiefly on the frontals. Its original low, rounded shape is like that seen in the ontogeny of the horns in cattle (Fig. 2).

3. *Horns of Cattle*

The phylogenesis of the horns in titanotheres (Fig. 3) is exactly similar to the ontogenesis of the horns in Bovidæ (Fig. 2), in which the dermal rudiments first appear soon after the complete formation of the bones of the skull in the unborn young, and the osseous rudiments appear as rounded protuberances in the 8th month.

In the ontogenesis of horns in cattle three distinct elements are involved: (*a*) a psychic predisposition to use the horn, (*b*) a dermal thickening over the bony horn region which in ontogeny precedes the bony swelling, (*c*) appearance of the bony swelling itself.

The ontogenesis is observed to be accompanied by a marked allometric change in the skull which shifts the horn backward from the side of the cranium to the side of the occiput by the obliteration of the parietal bones (Fig. 2).

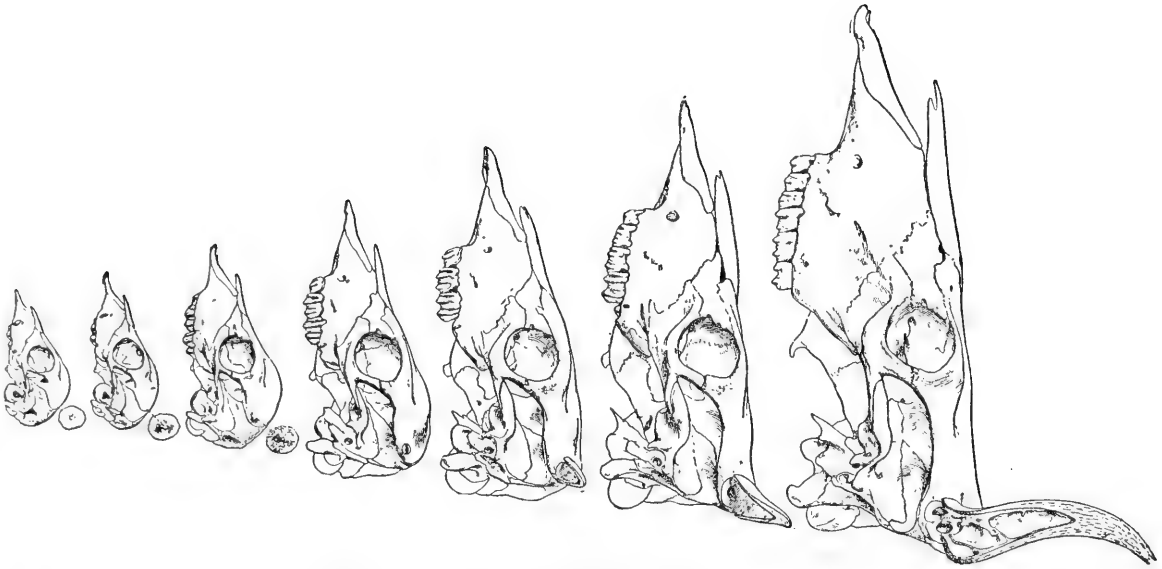

FIG. 2. CONTINUITY IN THE ONTOGENESIS OF THE HORN AND HORN SHEATH IN CATTLE IN SEVEN STAGES, 1–7. After preparations by Mr. S. H. Chubb in the collections of the American Museum of Natural History.

1. Adult, 9 years, completed osseous horn and horny sheath. 2. Yearling, 18 months, continuous shifting of osseous horn to occiput. 3. Calf, 2 months, continuous shifting of osseous horn to occiput. 4. Calf, 2 weeks, continuous shifting of osseous horn to occiput. 5. Fœtal stage, 9th month, bony swelling, and epidermal swelling pointed. 6. Fœtal stage, ?6–7th month, epidermal swelling, covered with pointed hair tuft. 7. Fœtal stage, ?5th month, epidermal swelling, covered with 40 scattered hairs.

4. *Cranium of Man*

A third instance of continuous development is that of the form of the cranium in man (Fig. 1), an allometric evolution, or change of proportion, which is of especial significance because, according to the unanimous testimony of anthropologists,[30] head form is the result of very gradual change either in the elongate (dolichocephalic) or broadened (brachycephalic) direction.

The matter is directly pertinent to the present discussion because human "long heads" and "broad heads" are continuously crossing and we know what the direction and ultimate effects of such crosses are. The evidence has important theoretical bearing also on the influence of selection, environment, and inheritance or the effects of use and disuse.

Determination of the proportions of the cranium or the cephalic index is one of the standard tests of race; it is an expression of the greatest breadth of the head above the ears and the percentage of its greatest length from the forehead (glabella) to back, the latter measurement being taken as 100. Three types adopted by anthropologists are:

	Extreme Range
Brachycephalic, 80.1 and above	100–80
Mesocephalic, 75.1–80	80–75
Dolichocephalic, 75 and below	75–62

Among the present races of Europe the widest limits of variation between brachycephaly and dolichocephaly are in the averages between 73 and 87; individual extremes of 62 and 100 have, however, been observed. These extremes in European head form do not coincide either with geographic or political boundaries, but are attributed to the entrance into Europe of brachycephalic and dolichocephalic types which evolved in Asia.

Similarly among the aborigines of America the indices range from a low dolichocephaly as among the Delaware, Pima Indians, etc., to a decided brachycephaly as among the

[30] Ripley, Wm. Z.: The Races of Europe, a Sociological Study, 8vo, D. Appleton & Co., 1899, 624 pp.

Athabascan tribes in Panama, Peru, and other localities. A significant fact in Europe is that dolichocephaly and brachycephaly are extremely stable characteristics in heredity. The significant fact again is that through a very long period of time the various races of Indians, who are believed to have had originally a similar origin, have acquired under conditions of geographic isolation considerable diversity in the proportions of the head.

Similarly A. Keith[31] from the present distribution of the Negro tribes in equatorial Africa has reached the following conclusions:

> There has been free intermigration; in the course of their evolution, the tendency of one tribe has been towards the accentuation of one set of characters, of another towards another set. Thus the Dinka acquire high stature and narrow heads; the typical Nigerians low stature and narrow heads; the Basoko wide, short heads and low stature; the Buruns wide heads and high stature. Interbreeding may have played its part; but if it had played a great part we should have found greater physical uniformity than there is. The influence of Arab blood on these tribes has probably been exaggerated.

It appears that environment has not any direct influence on head form, but that geographical isolation affords the several varieties of man as well as other mammals a chance to develop their peculiar head characters. Thus Elliot Smith states (letter, August 12, 1911):

> In my opinion the conditions of dolichocephaly and brachycephaly must have developed very slowly through exceedingly long periods of time and in widely separated areas amidst widely different environments. Brachycephaly is especially distinctive of the Central Asian high plateau populations, dolichocephaly of the littoral and plain-dwelling peoples; but these "unit characters" are now so fixed that environment is powerless to modify them in a thousand years or so. . . . I do not believe for a moment in Boas [that is, in Boas's observations (1911) on the rapid influence of environment in modifying head form].

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[31] Keith, A.: Journ. Royal Anthropological Institute, 1911. See Nature, vol. 88, No. 2195, November 23, 1911, p. 119.

Elliot Smith takes very strong ground as to the lack of evidence that environment directly produces any modification of head form; he implies that such modification, if natural, would only show itself after thousands of years of residence; environment no doubt has indirect influence. Hrdlička, on the other hand, believes he has obtained definite results in the influence of environment [or habit, H. F. O.] on the vault and face form of the Eskimo;[32] it remains to be shown how far these changes are ontogenic. The recent conclusions of Boas (1911)[33] that dolichocephaly and brachycephaly are congenitally altered by environment in the first generation are modified by his statement that this action in bringing diverse head forms together would not go so far as to establish a uniform general type.

No anthropologist has offered any satisfactory explanation as to the adaptive significance of dolichocephaly or brachycephaly. It is well known that these differences of head form are not associated with intellectual ability or mental aptitude. Boas writes (April 8, 1911):

> So far the matter is very perplexing to me. I feel, however, very strongly with you that changes in type are very liable to be progressive in definite directions. . . . To my mind it seems no more difficult to assume that this predetermined direction should continue from generation to generation than to make the much more difficult assumption that notwithstanding all internal changes the egg-cell of one generation should be absolutely identical with that of the preceding generation.

Apart from the disputed problems of the direct influence of environment and of human selection there is absolute unanimity of evidence and of opinion on the one point essential to the present discussion, namely, *as to the continuity of*

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[32] Hrdlička, Ales: Contribution to the Anthropology of Central and Smith Sound Eskimo, Anthr. Paper Am. M. N. H., v, Pt. II, 1910, p. 214.

[33] Boas, Franz: The Mind of Primitive Man, 8vo, Macmillan Company, New York, 1911, 924 pp.

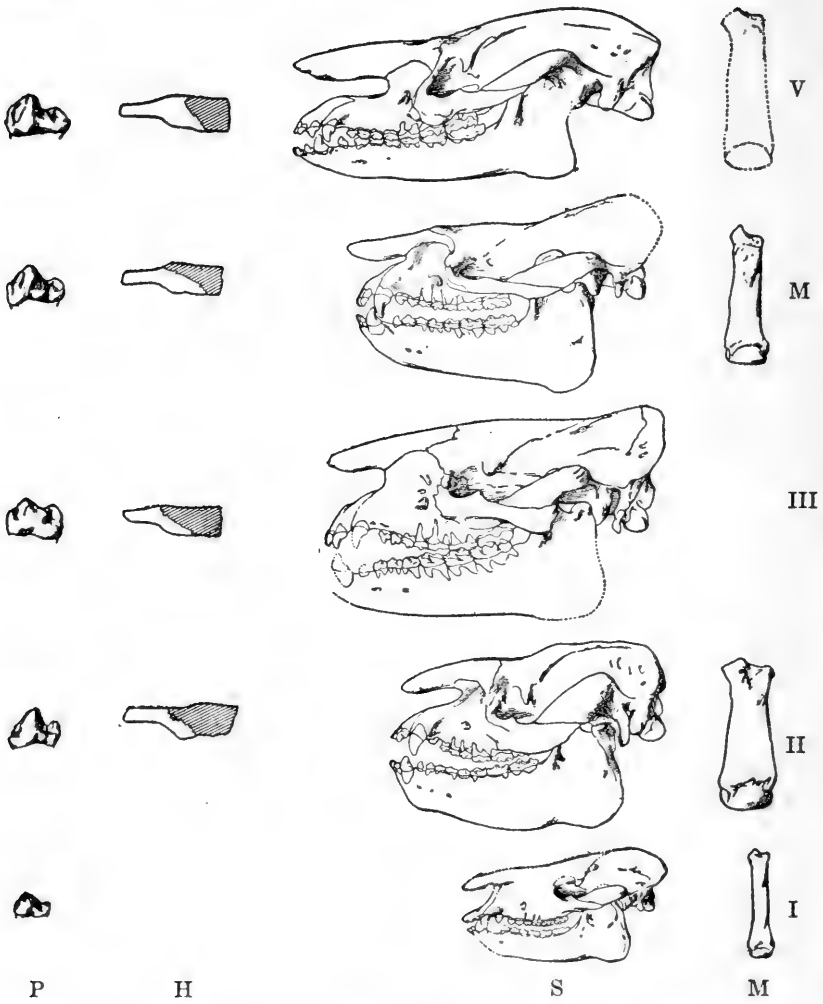


FIG. 3. RECTIGRADATIONS AND ALLOMETRONS IN TITANOTHERES. Continuity in the phylogenesis of osseous horns in titanotheres. P = 2d lower premolar; H = section of nasals and frontals (shaded) showing osseous horn; S = skulls; M = median metacarpal bones.

V. *Dolichorhinus*, a long-headed (dolichocephalic) titanothere.
IV. *Manteoceras*, a medium-headed (mesaticephalic) titanothere.
III. *Telmatherium*, a medium-headed (mesaticephalic) titanothere.
II. *Palæosyops*, a broad-headed (brachycephalic) titanothere.
I. *Eotitanops*, an ancestral (mesaticephalic) titanothere.

II–V belong to four independent phyla which diverge in their allometric evolution of head (S) and foot proportion (M) but give rise to independent similar rectigradations in the origin of cusps on the premolar teeth (P) and of osseous horn rudiments (H) on the skull.

allometric variation which establishes different extremes of head form under conditions of geographic isolation.

Granted that such extremes as dolichocephaly and brachycephaly evolve continuously, do they become discontinuous in heredity?

One of the general results of crossing long-headed and narrow-faced types with broad-headed and broad-faced types is what is known as disharmonic heredity, namely, that condition in which the face and cranium do not hold together, but broad faces may couple with long skulls, or *vice versa* (Boas, 1903).[34] Boas concludes that there can be no question that the mixture of a long-headed and of a short-headed race may lead to disharmonism, one race contributing head form, the other facial proportion.

As to stability or segregation in heredity the latest opinions of Boas, Elliot Smith and Hrdlička have been sought. Boas is one of the most positive as to the herditary stability of head form. He observes (1911, pp. 7–9):

> Among European peoples head proportions are considered among the most stable and permanent of all characteristics. In intermarriage of "dolichocephalic" and "brachycephalic" individuals the children do not form a blend between their parents but inherit either the dolichocephalic or brachycephalic head form. Head form thus constitutes a case of almost typical alternating heredity (p. 55). No evidence has been obtained, however, to show that either brachycephaly or dolichocephaly is dominant. Children exhibit one head form or the other, and the cephalic index or ratio of breadth to length undergoes only slight alteration during growth, or ontogeny.

Elliot Smith (letter of August 12, 1911) is "firmly convinced that the form of cranium, orbits, nose, jaws, limb bones, etc., in the 'Armenoid' and 'Proto-Egyptian' series are very stable or even fixed 'unit characters' which do not really blend, but that certain elements of a mosaic assemblage of characters may be grafted on to others belonging to the other race."

Opinions as to Blending.—It will be noted, however, that

[34] Boas, Franz: Heredity in Head Form, Amer. Anthropologist, vol. 5, No. 3, July–September, 1903, pp. 530–538.

Boas (1895) admits a certain blending of head form in crosses. Hrdlička (letter, November 1, 1911) speaks even more guardedly as to the hereditary stability of head form. He says:

> As to the head form constituting a "unit character" which does not blend in intermixture, I am not able to give a conclusive opinion, but my experience and other considerations lead me to be very skeptical that such is the case to any great extent. The subject is a very complex one and requires considerable direct investigation in different localities and with different peoples before the exact truth can be known. . . . As to the statement that long or broad head form is a stable or unit character not blending in intermixture, I think that only the first part of the proposition may be held as fairly settled. But even then I should change the word "stable" to "persistent," and qualify the phrase by adding "under no greatly differing and lasting environmental conditions."

That *prolonged* interbreeding or intermixture tends to break down the stability of hereditary head form is indicated by Boas, Elliot Smith, and Ripley, as well as by Hrdlička, as quoted above. Thus Ripley (1899, p. 55) observes:

> The plotting of cephalic indices on a map of Europe shows that there is a uniform gradation of head form from several specific centres of distribution outward.

In Italy over 300,000 individuals taken from every little hamlet have been measured. In the extreme south we find the dolichocephalic head form of the typical Mediterranean race; the type changes gradually as we go north until in Piedmont we find an extreme of brachycephaly in the Alpine type, recalling the broad-headed Asiatic type of skull. Thus (Ripley, p. 56) "pure physical types come in contact and this means ultimately the extinction of extremes." Applying these principles to the present case, it implies the ultimate blending of the long and the narrow heads and the substitution of one of medium breadth.

Elliot Smith also (letter, August 12, 1911) implies a gradual modification or blending of head form through prolonged intermixture. He observes:

Egypt does not give a clear answer to your queries because her exceedingly dolichocephalic brown race [related to the Mediterranean race of southern Europe] underwent a double admixture (circa 3000 B.C.) with moderately brachycephalic "Armenoids" from Asia

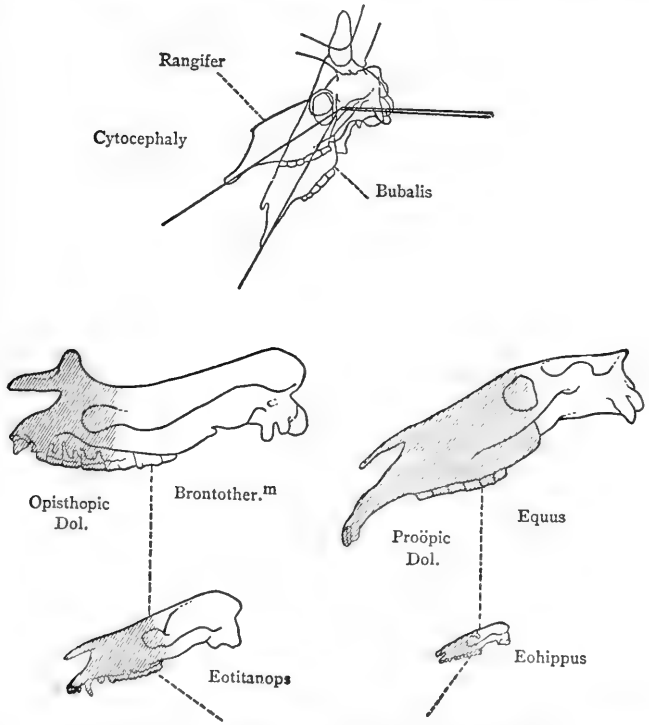


FIG. 4. CONTINUOUS ORIGIN OF ALLOMETRIC "UNIT CHARACTERS" IN THE SKULL OF VARIOUS UNGULATES.

C, Cytocephaly	*Bubalis*	*Rangifer*
D, Dolichocephaly	Opisthopic	Proöpic
	(Titanotheres)	(Equines)

In the ancestral *Eotitanops* and *Eohippus* the facio-cranial index is very similar. In the descendants of these animals, as indicated by the dotted lines, the facio-cranial indices are widely divergent; in the Titanotheres (*Brontotherium*) the cranium is elongated; in the horses (*Equus*) the face is elongated.

and dolichocephalic Negroes from Africa. The Mediterranean Egyptians are on the whole a little broader-headed than they were 6,000 years ago, and this *may* be due in part to a slow development toward mesaticephaly; but it is mainly the result of an admixture with alien

bracephalics and mesaticephalics. There is an unquestionable tendency toward the elimination of the extremes of narrowheadedness and broadheadedness.

Hrdlička (letter, December 5, 1911) observes:

As to the effect of the mixture of brachycephalic and dolichocephalic individuals or peoples, I am led to believe that there is in the results of such mixtures a large percentage of more or less intimate "blend" of the two forms, for such a condition is indicated by the curves of distribution of the cephalic index among such national conglomerates as the French, Germans, different tribes of the American Indians, etc. These curves, if sufficiently large numbers of individuals have been examined, all approach more or less the ideal camel-back curve. If no "blend" existed, we should be bound to get the double or dromedary-back curve. Of course the effects of mixture and the effects of environment are with our present means often impossible of separation, they often obscure each other. Yet the indications are that there is generally a considerable amount of more or less mixture of the many elementary constituents of the hereditary characters [known collectively as] dolichocephaly and brachycephaly. With this there coexists doubtless some tendency toward a differentiation into the two opposite forms of the head.

Thus in human head form we have strong evidence of continuous allometric change strictly comparable to that which occurs in the crania of lower mammals, especially as observed in the horses and titanotheres; the extremes are produced in so-called pure human races under conditions of geographic isolation; when these pure races are brought together there arises disharmonism or alternating heredity or both. Neither the dolichocephalic nor brachycephalic type is as yet known to be dominant; while opinion is divided as to whether in the first cross the heredity is pure or whether there may be a tendency to produce an intermediate form, opinion is nearly unanimous that prolonged interbreeding produces blends.[35]

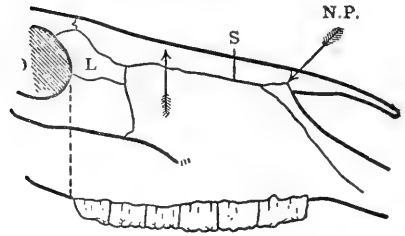
[35] T. H. Morgan observes that a blend may occur in the first generation, F_1, even where perfect segregation occurs in F_2. The results of crossing the equine skull as described below indicate a tendency to blend certain characters in the first cross.

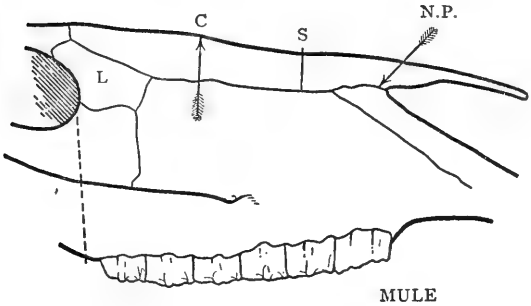
5. *Skull of Titanotheres*

The continuity of allometric evolution in the skull of the titanotheres (Fig. 4) has been the subject of prolonged investigation by the writer, assisted by Dr. W. K. Gregory, involving thousands of measurements, many of which belong in strictly successive phyletic series. Allometry (*i.e.*, the measurement of allometrons) here applies to the skull as a whole. We secure the cephalic index by dividing the breadth across the cheek arches by the total basilar length of the skull. There are also other indices, such as the facio-cranial, in which we measure continuous trends of allometric change. Brachycephaly and dolichocephaly arise independently in four different phyla or lines of descent. The adaptive significance is sometimes apparent, sometimes obscure. As shown in Fig. 1 the titanotheres, like man, exhibit facial abbreviation and cranial elongation (postopic dolichocephaly) in contrast with the facial elongation (proöpic dolichocephaly) of the horses. These phenomena are similar to those of cytocephaly, or the bending down of the face upon the base of the cranium as observed in the reindeer (*Rangifer*) and the hartbeest (*Bubalis*). Cytocephaly is an ontogenetic and phylogenetic new character, arising or developing continuously.

As in the case of the human skull, the causes of these profound changes in head form are entirely unknown; the mechanically adaptive significance is sometimes apparent, sometimes obscure. By the examination of the titanotheres the evidence is strengthened that human selection has little or no influence on human cranial form.

The great point to emphasize is that *this allometric evolution in the skull and all parts of the skeleton is the prevailing phenomenon of change in the skeleton of mammals.* It is constantly in progress and is universally, so far as we can observe, a continuous process. As displayed in the four phyla of titanothere (Fig. 3), the elongations or broadening of the foot bones proceed independently and are *divergent*, while in the same mammals the rectigradations exhibited in the rise of





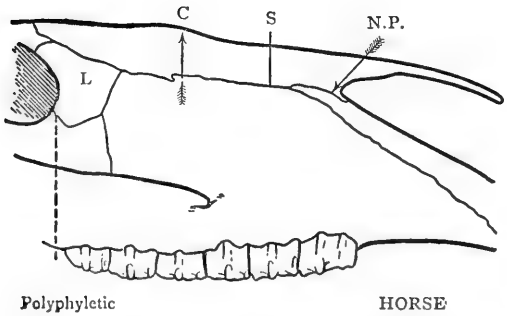


FIG. 5. CROSS-BREEDING AND IMPERFECT BLENDING OF ALLOMETRIC "UNIT CHARACTERS" OF THE FACIAL BONES IN ASS (MALE), HORSE (FEMALE) AND MULE.

Bones of the side of the face, Ass.
Bones of the side of the face, Mule.
Bones of the side of the face, Horse.

The horse is certainly polyphyletic, the ass is probably monophyletic. *C*. The arrow points to *C*, a distinct bump in the horse and mule, not observed in the ass. *S* = point at which the section of the nasals is taken. *L* = lachrymal. *N. P.* = naso-premaxillary suture.

similar cusplets on the teeth and similar horn rudiments on the face are convergent; in the former case no ancestral predisposition seems to be operating, in the latter case ancestral predisposition certainly seems to operate; this is why the internal laws controlling the origin of new allometrons and of new rectigradations and allometrons are regarded as essentially dissimilar.

Paleontological analysis of these rectigradations and allometrons, even unaided by experimental heredity, reveals the essential feature of the "unit character" principle, namely, *that what we are observing is an incredibly large number of unit elements each of which enjoys a certain independence of evolution at the same time that each unit is adaptively correlated with all the others.* For example, in the upper and lower grinding teeth of horses alone there are 504 cusp units, each of which has an independent origin and development; at the same time each cusp is more or less distinctly correlated in form with the all-pervading dolichocephaly or brachycephaly of the skull; in fact, from certain single cusps of the teeth we can often determine whether the animal is brachycephalic or dolichocephalic.

As a result of the somewhat conflicting evidence as to the crossing of brachycephals and dolichocephals in man, the question arises what happens when we cross two phyla of lower mammals which have been diverging along separate allometric lines and in the meantime have acquired a greater or less number of new characters which when sufficiently developed attain specific rank.

The answer is given very distinctly in the cross between the dolichocephalic horse (*E. caballus*) and the mesocephalic ass (*E. asinus*). Here we learn again that profound differences have been established through continuity and that we are enabled to split up these differences into distinct or partially blending units through cross breeding.

6. *Blended or Alternating Heredity in Horses*[36]

So high an authority as J. Cossar Ewart (1903) has sustained the prevailing view that in the mule there is generally an imperfect blending of the characters of the immediate parents; the same author, however, notes that mules occasionally serve as examples of unit or exclusive inheritance.[37] He cites two cases: (1) a mule out of a well-bred, flea-bitten New Forest pony closely resembles her sire, the ass; (2) a "calico" mule, on the other hand, is surprisingly like his dam, an Indian "painted" pony. This painted mule demonstrates that the ass is not always more prepotent than the horse. From this author's very extensive breeding experiments the following conclusions are reached: the less fixed or racially valuable characters of zebras either blend with or are dominated by the corresponding characters in their horse and ass mates. Thus, as influencing dominance or prepotency, the value which a character has attained in the past struggle for existence seems to count for something. In zebras and in horses certain physical and mental traits are more highly heritable than others. Among the characteristics which are often handed down unblended in zebra-horse hybrids and to a less extent in zebra-ass hybrids are the size of the ears, the form of the hoofs, the massiveness of the jaws; while among psychic characters are transmitted the extreme caution, the wonderful alertness and quickness.

The new results brought forward in this Harvey Lecture from the comparison of the skull and teeth of the horse, ass

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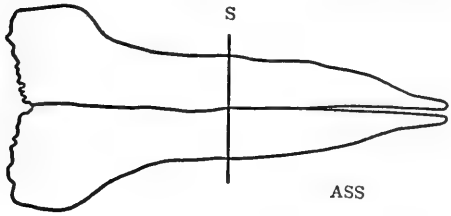
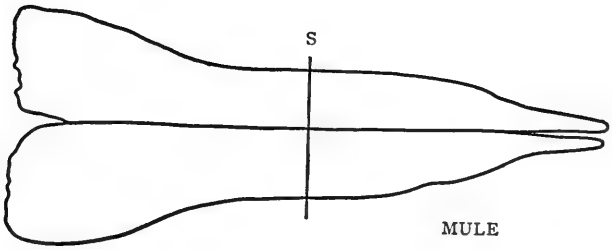
[36] The writer is indebted to Mr. S. H. Chubb, Mrs. Johanna Kroeber Mosenthal, and to Dr. W. K. Gregory for many of the observations and all of the measurements on which this comparison is based. The materials studied are three skulls of the ass (♂ *E. asinus*), ten of the horse (♀ *E. caballus*), and four of the mule, all adult with teeth in approximately the same stage of wear.

[37] The most recent (1912) opinion of Ewart is much more positive as to the operation of Mendel's law in pure breeding strains of horses. See Eugenics and the Breeding of Light Horses, The Field, February 10, 1912, pp. 288, 289.





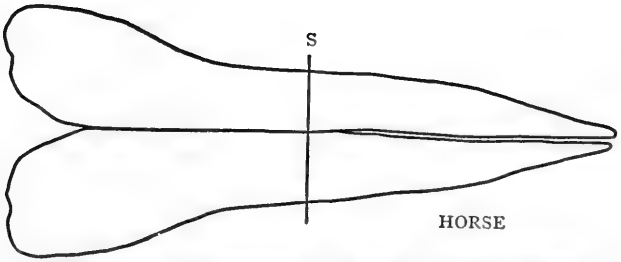


FIG. 6. CROSS-BREEDING AND IMPERFECT BLENDING OF SUB-ALLOMETRIC "UNIT CHARACTERS" OF THE NASAL BONES IN ASS (MALE) AND HORSE (FEMALE).

Top view of nasals and naso-frontal suture, Ass.
Top view of nasals and naso-frontal suture, Mule.
Top view of nasals and naso-frontal suture, Horse.
S=point of section shown in Figs. 3 and 5.

and mule on the whole strengthen the theory of unit inheritance both in rectigradations and in allometrons. The measure of unit character inheritance as contrasted with blended inheritance is very precisely brought out in the detailed study of the twenty-two characters which are examined below. Before discussing these characters in detail it is interesting to point out that the ancestors of the horse and the ass have probably been separated for at least 500,000 years. In the meantime the horse has become extremely dolichocephalic, the ass has remained comparatively mesocephalic; the horse has a relatively long, the ass a relatively short face; the horse has highly complex, the ass has somewhat simpler grinding teeth; the horse exhibits advanced adaptation to grazing habits and has become habituated to a forest and plains life in comparatively fertile countries, while the wild ass is by preference a browsing animal, finding its food in excessively arid countries where there is a marked dearth of water and water courses. The physical and psychical divergences in these two animals have developed over an enormously long period of time. Every single tooth and bone of the horse and ass shows differences both as to rectigradation and as to allometric evolution.

One feature which tends to make the results of the cross less clear and distinctive than they are is that while the ass is monophyletic (being descended with modification from the wild *E. asinus* of northern Africa), the domestic horse is not a pure strain and is certainly polyphyletic, having in its blood that of several races, such as the Arab and the Forest or Norse horse, animals which have specific distinctness although they still interbreed.[38] To this mixed strain or polyphyletic heredity of the horse, are probably attributable in the mule many of the allometric variations in the bones of the skull and in the enamel pattern of the teeth in some of which we observe a nearer approach to the ass type than in others. If we could cross the ass with a pure horse race like the Steppe or Prjevalsky horse

[38] There are many absolute characters which separate the Arab from the Norse horse, among them the invariable presence of one less vertebra in the lumbar region of the back.

we should probably obtain more precise results. Another disturbing feature in the comparisons and indices given below is that we do not know the exact structure of the skull of either

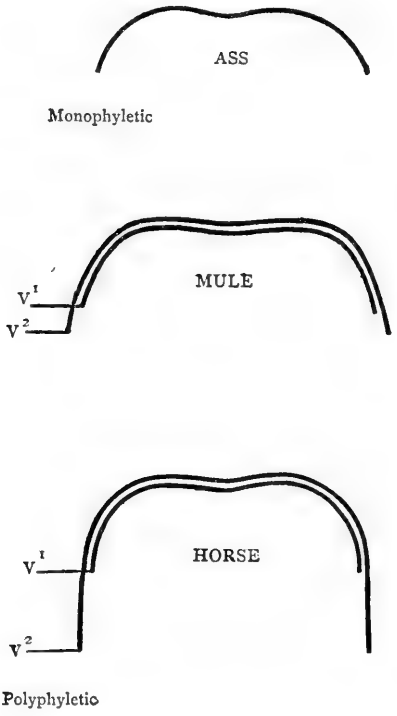


FIG. 7. CROSS-BREEDING AND IMPERFECT SEPARATION OF ALLOMETRIC "SUB-UNIT CHARACTERS" OF THE NASAL BONES IN ASS (MALE), HORSE (FEMALE) AND MULE.

Mid-section of nasal bones, Ass.
Mid-section of nasal bones, Mule.
Mid-section of nasal bones, Horse.

V^1, V^2=variations in the depth of the nasals in the mule. V^1, V^2=variations in the depth of the nasals in the horse.

of the parents from which the mule skulls examined were derived.

Despite these sources of fluctuation and of error, the general results obtained are fairly positive and definite.

The first point of interest as to the segregation of unit characters in the mule is that connected with the *three germinal layers,* namely, the epiblast, mesoblast and hypoblast.

All the characters of epiblastic origin appear to be derived from the sire, namely, the epidermal derivatives, the distribution of the hair, especially in the mane and tail, the hoofs, etc., are those of the ass, although the color pattern, as in the "calico" mules described by Ewart, may be derived from the mare. The nervous system and psychic tendencies, also of epiblastic origin, are also derived from the ass, including minor psychic characteristics, such as aversion to water. Still more striking, perhaps, is the fact that the enamel pattern of the grinding teeth, again of epiblastic origin, is mainly that of the ass, although, as shown below, there are some intermediate and some distinctive horse-like characters in the teeth of the mule; this may be partly connected with the mesoblastic derivation of the dentine of the teeth.

Mesoblastic derivatives, on the other hand, are divided between the sire and dam, the skeleton and limbs of the mule being mainly proportioned as in the ass, while the skull of the mule, as we shall see, is almost purely that of the horse.

Blending and Pure Inheritance in the Bones of the Face

Blending.—A comparison of the bones of the side of the facial or preorbital region shows intermediate or partly blended form and proportions both of the *nasals, premaxillaries, frontals,* and *lachrymals,* in which, however, the mule approaches *E. caballus* rather than *E. asinus.* Attention may be called to some of the details of the comparison: (1) *Suture between the nasals and premaxillaries:* in *E. asinus* short and elevated, in the mule intermediate but more like the horse; in the horse elongated and depressed (see Fig. 5). (2) *Naso-frontal suture on the top of the skull:* in the ass straight or transverse; in the mule incurved, more like the horse than the ass; in the horse arched or incurved (see Fig. 6). (3) *Depth and convexity of the nasals:* in the ass shallow and flattened; in the mule deeper, more like the horse; in the horse highly

arched. (4) *Bump or convexity on posterior third of nasals:* in the ass very slight; in the mule moderate, more like the horse than the ass; in the horse strong (see Fig. 7).

The same tendency in the mule to exhibit a slight departure from the horse toward the ass type is shown in the outlines of the bones of the face (Figs. 3, 4, 5). Comparing step by step the premaxillaries, maxillaries, nasals, and lachrymals, while the proportions and the sutural outlines are mainly those of the horse, there is a more or less distinct blending, or intermediate character in the direction of the ass; see especially the naso-premaxillary suture, and the degrees to which the nasals extend on the sides of the face to join the maxillaries. In this naso-maxillary junction certain horses approach the ass type. The characteristic bump on top of the nasals of the horse is transmitted to the mule, and the highly characteristic transverse suture between the frontals and the nasals, as seen from the top (Fig. 4), is rather that of the horse than of the mule.

Non-blending indices.—More definite results are shown in the heredity of the indices or ratios between the various portions of the skull and of the teeth; these indices are extremely constant allometric specific characters, they are independent of size. For example, the indices of a diminutive pony and of a giant percheron would be the same. Similarly the indices of a diminutive donkey and of a very large ass would be the same.

The index is the best and most exact form of expressing mathematically the profound differences between the skull of the horse and that of the ass. Indices have the value of specific characters; they are of especial significance in the present discussion in comparison with those in the face, cranium and palate of man and of the titanotheres above considered.

Chief among the allometric differences are the following: (1) In its proportions the ass has a relatively shorter space between its grinding and its cutting teeth, the bit-opening; this is correlated with the fact (2) that the ass has a relatively broader and shorter skull than the horse; also with (3) the

fact that the ass has a relatively longer cranium (postorbital space) and shorter face (preorbital space) than the horse; (5) the ass also has relatively broader grinding teeth correlated with the broader skull; (6) correlated also with its less elongate skull the ass has a relatively rounder orbit than the horse, *i.e.*, the vertical and horizontal diameters are more nearly equal. (7) A very distinctive feature is the angle which the occiput makes with the skull; this is one of the marked specific features of the ass.

NON-BLENDING OR PURE INHERITANCE INDICES IN THE SKULL

1. Cephalic Index:	$\frac{\text{Width of skull} \times 100}{\text{Basilar length}}$	Ass 46.9– 49.9 Mule 40.8– 43.6 Horse 40.4– 44.1
2. Diastema Index:	$\frac{\text{Diastema} \times 100}{\text{Basilar length of skull}}$	Ass 15.6– 17.6 Mule 18.6– 21.9 Horse 18.2– 23.0
3. Cranio-facial Index:	$\frac{\text{Length of cranium} \times 100}{\text{Length of face}}$	Ass 56.3– 61.0 Mule 48.9– 51.8 Horse 45.3– 49.9
4. Orbital Index:	$\frac{\text{Vertical diameter of orbit} \times 100}{\text{Horizontal diameter}}$	Ass 96.0–104.2 Mule 78.7– 99.1 Horse 84.2– 93.5
5. Molar Index:	$\frac{\text{Transverse diameter of } M^2 \times 100}{\text{Total length of entire molar series}}$	Ass 15.2– 16.0 Mule 14.2– 14.9 Horse 13.9– 15.7
6. Occiput-vertex angle Index:	Angle between vertex of skull and line connecting most posterior points of occipital crest with condyles, *i. e.*, nearly all horse skulls will stand when set up on end, some mule skulls (one out of four), no ass skulls	Ass 52.5– 60.0 Mule 61.0– 66.5 Horse 64.0– 76.5
7. Vomer Index:	$\frac{\text{Distance from palate to posterior end of vomer} \times 100}{\text{Distance from vomer to foramen magnum}}$	Ass 93.8–111.7 Mule 95.5–110.3 Horse 72.8– 86.5

The above indices prove that the mule has not a primitive skull like that of the ass on a larger scale, but has essentially the skull of the horse, namely:

1. A long, narrow skull, as a whole.
2. A long diastema, or space for the bit.
3. A short cranium and a long face.
4. A long, oval orbit.
5. A relatively elongate and narrow set of grinding teeth.
6. A vertically placed occiput.

The one character in which the mule resembles the ass is the elongation of the vomer behind the bony palate. It should, however, be distinctly stated that while the indices given above are those which probably prevail in mules, there are overlaps in the (4) orbital index and (6) occiput-vertex angle. Thus in one mule the orbital index agrees with that of one of the asses.

Enamel Pattern of Grinding Teeth.—In the marvellously complex pattern of the grinding teeth the "unit character" transmission is quite sharply defined in the majority of characters, while intermediate or slightly blended in the minority. In general in the grinding teeth of the ass the main enamel folds are less complicated than in the horse and there are fewer secondary or subsidiary folds; the ass especially lacks the "pli caballin" (fold 5) which is usually a very pronounced specific character of the horse. The mule shows a very slight indication of this fold and thus resembles the ass. The subsidiary folds in the grinders of the mule are simpler than those in either the horse or the ass. The grinder of the mule would be pronounced by any systematist not knowing its mixed parentage to belong to the ass rather than to the horse, especially in the absence of the " pli caballin " (fold 5), in the form of the hypostyle (*hs*, fold 6), in the smaller size of the protocone (*pr*), the large size of which is very distinctive of the horse. A very detailed study and comparison of the grinding

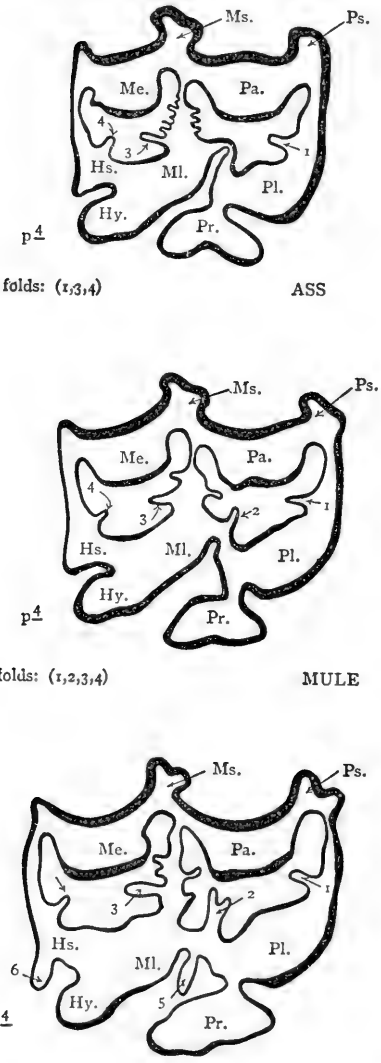


FIG. 8. CROSS-BREEDING AND SEPARATION OF RECTIGRADATIONS, DISTINCT "UNIT CHARACTERS" IN THE ENAMEL FOLDINGS AND PATTERN OF THE GRINDING TEETH OF THE ASS, MULE AND HORSE. Section through the crown of the third superior grinder (p^4 or 4th premolar) ass (male), horse (female) and mule.

teeth in the horse, ass and mule made by an independent observer, Dr. W. K. Gregory, gives the following result:

Primary elements:	protocone,	*pr.*	Key to Figure 8.
	paracone,	*pa.*	
	metacone,	*me.*	
	hypocone,	*hy.*	
	protoconule,	*pl.*	
	metaconule,	*ml.*	
Secondary elements:	parastyle,	*ps.*	
	mesostyle,	*ms.*	
	hypostyle,	*hs.*	

Secondary folds:

fold 1.....	Horse	Mule	Ass.
fold 2	Horse	Mule	
fold 3	Horse	Mule	Ass.
fold 4	Horse	Mule	Ass.
fold 5	Horse		

Unit Characters in Grinding Tooth of the Mule

Distinctly ass-like:	5 characters	11 peculiar to ass.
Less distinctly ass-like:	6 characters	
Common to horse and ass:	5 characters	5 common to horse and ass.
Distinctly horse-like:	2 characters	6 peculiar to horse.
Less distinctly horse-like:	4 characters	

It would be especially desirable to compare the same enamel characters in the hinny, which is a cross between the male horse and the female ass, in which it is well known that the *E. caballus* and *E. asinus* characters are differently distributed.

Summary.—Out of the 28 characters examined in the skull and teeth of the mule, 18 are distinctly derived either from one parent or the other with very slight, if any, tendency to blend, while 10 characters show a distinct tendency to blend.

This evidence, in the opinion of T. H. Morgan, is in entire accord with the modern views of hybridizing; parallels for each instance can be given; without the evidence of the F_2 generation no conclusions adverse to Mendelism are possible. Even the differences in reciprocal crosses, *i.e.*, horse ♂, ass ♀, can be understood if sex-limited inheritance prevails in some characters.

To confirm the results suggested by this F_1 generation of the horse and ass, it would be necessary to interbreed races of

mammals to F_2 or F_3 to ascertain whether these characters of the skull and teeth really mendelize. It is doubtful whether such specific types of mammals can be found, and whether sufficient stability of character exists in artificially produced races.

Sufficient evidence has been adduced, however, to show that a very large number of characters which are to the best of our knowledge of continuous origin present all the appearance of "unit characters" in the first generation of hybrids.

Conclusions

Is it not demonstrated by this comparison of results obtained in such widely different families as the Bovidæ, Hominidæ, Titanotheriidæ and Equidæ that *discontinuity in heredity affords no evidence whatever of discontinuity of origin?*

As to *origin* is it not demonstrated in paleontology that certain new characters arise by excessively fine gradations which appear to be continuous? If discontinuities or steps exist they are so minute in these characters as to be indistinguishable from those fluctuations around a mean which seem to accompany every stage in the evolution and ontogeny of unit characters.

III. THEORETICAL CONSIDERATIONS

After having attempted to confine our lecture to opinions and facts it is a pleasure to relax into the more genial atmosphere of speculation.

The principle of pre-determination, which results in the appearance of rectigradations, involves us in radical opposition to the opinions of the Bateson-DeVries-Johannsen school. There is an unknown law operating in the genesis of many new characters and entirely distinct from any form of indirect law which would spring out of the selection of the lawful from the lawless. This great wedge between the "law" and the "chance" conception in the origin of new characters which since the time of Aristotle has divided biologists into two schools of opinion, is driven home by modern paleontology.

Paleontology, in the origin of certain new characters at least, compels us to support the truly marvellous philosophic opinion of Aristotle, namely:

Nature produces those things which, being continuously moved by a certain principle contained in themselves, arrive at a certain end.

While recent biology has tended to distinguish sharply bodily from germinal processes and to place chief emphasis upon evolution appearing to originate in the germ cells, we must not forget that for a hundred million years or more, or from the beginning of life, the germ plasm has had both its immediate somatic and its more remote environmental influences. Because the grosser form of Lamarckian interpretation of transmission of acquired characters has apparently been disproved, we must not exclude the possibility of the discovery of finer, more subtle relations between the germ plasm and the soma, as well as the external environment. There are several phenomena, which have been observed only in paleontology, that afford evidence for the existence of such a *nexus;* because it appears that certain germinal predispositions to the formation of new characters, connected, as Darwin conjectured, in some way with community of descent, are only evoked under certain somatic and environmental conditions, without which they appear to lie in a latent, potential or unexpressed form.

All that we ever may be able to *observe* are the *modes* of operation in the genesis of new characters and in the adaptive trends of allometric evolution without gaining any intimate knowledge of what the *causes* are.

This thought may be made clear through the following analogy. Naturalists observed and measured the rise and fall of the tides long before Newton discovered the law of gravitation; we biologists are simply observing and measuring the rise and fall of the greater currents of life. It is possible that a second Darwin may discover a law underlying these phenomena bearing the same relation to biology that the law of gravity has to physics, or it is possible that such law may remain forever undiscovered.

Another analogy may make our meaning still clearer. Ontogenesis is inconceivable—for instance, the transformation of an infinitesimal speck of fertilized matter into a gigantic whale or dinosaur; we may watch every step in the process of embryogeny and ontogeny without becoming any wiser; in a similar sense phylogenesis may be inconceivable or beyond the power of human discovery.

Not that we accept Driesch's idea of an entelechy or Bergson's metaphysical projection of the organic world as an individual, because we must believe that the entire secret of evolution and adaptation is wrapped up in the interactions of the four relations [39] that we know of, namely, the germinal, the bodily, the environmental, with selection operating incessantly as the arbiter of fitness in the results produced.

In the meantime [40] we paleontologists have made what appears to be a substantial advance in finding ever more convincing evidence of the operation of law rather than of chance in the origin and development of new characters, something which Darwin had in his prophetic mind.[41]

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[39] Four Factors, etc.

[40] Osborn, H. F.: The Hereditary Mechanism and the Search for the Unknown Factors of Evolution, Biol. Lect. Marine Biol. Lab., 1894, Amer. Naturalist, vol. xxxix, No. 341, May, 1895, pp. 418–439.

[41] Darwin, Chas.: "I have spoken of variations sometimes as if they were due to chance. This is a wholly incorrect expression; it merely serves to acknowledge plainly our ignorance of the *cause* of each particular variation."

THE RELATION OF MODERN CHEMISTRY TO MEDICINE*

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FOUR centuries ago, in the days of Paracelsus, chemistry was called "the handmaid of medicine," and the chief office of the immature science was to serve the art of healing by the preparation of drugs. If her service was often of doubtful value, the defect lay not so much in the lack of latent possibilities as in their exceedingly inadequate development. To-day, opportunities of usefulness for the still youthful science in the service of the ancient art are immeasurably widened. Not only in the mere preparation of drugs, but in countless deeper and farther-reaching ways, are the two branches of learning united in a common cause. Indeed, it is no exaggeration to say that chemistry holds the key which alone can unlock the gate to really fundamental knowledge of the hidden causes of health and disease. This is one of the most precious and vital ways in which any branch of science can serve humanity in the years to come.

The lecture to-night is designed to present a brief logical summary of the more important relations of chemistry to those parts of biology especially pertaining to medicine, as viewed from the stand-point of the theoretical chemist. Not only the present state of these relations, but also their probable development in the near future, will be briefly indicated. In thus especially emphasizing the chemical side of life, I do not wish to detract from the likewise essential messages of the

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physiologist, anatomist, pathologist, bacteriologist, and psychologist. All must work together towards a common end.

That a close relationship between chemistry and medicine exists is clear to every one. Our bodies are wholly built up of chemical substances, and all the manifold functions of the living organism depend in great measure upon chemical reactions. Chemical processes enable us to digest our food, keep us warm, and supply us with muscular energy. It is highly probable that even the impressions of our senses and the thoughts of our brains, as well as the mode of conveying these through the nerves, are all concerned more or less intimately with chemical reactions. In short, the human body is a wonderfully intricate chemical machine; and its health and illness, its life and death, are essentially connected with the coordination of a variety of complex chemical changes.

Why, then, if this relation of chemistry to medicine is so obvious, has chemistry only so very recently been able to render medicine any signal service? The answer is manifest. The intricacy of the living body demands clear sight and profound knowledge for its full understanding; and the chemistry of former days was much too simple and superficial to be a very useful guide in the puzzling labyrinth of many converging and crossing paths. Now, circumstances have greatly changed, and bid fair to change yet more in the near future. Chemistry is fast approaching physics in accuracy, and is expanding beyond physics in scope. As chemical knowledge has increased, the gap between the simpler phenomena of the chemical laboratory and the more complicated changes underlying organic life has become smaller and smaller. The intelligent physician, perceiving this, welcomes the help which the rapidly advancing science of chemistry can give him. Both physiologist and pathologist in the study of the cell and its normal or abnormal growth must ultimately fall back upon chemical knowledge, because the action of the cell depends essentially upon the nature and quantity of the various chemical substances of which it is made. As the cell

is the basis of all life, and as our bodies consist simply of aggregations of a great variety of cells, each of which is governed by chemical laws, chemistry must underlie all the vital functions.

Chemistry may be of use to medicine in at least three quite different ways besides the practical preparation of the substances described in the Pharmacopœia. One of these is concerned with ascertaining the composition of all the substances pertaining to organic life. This kind of chemistry is, as you know, called analytical chemistry. Another way in which chemistry can help medicine depends upon the ability of the modern chemist not only to discover the elements present, but also to find how the parts are put together. This branch of chemistry is called structural chemistry, because it has to do not only with the materials but also with the way in which these materials are arranged. Yet another method of helpfulness comes from a still more recent development of chemistry, commonly called physical chemistry, which deals with the relation of energy to chemical change. The physical chemist must know not only the composition and structure of the substances, but also what kind and quantity of energy is concerned in putting them together, and how this is set free when they are decomposed. He deals with chemical change in action, and studies its method of working.

Each of these three kinds of chemistry can greatly aid the science and art of medicine—and no philosopher is needed to predict how much more effective their assistance may be than the old method of observing merely the outward appearance of fluid and tissue.

Let us now briefly glance in detail at the various aspects of these three modes of helpfulness, taking them in the order in which they have just been mentioned. First comes the field of the analytical chemist. As has been said, the human body is a chemical machine. It is composed entirely of "chemicals," and is actuated exclusively by chemical energy. The analytical chemist is able to tell us the composition of each

one of the manifold substances that compose this intricate machine. He tells us that much of the body consists merely of the simplest compound of oxygen and hydrogen, namely, water; that fat is a more complex compound containing the same two elements with the addition of carbon; that the proteins of muscle contain nitrogen, that the nerves and bones contain phosphorus, and so forth. He is able not only to discover the various elements which are present, but also to estimate with considerable precision their exact amounts. Moreover, he can often isolate the various compounds of these elements which may be mixed together in any given tissue. These facts are not only the essential basis for the intelligent development of the structural and physical chemistry of the body, but they also have immediate practical applications of great importance. The analytical chemist can analyze food and drink, as well as the various parts and secretions of the body, and can determine the relation between the composition of that which is eaten and the resulting bodily substance. This is obviously of great value, for it shows us at once in a general way what substances ought to enter into our diet, and moreover, in cases of disease, it gives us excellent clues to the manner in which the various functions of the body depart from the normal, and thus confers important aid in diagnosis and prognosis and the suggestion of suitable treatment. Analyses of the secretions of the kidney and the stomach have long been used in this way. Another quite different office—the detection of poisons—is a matter of great importance in medicine as well as in criminal law.

All these relations of chemical analysis to the art of healing are well known to most intelligent people, hence I will not dwell further upon the analytical side of the application of chemistry to medicine, important as it is.

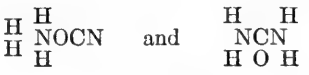
Let us now turn to the second aspect of the subject, namely, the relation of structural chemistry to medicine. So recent is the development of the subject that the very idea of structural chemistry is not yet a part of the average liberally educated man's equipment.

Structural chemistry had its origin in the discovery that two substances might be made up of exactly the same percentage amounts of exactly the same elements, and yet be entirely different from one another. This fact, that two things may be exactly alike as to their constituents, but very different in their properties, implies that there must be a difference of arrangement of some kind or other. We can obtain the clearest conception of this idea with the help of the atomic hypothesis. If the smallest particles of any given compound substance are built up of still smaller atoms of the various elements concerned, it is clear that we can conceive of different arrangements of these atoms, and it is reasonable to suppose that the particular arrangements might make considerable difference in the nature of the resulting compounds. Everywhere in life arrangement is significant. In spelling even simple words, different arrangements of letters cause wholly different effects, as for example in " art " and " rat "; and countless other cases might be cited. Why may not arrangement be significant in the case of atoms?

It is not possible in this brief address to explain exactly how chemists obtain a notion of the arrangement of atoms which build up the particles (or molecules) of each substance. We depend upon two methods of working, one the splitting up of the compound and finding into what groups it decomposes, the other, the building up from these or similar groups the original compound. Just as among the fragments of a collapsed building you will find bits enough to show whether it was a dwelling, a stable, or a machine shop, so among the fragments of a broken-down substance you will find bits of its structure still remaining together, enough to indicate something of the original grouping. Each different chemical structure will leave a different kind of chemical débris. If from similar fragments the original substance can be reconstructed by suitable means, the evidence is strong that some knowledge of the structure has been gained. Albrecht Kossel in his recent Harvey Lecture doubtless dwelt at length upon

this matter, but a moment's recapitulation and a few concrete cases may not be out of place.

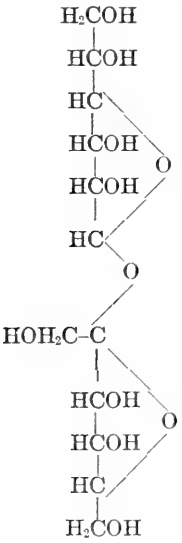
For example, two well-known substances, ammonium cyanate and urea, have each the formula CH_4ON_2. That is to say, since each letter stands for a definite quantity of each element, these two compounds are absolutely identical in composition. Nevertheless, the merest beginner, who takes the two substances into his hands, can see that they themselves are entirely different from one another in their appearance and behavior. By heating the first substance in solution in water it may be converted into the second, without any loss or gain of material. The only way in which we can explain the likeness of composition is by supposing that the atoms, alike in numbers in each case, are arranged differently; and long study has led to the conclusion that the two arrangements are best expressed by the following diagrams:



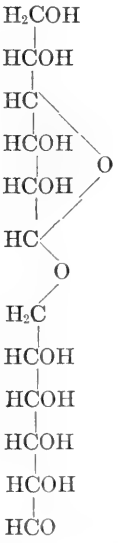
The second, more symmetrical arrangement, urea, is the stabler of the two. That these two different arrangements should cause different properties is not surprising.

Let me cite yet another case among the countless instances which might be brought forward. Milk sugar and cane sugar are unquestionably different in their physiological action, as every physician knows. The difference, while unimportant to most adults, is a very serious one for infants. Now these two substances have exactly the same formula, $C_{12}H_{22}O_{11}$; in other words, each molecule of each sugar is composed of 12 atoms of carbon, 22 atoms of hydrogen, and 11 atoms of oxygen; or 42.1 per cent. of carbon, the remainder being oxygen and hydrogen in the same proportion as in water. Both, unquestionably different from one another, are evidently very different from a mixture of charcoal and water possessing the same percentage composition. These differences are ascribed, as before, to differences in arrangement of the atoms, the case

being analogous to that of ammonium cyanate and urea, just cited. The detailed unravelling of the structure of the sugars seemed until recently to be almost impossible, because the number of possible combinations to be obtained from 45 atoms in one molecule is so great. Nevertheless, this problem has been almost if not quite solved by Emil Fischer, and we are now able to say with some confidence wherein the differences lie. The arrangements depicted in the two accompanying diagrams due to Fischer, probably come very near the relative structures of the two substances.



Cane Sugar



Milk Sugar

These formulæ, being depicted upon a flat surface, cannot represent exactly the true arrangement of the atoms in space, where the molecules occupy three dimensions instead of only two. The tridimensional distribution of atoms is a subject of much importance, and since 1874 has grown into a special branch of chemistry, called stereochemistry. No attempt is made in the above formulæ to represent even by the usual conventional arrangement the supposed space-configuration of the

atoms of either kind of sugar, because the most recent investigations seem to indicate that this matter is not finally settled; but even without taking differences of this kind into consideration, a glance is enough to show that the lower halves of the two arrangements are not alike; and the difference is enough to account for the difference in the physiological action of the two sugars.

I cannot emphasize too strongly the fact that such different groupings are not a mere question of mixture in the ordinary sense. No possible fashion of mixing together 42.1 grams of charcoal and 57.9 grams of water will produce 100 grams of any kind of sugar. The matter is far subtler than this. It is a question of arranging almost inconceivably minute atoms within a molecule almost as small. That human beings may thus imagine the relations which they cannot see, devise a nomenclature for expressing these invisible relations, and then pursue their quest even into prophesying unknown relations which can be and very often have been verified by the actual preparation of definite substances, seems to me one of the most remarkable outcomes of the human imagination.

As regards the usefulness of structural chemistry to medicine, we cannot but see at once its vast importance. If the binding together of infinitesimal atoms in different ways produces different properties in the resulting substances, it is obvious that the particular mode of binding together every one of the complicated compounds constituting our bodies is of vital importance to us. As the substances in the body usually have many atoms in each of their molecules, there are a great many different ways in which the atoms may be arranged; and each one of these many arrangements may have different effects. Among the many substances now under investigation of this sort, the proteins or albuminous substances stand out prominently, for they play so essential a part in the animal mechanism. The recent synthesis by Emil Fischer of complex amino-acids into protein-like compounds points the way towards a better chemical understanding of these highly

important bodies, and this knowledge will doubtless be the stepping-stone to more. The work of Willstätter concerning the structure of hæmoglobin is also of great importance to physiology.

Living, in the case of all animals, is a continual process of breaking down more complicated structures into simpler ones; and it is clear that this breaking down will happen in different ways with different groupings, and thus produce different results. In the case of food, the arrangement alone of the atoms may make all the difference between nourishment and poison.

The knowledge of the atomic arrangement of the various substances composing the body is not only bound to furnish an invaluable guide in the study of physiology, pathology, and hygiene, but has already led to the logical discovery of entirely new medicines, built up artificially in the laboratory to fit the especial needs of particular ailments. Examples of this sort will occur to every physician. The narcotic, veronal, was deliberately sought by Emil Fischer, who based his research upon the known physiological action of sulphonal and other similar substances. He sought to put into the molecule the groups which were effective in diminishing nervous activity and to take out of the molecule such groups as had been proved to have depressing action on the heart. Again, the newer and still more astonishing substance, salvarsan, of Ehrlich, was the result of an extended experimental search in which successive groups were attached to the arsenic nucleus until its virulent action on the human organism was sufficiently diminished, without essentially overcoming its destructive effect on the germs of the loathsome contagion which it was designed to destroy.

We all appreciate the profound revolution in medicine produced by serum treatment, and rejoice in its high promise. Here in New York especially, epoch-making work along this line has been accomplished by Dr. Flexner and his able assistants in the already famous Rockefeller Institute for Medical Research. But cannot pure chemistry in the future bring a

most helpful improvement into this noble work? At present, various serums are prepared in the hidden laboratory of living tissues; there is no other way. Nevertheless these serums work unquestionably through the agency of chemical substances, which very probably may be capable of production in a chemical laboratory, provided that their true nature can be discovered. Thus could be manufactured antitoxins uncontaminated with other substances of doubtful value and possibly deleterious effect; and the antitoxin treatment would lose its most grievous handicap. In the future the physician may do his work, not with a serum or virus of doubtful composition and value, but rather with pure substances built up in the chemical laboratory—substances with their groups of atoms so arranged by subtle science as to accomplish the reconstruction of worn-out organs or the destruction of malignant germs without working harm of any kind. We may thus dream of the attainment of an artificial immunity from smallpox, for example, as much superior to vaccination as this is superior to the old inoculation. That the whole subject of immunity, already explained by a somewhat vague chemical hypothesis, will lose its uncertainty and steadily gain in clearness as chemical knowledge advances, no one can doubt.

The true chemical nature of the antitoxins and the real nature of the chemical changes which establish immunity will not be discovered by accident, however; the complexity of the compounds and circumstances concerned is far too great. Clearly, in order to know all there is to be known about the matter, the structure of each intricate substance existing in the body must be found, and the arrangement of the atoms in each particle of our complex organism. Until this shall be done, we cannot be in a position to predict with any reasonable certainty what is going to happen to these substances in the round of their daily functions, or how they are likely to be influenced by disease. This is a problem so vitally important that it would be hard to exaggerate its significance to posterity.

Such researches will be of enormous value not only to curative medicine, but also to preventive medicine and the hygiene of every-day life. If we know the structure of the proteins in food and the way in which they react in the body, we shall be able to choose intelligently the proper balance between the different foods, towards which we are now groping rather blindly. As it is, for all we know, a "nitrogen balance" between intake and outgo may be established in the body, the bodily weight remaining constant, while some very important substance is wasting away for lack of the particular groups which are capable of replenishing its store. To obviate such a catastrophe we need to know not only that a given food contains so much nitrogen; we must know also how the nitrogen is combined, for this latter fact makes a vital difference. Grove and Hopkins's work alone is enough to prove this. The admirable research of Osborne and Mendel upon the physiological effect of pure proteins will doubtless throw much light on these questions. Moreover, there are other elements, such as iron in the essential red coloring matter of blood, and phosphorus in nerves, where also the special form of combination is of vital importance. Chemistry has gone far enough to see where the problem lies, but not quite far enough yet to solve it. Such a prospect is especially inviting to the investigator; he feels confidence that he is reaching after truths within the mental grasp of man, and therefore that he may rightfully hope to succeed.

Let me emphasize once more the fact that these are essentially chemical problems, to be solved in chemical laboratories in the same way that Fischer unravelled the constitution of the sugars; and upon work of this kind the medicine and hygiene of the future must be dependent to an extent not at all realized by most physicians to-day. The progress of both curative and preventive medicine will be grievously handicapped if chemistry is not permitted and encouraged to advance; only a short-sighted community will put all its energy into the comparatively superficial observation of complicated outward phe-

nomena of life, without stimulating also the thoughtful study of the fundamental chemical changes upon which everything depends.

As I have said, the complete chemist must now know not only what things are made of and how the elements are put together, but also what forms of energy are concerned in putting them together, and how much energy is set free when they are decomposed. This applies to the biological chemist, as well as to the theoretical and technical chemist.

There is no doubt that energy is the immediate cause of every event in the known universe. Several well-known kinds of energy exist; the chief forms are mechanical energy, heat, light, electrical energy, and chemical energy. Each is capable of transformation into each other form, and so far as we can tell the sum total of the energy in the universe can neither wax nor wane. Without any kind of energy, the whole universe would be chaotic, quiescent, dark, piercingly cold, asleep. We can conceive, on the other hand, of a world possessing the so-called physical forms of energy without chemical affinity. What would it be like? Such a world, composed of elements like argon, might revolve and have light and warmth, sea and rocks, clouds, rain and tides; but it could possess no organic life, for life is based upon the action of chemical energy. Thus the study of chemical energy is of profound importance to the student of organic life.

As has been said, the branch of chemistry which treats of energy is called physical chemistry; it deals with the acting, driving forces which make life possible, and in each of its many aspects it brings new intelligence to bear upon the working of the living mechanism.

Physical chemistry treats, among other topics, the chemical relations of the changes from solid to liquid, and from liquid to gas, and discusses the nature and behavior of solutions and mixtures of all kinds. As the living body is composed of solids and liquids and depends upon the gases of the atmosphere for promotion of the chemical changes animating it, and as solu-

tions and mixtures are present in every cell, the laws and theories of physical chemistry are intertwined with every fact of physiology.

Among the discoveries in these directions, none is of more immediate importance to physiology and pathology than the outcome of recent study of the behavior of liquids in relation to partly permeable or porous cell-walls of partitions. The behavior is obviously capable of throwing light on the nature of both liquids and porous partitions, and is of peculiar importance in the animal economy, because most physiological action has to do with liquids and cell-walls.

As the minute openings in a porous wall between two liquids are made finer and finer, at first fine powders are unable to penetrate, then bacteria are caught on the surface; then, as the holes are made yet smaller, some of the dissolved substances, such as gelatin, are refused transmission; and at last with the most finely porous wall, nothing but pure water goes through. Even a solution of common salt, for example, becomes entirely sweet and fresh upon being pressed through such a semipermeable membrane; it has been freed from the almost infinitesimal particles of dissolved salt in somewhat the same way that a jelly is freed from fruit seeds by straining or filtering through cloth, or water has been freed from bacteria by a Pasteur filter. The work of Bechhold with the ultrafilter and of Zsigmondy with the ultramicroscope have especially demonstrated even to the layman this difference in the size of dissolved particles, first discovered by Graham long ago. As regards the mechanism of the penetration of solvents through diaphragms, we may distinguish two classes of action—the first class depending merely upon transmission through holes, the size of which determines the separation of dissolved substance, and the other class depending upon the true dissolving (to form a so-called "solid solution") of the solvent in the material of the dividing wall on one side, and its escape from this "solid solution" on the other.

One highly important feature of the action of a semiper-

meable diaphragm is the same, no matter which cause determines the mechanism of its action. So far as we can tell, each separate dissolved particle, restrained from passing through, exerts a certain definite pressure upon the dividing wall—a pressure which Pfeffer first measured and which van't Hoff showed to be in dilute solutions essentially equal to that exerted by any molecule at the same temperature in a gaseous condition, and not dependent upon the nature of the dissolved substance or of the solvent. The resulting effect, which thus depends upon the number of the dissolved particles in a given space, and not upon their character, is called osmotic pressure, and may be actually measured. To give an idea of the magnitude of these effects, it is enough to state that the osmotic pressure of the blood of mammals is over one hundred pounds to the square inch, or enough to support a column of water nearly two hundred and forty feet high. Even the novice must perceive the enormous significance of such conditions.

With the help of these and other allied phenomena, the study of aqueous solutions has enabled us to discriminate between the various sizes and conditions of the smallest particles of different dissolved substances. We find that some substances act as if their molecules split up into their so-called ions, when dissolved, and these ions behave as if they were electrically charged; this is the outcome of the theory of van't Hoff and Arrhenius. Other substances split up in another way, called hydrolysis, combining with some of the water, and yielding often a weak acid and base as the result of their decomposition. Yet others apparently dissolve unchanged; and among them some, called colloids, act as if they had very large molecules, almost like very fine particles of a powder suspended in the solution, or the fine drops of an emulsion.

It is clear that each of these different types of solutions might be expected to act differently with regard to the walls of the living cells which contain them. Some will penetrate freely, perhaps; in others the dissolved molecules will be denied entrance or exit, because of their mere size; in yet others

the chemical nature of the individual particles will have peculiar relations to the substance of the cell-walls, thus permitting selective transmission and absorption in special fashion. Probably the secretion of most animal fluids involves the combined action of all these effects; and so does permeability of the cell to outside mixtures, such as the blood plasma or any given antitoxin.[1]

Profound insight as well as careful experiment will doubtless be necessary to unravel the tangled result. Nevertheless, armed with a knowledge of the nature of solutions, the biologist may hope to conquer; without it, he must inevitably be defeated. The study has already made good progress in attacking the outposts; one may cite for example the highly interesting and important work of J. Loeb upon the artificial fertilization of some of the lower forms of animals, and that of Henderson on the neutrality of the blood; here the physico-chemical facts are seen to bear on some of the most fundamental and mysterious of the biologist's problems. Indeed, as Hamburger has recently said, "Quite inestimable has been the influence exerted by the theory of solutions on our science. There is hardly a chapter in physiology which does not bear signs of this influence."[2]

The very large dissolved molecules of the colloids (or glue-like substances) have peculiar properties, which are so important as to have given rise to a special branch of chemistry called " colloid-chemistry." Colloids are plentiful in the human body; and every fact concerning their behavior is of the greatest value in interpreting the many complex changes in which they take part. One of their remarkable characteristics, for example, is their power of clinging to substances in contact with them; the large surface exposed by their extended and diversified molecules seems to be especially able to hold with a sort of adhesive attraction called " adsorption " not

[1] See Flexner, Biological Basis of Specific Therapy, Ether Day Address, Massachusetts General Hospital, 1911.

[2] Science, Nov. 3, 1911.

only large quantities of water, but also salts and everything else within reach.

Another highly important aspect of physical chemistry is that which concerns the *speed* of chemical reactions, and the mechanism by which this speed gradually decreases in a given mixture until a balancing or equilibrium of all the reacting tendencies is attained. The speed of the chemical changes in the human body is a matter of capital importance to man. Indeed, it may be said that the difference between health and disease, between life and death, is primarily a question of the relative speeds of the various reactions concerned in the act of living. There is fortunately a wide margin of safety, but nevertheless if any one of the more essential chemical changes takes place too fast or too slowly, illness is a certain consequence.

All chemical reactions are dependent for their speed upon a few very definite circumstances, to wit: the *special affinities* of the substances concerned, the *concentration* of the reacting substances, the *temperature* of the mixtures, and the presence or absence of certain other substances (called *catalyzers* or *catalysts*) which do not themselves take part, but which stimulate the reacting substances to enter into combination. Each of these factors in the result is of great importance to the biologist. The effect of concentration is especially interesting; it influences all the various kinds of reactions, whether between a liquid and a solid, between a liquid and a gas, or between several substances, dissolved in a single liquid. Whenever to a nearly balanced mixture more of any reacting substance is added, it tends to push faster and farther all the changes in which it takes part, so that some of the added substance is used up. For example, if more water is added, all the reactions which tend to use up or absorb water are accelerated, and so forth. This is a very general law, which is susceptible of mathematical expression in each separate case; and so is the somewhat analogous fact that increase of tempera-

ture, which accelerates all reactions, especially furthers those tending to absorb heat.

Again, the fourth cause affecting the speed of reactions, namely, the action of catalysts, underlies many of our vital processes. A class of catalysts, known as enzymes, the behavior of which has only recently been carefully studied, have been shown to be of fundamental importance in the animal economy, for they influence the essential progress of digestion and assimilation, as well as many other vital functions.

The development of the heat and muscular energy of the body by the slow combustion of its substances presents another set of chemical effects without which life would be impossible. The chemical mechanism of these changes is being investigated by Dakin, who has been prosecuting his work in the inspiring atmosphere of the laboratory of the late Christian Herter. Dakin has found much of interest concerning the way in which this combustion occurs at the comparatively low temperature of the body, and his researches throw light on the manner in which the complex substances constituting the body yield energy by breaking up into the simpler products, eliminated from the body through the lungs, skin, and kidneys. The recent work of Rubner and of Atwater and Benedict has shown that the conservation of energy applies to this burning just as much as to the reactions in our beakers and test-tubes; the marvellously complex living organism is not beyond the domain of this simple and fundamental law.

The dynamic chemistry of the future does not stop here, however. Within its province lie also the recently found relations of chemistry and electricity, bearing perhaps upon some of the partly chemical and partly physical mysteries of nervous action, and furnishing much intelligence concerning the nature of solutions in general. The new science of radioactivity, too, is a part of physical chemistry. The sterilizing action of the X-rays and radium rays and emanations on the germs both of life and of disease have highly important bearings upon medicine. More significant perhaps than all this,

because more general, is the branch of physical chemistry called photochemistry—the chemistry of light—which promises to give great assistance in the interpretation of the changes occurring in the leaves of plants under the influence of sunlight. Through the agency of light alone nature is able to build up the intricate compounds needed to provide all animals with food; and until we understand the growth of the vegetable we cannot hope to understand that of the animal. Moreover, the photochemical analogies and differences between the green coloring matter of plants and red coloring matter of blood are full of suggestiveness; and the peculiar relations of many natural substances to polarized light furnish a fund of data for deep thought, not only concerning the arrangement of the atoms in space, but also concerning the nature of life. That the sense of sight depends upon photochemical reactions in the retina, analogous perhaps to those which occur in sensitized films prepared artificially, one can hardly doubt; thus photochemistry may perhaps some day throw light on otherwise hopeless forms of disease of the eye, as well as upon the normal working of that highly important organ.

Indeed no aspect of physical chemistry which has to do with the effect of energy upon material is too remote from every-day life to be valuable, for everything which throws light upon the nature of matter is a help in the interpretation of the action of the substances composing our bodies. For example, the recent theory which suggests that the atoms themselves are compressible may bear fruit not now easily predicted, because this theory has to do with some of the ultimate and most fundamental of the properties of all substances.[3]

In brief, the chemistry of energy promises incalculable helpfulness to future generations of mankind. From the study of inert substance from which life has departed, we cannot infer certainly its real office, any more than we can predict from the appearance of a stuffed bird in a museum its complete habit of life. In order to understand the process of liv-

[3] The Faraday Lecture of 1911, Science, xxxiv, 537, Oct. 27, 1911.

ing, one must study each substance in action, and examine its behavior under the influence of the manifold forces which play around it; and this is the aim of physical chemistry.

I have outlined very briefly a few of the ways in which chemistry holds out great promise of help to suffering humanity in the future. A few decades ago Pasteur and Lister revolutionized the science of medicine and made a greater advance than had been made in a thousand years before. One of the great tasks of the future is to discover the ultimate chemical reasons which underlie not only the mechanism of bacterial action but also those upon which life itself is based.

What indeed is life? Is it nothing but a bundle of chemical reactions? From dead material alone man as yet has been unable to create the simplest living cell, and yet these cells seem to be entirely chemical in their action. Wherein lies the explanation of the paradox? As Cuvier pointed out long ago, life seems to be a directive tendency rather than a form of energy. In a living organism actuated by chemical reactions, using in accordance with definite laws the energy of the sun while it runs down from a higher to a lower potential through a complicated chemical mechanism, life directs the simultaneous processes in such a way that the body grows and flourishes. How this is accomplished no man knows; but if the mystery is ever explained, the explanation cannot ignore the chemical changes which are bound up with every step. Even psychology must take chemistry into account in its ultimate reckoning; for are not our thoughts and nervous impulses inextricably associated with chemical changes in the nervous tissue, and must not memory be due to permanent alterations of chemical structure? Perhaps heredity, too—that most recent concern of biologist and psychologist alike—may be found, as has been repeatedly suggested, to depend in the last analysis upon the existence of definite chemical substances—possibly special catalysts—in the several chromosomes carrying on the process of reproduction, by which we now explain Mendel's law.

The outlook for the future is thrilling in its possibilities. Nevertheless, as du Bois Raymond insisted, we can never hope to understand the whole of the wonderful secret. We are here living in a small restricted world with an infinity of space on all sides of us; we crowd our little deeds into a relatively infinitesimal limit of time, with eternity beyond us and in front; and both infinity and eternity are beyond the grasp of our finite minds. But let us not be impatient. Even if a complete understanding of the secret of life and death is unattainable, step by step we shall gain in knowledge. Each advance furnishes new vantage ground for further progress and new inspiration for fresh effort; and with our steadily increasing knowledge grows our ability to help suffering humanity and to strengthen coming generations. Thus we may look forward with high hope toward the undiscovered future.

SOME CURRENT VIEWS REGARDING THE NUTRITION OF MAN*

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TO all who are truly interested in the development of knowledge, information counts for more than argument, truth for more than tradition; facts weigh more than opinions. Controversial argument sometimes makes interesting reading, but it rarely convinces unless based upon a foundation of fact that will in itself convince. In what I have to say this evening I shall try to avoid so far as possible controversial statements and arguments, emphasizing rather those views that seem warranted by the facts at our disposal.

The modern conception of nutrition finds its beginning in the discoveries of Lavoisier, who made clear the important part played by oxygen in the two processes of combustion and respiration. He soon came to see that the processes of life are essentially processes of oxidation, in which carbon dioxide is a conspicuous waste product while heat is another resultant, proportional in amount to the degree of combustion or oxidation. Lavoisier, though working with apparatus and methods far less refined than those at our disposal to-day, quickly determined that man takes in oxygen and gives off carbon dioxide in amounts which vary with the quantity of food consumed, the amount of work done, and the temperature of the surrounding air. At first, it was conjectured that the oxidation occurring within the body took place in the lungs or in the blood, and that it was carbon and hydrogen that underwent combustion. The work of Liebig, however, eventually made

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it quite clear that the substances undergoing oxidation in the body were the proteins, fats, and carbohydrates of the food and tissues, and further, that while carbon dioxide was a measure of the amount of carbonaceous matter burned up, the nitrogen eliminated constituted a measure of the amount of protein or nitrogenous matter broken down. This view, which was advanced by Liebig about 1842, was confirmed and strengthened by the experimental work of Bidder and Schmidt and of Carl Voit during the period from 1850 to 1860. Moreover, it became apparent that the processes of oxidation were not limited to any one place, to any one tissue or organ, but were common to all tissue cells, wherever there was life and activity.

Liebig maintained that fats and carbohydrates were respiratory foods, that they were destroyed or burned by oxygen; protein, on the other hand, he believed to be a plastic food, and that its metabolism was regulated solely by the amount of muscular work performed. This statement, however, has been disproved by the work of many investigators, who agree in finding that muscle work does not materially increase protein metabolism, as measured by the output of nitrogen, at least not under conditions where there is available fat and carbohydrate to draw upon. In some conditions of the tissue cells, as during starvation or on an exclusively protein diet, protein alone may undergo metabolism, and the requirement of energy for muscular work and the production of heat may both come from the breaking down of protein. On the other hand, with available fat and carbohydrate within reach, protein may be metabolized in relatively small amount, while the non-nitrogenous material is oxidized in large measure. It is well understood to-day, as pointed out by Voit, that there are many influences acting upon the cells of the body that may serve to modify qualitatively and quantitatively cell metabolism.

It is a testimonial to the power and influence of Liebig that views advanced by him, though long disproved, still come forward from time to time, and influence in no slight degree the thoughts and habits of many people. There is, I think, an underlying current of belief quite prevalent that a high protein

food, such as meat, is essential for full muscular vigor; that animal food in general is, for some unknown reason, endowed with semi-miraculous power, which renders it peculiarly fitted to meet the needs of the body where much muscle work is to be done. Physiologists, however, have for a long time been occupied with a study of the many intricacies of human nutrition and have acquired a fund of information as to what substances are metabolized under different conditions of work and rest, under varying conditions of temperature, under different conditions of diet, and to what extent the different foodstuffs must be taken into the body in order to maintain body-weight, nitrogen equilibrium, and a full measure of physical and mental vigor. In the light of facts so obtained, old-time views, theories founded upon false assumptions or inaccurate data, must eventually give place to views more closely in harmony with modern data. Facts must in time outweigh opinions.

To-day, we recognize certain close resemblances between the human body and machines of artificial construction; a view which merely serves to emphasize the importance of the physico-chemical laws which govern both, without compelling belief in a mechanistic conception of the animal body. We may qualify the above statement by adding that the human machine is characterized by great complexity of function and that some of these functions cannot, at present at least, be explained by any known methods of analysis. Consequently, we must admit at once that the human body is something more than a mere machine. But so far as the general processes of nutrition are concerned, there is help in the thought that the human body, like the machines constructed by the hand of man, is able to generate and expend energy, and that the law of the conservation of energy is just as applicable to the human machine as to those of simpler construction of iron and steel. In other words, the human body is a mechanical structure, governed, in a measure at least, by the same laws that control unorganized matter and endowed with the power of transforming energy, as from motion into heat or from heat into

motion, though lacking the power to create new energy. To be more specific, the human body in the process of nutrition transforms the potential energy of the proteins, fats and carbohydrates, which constitute the food of man, into the two forms of energy, heat and motion, in a manner analogous to that by which the engine utilizes the energy coming from the combustion of the gas, coal, or wood which serves as its fuel.

While these statements testify to a close relationship between the animal body and a machine, so far as the transformation of energy is concerned, there are several fundamental differences in structure and function that demand attention. The human machine has the power of growth, the power of adding on to itself new material from the food supplied, by which its framework or structure is made larger. Along with this, and retained long after, is the power of repair. As growth, under proper nutritive conditions, follows a certain general law, it is obvious that there must be some kind of regulating mechanism which influences and controls this peculiar process. Whether this peculiarity of growth is dependent upon the character of the fuel or food fed, or upon some other factor, we need not now stop to consider. The fact, however, deserves emphasis at this point. Again, the chemical structure of the human machine, or the make-up of its component parts, is worthy of special attention. The living protoplasm of the individual cells of the various tissues and organs of the body represents a peculiar organic complex, which is subject to wear and tear during life, and which on this account introduces an important feature into our conception of human nutrition. The major part of this tissue protoplasm is composed of proteins of various kinds; all nitrogenous bodies more or less closely related in composition, but possessed of a certain degree of individuality, dependent upon their inner or chemical structure. This brings us to a third point of difference between the human body and an ordinary machine, viz., that the structural material, the cell protoplasm, of the tissues of the body is constantly changing by processes of upbuilding and breaking down, which are ordinarily referred to collectively as processes of metabolism.

It is thus apparent that in the human body we have to deal with a machine which not merely transforms the potential energy of the food or fuel into heat and work, but the structural framework of the machine is constantly in a state of flux, a state of metabolic activity, in which there is a building up of some substances and a breaking down of others. Synthesis and destruction are taking place constantly side by side. In the adult, in good health, the two processes practically balance each other, thus maintaining a certain degree of equilibrium. In old age, all the metabolic processes are less intense, while early in life the constructive processes are more active, thus leading to growth. The point to be emphasized, however, is that in the animal body the transformation of the potential energy of the foodstuffs takes place in a machine of peculiar complexity, the substance of which, unlike that of an artificial machine, is itself constantly undergoing change, and the character and extent of its metabolism influences and modifies the metabolism of the body as a whole. Here, then, the analogy with a machine ceases, for it is quite apparent that the integrity of the human body is of paramount importance; the needs of its structural framework are to be considered constantly; fuel or food is to be supplied not merely to meet the necessities for transformation of energy, for heat and work, but to maintain the machine in good working order, without which normal metabolism is impossible.

From these statements, it is plain that the fuel for the human machine, the food needed by the animal body, must not only meet the requirements for energy, but it must also satisfy the specific demands of the tissues and organs, in order that the various parts of the machine may be maintained in a high degree of efficiency. In fact, it is easy to see that the phenomena of nutrition are attributable to the activities of the living cells of the body. As Voit has expressed it: "The unknown causes of metabolism are found in the cells of the organism. The mass of these cells and their power to decompose materials determine the metabolism." How necessary, therefore, that these cells be kept in good nutritive condition.

It is the purpose of the daily food to maintain that even balance of income and output necessary for the welfare of the tissue cells, as well as to supply fuel for the needed energy. This twofold function of the food must be kept clearly in mind, for upon this depends the character and amount of the daily food required for meeting the needs of the body.

In a general way, observation and experiment have taught us that a mixture of the different foodstuffs, animal and vegetable proteins, fats and carbohydrates, together with mineral salts and water, is the most economical physiologically and the best adapted for supplying the needs of the organism. We are prone to emphasize the energy needs of the body in terms of heat units or calories, and the protein needs in terms of nitrogen, without perhaps recognizing sufficiently the importance of various unknown substances in our daily dietary, which may play a very significant part in the maintenance of a proper state of nutrition. It is quite conceivable that a mixture of foodstuffs derived from various sources is safer, because under such condition there is less danger of the organism being deprived of some of these unknown components, at present of an undefinable nature, which we have reason to think are essential for the body's welfare.

Since carbohydrates and proteins have essentially the same fuel value, it might be assumed that in meeting the wants of the body for energy either one of these foodstuffs might be used, in harmony with the taste, or fancy, of the individual. This, however, is not the case owing to the complexities of the human machine. The body cannot long survive on a diet of carbohydrate alone, neither on a diet of carbohydrate and fat, because of the ever-present need for a certain amount of protein food to make good the loss of protein, incidental to the life of the protoplasmic tissues of the body. Physiologists may not agree as to the exact amount of protein food required daily, but there is no disagreement as to the necessity of supplying some protein, in order to prevent protein or nitrogen starvation. Otherwise, death soon follows.

Again, bearing in mind the far greater fuel value of fats

as compared with carbohydrates, it might be assumed that the bulk of the daily food could be greatly reduced by substituting fats for starches and sugar. Here, again, we meet with an obstacle in the difficult utilization of fats. Under ordinary conditions of life, there is a limit to the amount of fat the average individual can digest and absorb. Any attempt to go beyond this limit is attended with serious disturbance. Consequently, the fat of the daily diet is, more or less unconsciously perhaps, restricted to a level far below that of the carbohydrates. The customs and habits of mankind, as a rule, all agree in giving first place, as regards quantity, to the carbohydrate foods. This is in harmony with physiological teaching. Carbohydrates, as a class, are relatively easy of digestion, they are quickly available, they are completely oxidized, they are highly palatable, and, lastly, they are generally economical and easily obtainable foods. Voit, who has defined a food as "a well-tasting mixture of foodstuffs in proper quantity and in such proportion as will least burden the organism," gave the daily diet of a laboring man as 118 grams of protein, 56 grams of fat and 500 grams of carbohydrate, with a total fuel value of 3055 calories. This has been for many years the generally accepted standard of the daily food requirement for a man doing a moderate amount of work. The figures are given here, however, as showing the usual proportion of fats, carbohydrates, and protein entering into the daily diet of most civilized peoples. Naturally, individual likes and dislikes cause fluctuations in the proportion of fat and carbohydrate, but rarely does the daily intake of fat exceed 150 grams, carbohydrate almost invariably being largely in excess. Water is of course likewise essential, and also a certain amount of inorganic salts, many of which are furnished admixed with the various foodstuffs. Mineral matter is obviously not a source of energy, but its value in the nutritive processes of the body is not to be belittled on that account. Hardly yet have we arrived at a full appreciation of the real significance of these inorganic salts in controlling and modifying many of the processes of the organism. Their absence, or a disturbance of

their proper proportion, may be quite sufficient to induce an abnormality of function fatal to the life of the tissue cells.

As to the amount of the various foodstuffs required to meet the physiological needs of the body, we find a great divergence of opinion. There is, however, practical agreement among physiologists that the ideal diet is one that furnishes protein and energy sufficient to insure a condition of physiological and nitrogenous equilibrium, with maintenance of health, strength, and vigor, combined with ordinary resistance to disease. Anything beyond such an amount is not only an unnecessary excess, but may prove an evil of varying magnitude. Yet hereditary customs, acquired habits, the insistent demands of capricious appetites, have all combined to create more or less artificial standards, for which physiological justification is frequently sought. From the stand-point of energy requirements, it is not difficult to see that there must be a definite relationship between the amount of fuel needed and the amount of physical work to be performed. The same rule holds here as in any energy-yielding machine. The man who spends his day in exercise on a golf course plainly requires more food, especially carbohydrate and fat, than he who sits quietly at his desk. The fuel value of the daily food must, on an average, be proportional to the physical work performed. On this question there is no difference of opinion. This, however, does not hold good in regard to the amount of protein food. Physiologists have gradually come to see that Liebig's dictum as to the importance of protein food for muscle work is incorrect. The energy of muscle work, of muscular contraction, does not come from the breaking down of protein material. As already stated, Lavoisier discovered that mechanical exercise increased the absorption of oxygen, thus indicating that work is associated with accelerated oxidation, or as we should say to-day with increased metabolism. Since then, many experimenters have demonstrated that the increased metabolism which attends muscular work is accompanied by an increased output of carbon dioxide and water, and not by any material increase in the output of nitrogen. In other words, the power to do

muscular work is not, ordinarily at least, derived from the breaking down of protein material, but comes from the combustion or oxidation of carbohydrate and fat. Protein food, therefore, does not need to be increased in proportion to increase of muscular work. Further, the results of experiments in my own laboratory have shown quite conclusively, I think, that large amounts of protein food are not needed for the maintenance of full physical vigor.

What is it then that determines the amount of protein food required? In attempting to answer this question we are confronted with several physiological peculiarities of protein which demand our attention. When taken alone by a normal adult, protein food undergoes oxidation with great ease, and practically none of it is retained within the body to form new tissue; its nitrogen appears in the urine very speedily. If, as was shown years ago, a fasting dog is fed a large amount of protein in the form of meat, the greater part, if not all, of the ingested nitrogen appears shortly in the urine of the animal, *i.e.*, in spite of the under-nourished condition of the dog's tissues, little or none of the protein fed is retained. Again, as Bischoff and Voit first pointed out, a dog of 35 kilograms, for example, fed say five pounds of lean meat, will excrete in the following 24 hours fifteen times as much urea as would be excreted without the heavy protein diet. In other words, the results of these simple experiments testify to the general truth of the statement that the extent of protein metabolism in the animal body is in large measure proportional to the amount of protein food ingested. The tissues of the adult have little or no power to hold on to protein; it cannot be stored up as can fat and carbohydrate for future use; it is not possible to create a large surplus for emergencies. Such being the case, there is obviously no ground for the belief that a surplus of protein food constitutes one of the so-called "factors of safety." Decomposed in the body, its energy is available in the same manner as the energy of fat and carbohydrate, although it is not burned completely to gaseous products. The nitrogenous part of the molecule is excreted through the kid-

neys, leaving a non-nitrogenous portion which behaves in the body much as the ordinary non-nitrogenous foods. The available fuel value of protein, however, is the same as that of carbohydrate, hence so far as the energy requirement of the body is concerned protein has no advantage over starch and sugar. But there are certain limitations attending the use of protein that must not be overlooked. The large amount of nitrogenous waste formed in the metabolism of protein entails some strain on the excretory organs that cannot be ignored, to say nothing of the physiological action of the nitrogenous catabolites, that must float about in the circulation prior to their excretion. Certainly, protein alone is not physiologically economical as a food. As Rubner has said, "Man cannot live on meat alone, not because the intestinal tract cannot digest it, but because of the physical limitations of the apparatus of mastication." However true this may be, it is quite clear that, on the surface at least, there appears no good reason for believing that a large proportion of man's food should be made up of protein.

Another peculiarity of protein that must be considered is its influence on the metabolism of carbohydrate and fat. As has already been suggested, protein food has a marked stimulating effect on the metabolism of protein matter. Thus, if a man in nitrogen equilibrium—nitrogen intake and nitrogen output just balancing—is fed a larger amount of protein food, protein metabolism is at once increased and eventually nitrogen equilibrium is re-established, but at a higher level. Similarly, increase in the amount of protein food augments the intensity of the metabolism of both fat and carbohydrate. Meat, for example, stimulates the oxidation of the non-nitrogenous materials of the body. Thus, as has long been known, excessive eating of protein foods tends to reduce obesity, through stimulation of the metabolism of the body fat. Hence, we see that protein is endowed with a general power of stimulating or exciting the processes of metabolism, so that the combustion or oxidation of all three classes of foodstuffs is greatly augmented as the intake of protein is increased. How far this is a desir-

able attribute we shall consider later. Conversely, fats and carbohydrates incline to inhibit the metabolism of protein matter. Thus, if nitrogen equilibrium is established at a certain level of protein intake, increase in the amount of carbohydrate or fat fed will at once check very decidedly the rate of protein metabolism. Hence, while protein food increases the rate of protein metabolism, carbohydrates and fats produce the opposite effect. It is for this reason that in typhoid fever, for example, there is physiological justification for relatively high carbohydrate feeding, coupled with a relatively low protein intake, as a means of preventing undue tissue waste, thereby conserving the vitality of the body and leading to a speedier convalescence.

Again, if we adopt Rubner's views regarding the specific dynamic action of the foodstuffs, we may emphasize still another peculiarity of protein. Attention has already been called to the fact that in the utilization of protein by the body, this form of matter must undergo a preliminary cleavage into a nitrogen-containing residue, which is at once eliminated as urea, and a carbonaceous residue capable of furnishing energy for the body. According to Lusk, meat protein yields 58 per cent. of dextrose in metabolism. It is generally understood that the early stages in the metabolism of protein, by which the above cleavage results and sugar is formed, give rise to heat, but this heat is dissipated and cannot be used for the life processes of the cells; the energy is not available for the cell protoplasm. In other words, when protein is metabolized, about 28 per cent. of its energy content is liberated as free heat, and cannot be used for the benefit of the body, except to give warmth. Only 71 per cent. of the energy of the protein food can be utilized for the benefit of cell life. When sugar, such as saccharose, on the other hand, is taken into the body, only about 3 per cent. of its contained energy is lost as heat, in the stages incidental to its digestion and preliminary cleavage. This marked difference in the so-called specific dynamic action of protein and carbohydrate in metabolism is worthy of careful attention, as indicating a radical dissimilarity in the economic utilization of the two classes of foodstuffs.

Recurring now to the amount of protein food that is needed to supply the wants of the body, it would seem from what has been stated that the indications physiologically are all opposed to the free use of this foodstuff for meeting the energy requirements of the organism. These are supplied far more advantageously and economically by the non-nitrogenous foods. Further, with the normal adult, excessive intake of protein does not materially increase the store of tissue protein; it is speedily burned up and its nitrogenous portion is quickly eliminated, while at the same time the fats and carbohydrates of the body are burned more freely. Evidently, the true function of protein food, in the adult, is primarily to maintain the integrity of the protoplasmic cells of the body. These cells are composed largely of protein material, which undergoes a more or less steady rate of metabolism during life. In these cells are evolved all those metabolic and other processes upon which the life of the organism as a whole depends. On these cells rests the full responsibility for the maintenance of the normal physiological rhythm. Without protein in some form to rehabilitate the cells of the body, life is impossible, but the amount needed is simply what will suffice to maintain equilibrium, to make good the daily loss of tissue protein. Anything beyond this amount, seemingly, has no physiological justification; the body has at command no facilities for making special use of it; it is burned up as quickly as possible and so gotten rid of. At least, such a view seems in harmony with the facts which have been presented. These statements, however, apply to the normal adult. With the growing child, the conditions are plainly different. Here, there is a specific need for protein to supply new material for the developing and growing tissues, and in accord with this need there is a retention of protein such as is not seen in the adult. Further, after a wasting illness, when the tissue cells have been largely depleted, recovery is attended with a retention of portions of the protein of the daily food, until the cells have become filled out to their former volume. Yet in neither of these conditions is there any apparent need for a large excess of protein food, since only a small fraction of protein is stored daily.

It is perhaps true, as stated by Lusk, that individual food standards "will ever be controlled by climate, the kind and amount of mechanical effort; by appetite, purse, and dietetic prejudice." Yet, it is equally true that there should be a definite answer to the question, What is the amount of protein food required, or best adapted for the physiological needs of the body? There is no argument as to the importance of the problem, from either a physiological, economical, or sociological stand-point. Every civilized country has considered the question, and physiologists from every nation have contributed towards its solution. It is somewhat strange, however, that the main work done has been in the direction of statistical inquiry. The dietetic habits of mankind have been studied, and great masses of data have been brought together, showing what the average man of different countries is in the habit of eating. While all this is very illuminating and interesting, it does not promise much help in determining what amounts of food are required to meet the real needs of the body, and to serve most economically and healthfully the best interests of the organism. Public opinion and even scientific opinion have, however, shaped themselves largely on the results of these statistical inquiries. Opinion even sanctions, in the words of Sir James Crichton-Browne, basing the science of dietetics on common observations, and on the hereditary customs and habits of mankind. There is a tendency to magnify natural instinct and primitive experience, as guides in the choice and construction of the daily dietary, esteeming them of greater value than any help chemical or physiological science can offer. In harmony with this tendency, statistical data have been much in evidence, for many years, as representing the food requirements of man. Why this should be is somewhat difficult to understand, since man is a creature of habits and might quite naturally have acquired some customs the reverse of physiological. However this may be, Rubner in Germany, Atwater in America, Lichtenfelt in Italy, and others have advocated 125 grams of protein food daily for the laboring man, because the laboring man of these countries consumes on an average this amount of protein.

This conclusion does not seem very scientific, nor very convincing, but all the same it finds wide acceptance. Further, for men at *hard* labor still higher quantities of protein are recommended by Voit, Rubner, and Atwater, up to 165 grams of protein per day. Rubner, indeed, has stated "that a large protein allowance is the right of civilized man," and the general idea of a "luxus consumption" as applied to protein food finds no lack of supporters. Opinions seemingly outweigh facts, while reasoning along physiological lines fails to prove convincing to those who bow to the testimony of hereditary custom and acquired habit. Civilized man may have assumed the right to a large allowance of protein, as he has assumed the right to alcohol, tobacco, and other questionable practices, but this is not evidence of physiological value.

What, for example, is the significance of the chain of events which follow the ingestion of protein food? Its prompt cleavage in the alimentary tract, the denitrogenation of the cleavage products in the intestine and liver, and the prompt conversion of the nitrogenous fragments into urea, all bespeak a quick and ready method of ridding the system of the greater part of this nitrogen, for which it apparently has no need. Further, as has been indicated previously, the facts regarding nitrogen equilibrium can be interpreted only as showing that excess of nitrogen is not stored in the body. Of what use then is a large allowance of protein or nitrogen? In the words of Folin, "The ordinary food of the average man contains more nitrogen than the organism can use, and increasing the nitrogen still further will therefore, necessarily, only lead to an immediate increase in the elimination of urea, and does not increase the protein catabolism involved in the creatinin formation, any more than does an increased supply of fats and carbohydrates. The normal human organism can be made at almost any time to store up fats and carbohydrates. The catabolism of these products consists chiefly of oxidation, a decomposition which sets free large quantities of heat, which can be converted into mechanical energy useful to the organism. The hydrolytic removal of nitrogen from the protein involves by comparison a

very small transformation of energy, and yields a non-nitrogenous rest of great fuel value. This non-nitrogenous rest derived from protein may partly be directly transported to the different tissues and thus at once supply oxidative material where needed, but in all probability is partly converted into fats, or at least into carbohydrates, and then becomes subject to the laws governing the catabolism of these two groups of food products." The value attaching to the major part of the protein is, therefore, that of the non-nitrogenous portion which comes from the denitrogenation of the cleavage products.

Is it possible that this denitrogenized residue of the protein molecule plays some part in the organism which fats and carbohydrates cannot fill, and that on this account there exists a real demand for a large allowance of protein? Some years ago, I ventured the opinion that there are only two possible reasons for assuming a need for the high exogenous catabolism of protein so commonly observed. The one is that the carbonaceous residue, left after the cleavage of nitrogen from the protein, is possessed of some quality which renders it better adapted for meeting the needs of the body than either fat or carbohydrate. But experiment has furnished no evidence to warrant such an assumption. The other possibility is that the body may derive some advantage from the presence in the tissues and fluids of the nitrogenous cleavage products of the protein. It is equally plausible, however, that the many nitrogenous fragments, formed in the efforts of the organism to prevent undue accumulation of reserve protein, may in the long run do as much harm as good. A high exogenous metabolism thus becomes subject to the suspicion that, at the level ordinarily maintained, it constitutes a menace to the preservation of that high degree of efficiency which is the attribute of good health. Again, it is well to remember that while, normally, excess of nitrogen in the food is quickly converted into urea and thus eliminated, the continuous excessive use of protein may lead, as Folin has suggested, to an accumulation of a larger amount of floating protein than the organism can with advantage retain in its fluid media. This being so, it is quite possible that the

continuous maintenance of such an unnecessarily large supply of unorganized protein material may sooner or later weaken one or more of the living tissues of the body.

Experiments to determine the physiological needs of the human body for protein have been attempted at various times, but mostly in a semi-apologetic fashion, and under the dominance of a faith in the virtue of high protein that has obscured the vision and weakened the force of the conclusions. Gradually, however, data from many sources, more or less in agreement, have combined to emphasize the fact that in man nitrogenous equilibrium can be maintained, for short periods of time at least, on amounts of protein food far below the accepted standards. Such a conclusion, while by no means proving that the smaller amount of protein is adequate for meeting all of the needs of the body, or maintaining the highest degree of efficiency, is obviously very significant. If the taking of a relatively small amount of protein day by day is followed by a minus nitrogen balance, it would be evidence most convincing that the amount of protein in question was not adequate, that the body was compelled to draw upon its store of protein to make good the deficiency. Plainly, such a procedure long continued would bankrupt the organism. On the other hand, we should be equally ready to admit that a daily plus nitrogen balance, obtained with small amounts of protein, is to be given equal weight, as at least indicating the probability or possibility that the protein fed was adequate for the body's needs. It might be argued that the simplest way to determine the minimum amount of nitrogen, or protein, needed daily by man would be to ascertain the output of nitrogen during fasting. Such data, however, have little value in this connection, since in long fasting, where no non-nitrogenous food is being consumed and the store of tissue fat and carbohydrate is exhausted, the body must of necessity live solely at the expense of the tissue proteins. Still, in Succi's case, with a body-weight of 63 kilograms, the nitrogen eliminated on the tenth day of fasting was in one experiment 7.4 grams, in a second experiment 5.4 grams, and in a third 7.1 grams; amounts equal approximately

to the metabolism of 46 grams and 34 grams of protein per day respectively.

The taking of non-nitrogenous food naturally diminishes the dynamogenic utilization of the tissue protein, and the proper method to be employed in arriving at a clearer conception of the physiological requirement for protein is to study the effect of a lowered intake of protein, when admixed with suitable quantities of non-nitrogenous foods. By such a method Siven, with a body-weight of 60 kilograms, found it possible to establish nitrogen equilibrium on 6.2 grams of nitrogen daily, for a short period of time, without taking any undue excess of either fat or carbohydrate. This amount of nitrogen corresponds to 38.75 grams of protein. Siven's experiments, made in 1900, attracted considerable attention, but they availed little in influencing opinion, which was as strongly as ever opposed to the idea that continued health, strength, and general efficiency can be maintained on a low protein intake. Siven's results, however, are in general harmony with a large number of experiments by various observers, some of earlier date and some later, all duly recorded in the literature, and all testifying to the possibility of maintaining the body in nitrogen equilibrium on amounts of protein far below the accepted standard.

Probably, the strongest argument against the safety of a continued low intake of protein was that based on the experimental work of Munk, Rosenheim, and of Jägerroos with dogs, all of whom found that with these carnivorous, high-protein feeders the giving of protein just sufficient to maintain nitrogen equilibrium was attended by a gradual loss of strength and serious digestive disturbances. During the past eight years, these results have been widely quoted as confirming the view that more protein is needed than suffices to maintain nitrogenous equilibrium; that a daily surplus is called for, if health and strength are to be secured. My own later experiments, however, have, I think, clearly shown that the unfortunate results reported by the above observers were due entirely to other causes than the diet. Kept under suitable hygienic conditions, it is quite possible to maintain dogs—in my own experiments

for a year—not only in nitrogen equilibrium on amounts of protein and non-nitrogenous food, per kilogram, far below the quantities employed by Munk and Rosenheim, but on this relatively low protein diet they may gain in body-weight and lay by some nitrogen. Further, there was no loss in the power of digestion, no falling off in the utilization of either fat or protein. In other words, there was no evidence of diminished power of absorption from the intestinal tract, no evidence of lowered utilization of the ingested food. The more or less broad deductions inimical to low protein, so widely drawn from the experiments of Munk and Rosenheim on dogs, and applied freely to mankind are entirely unwarranted and without foundation in fact. It is, however, interesting to note the failure of the dogs—in our experiments—to thrive on the purely vegetable dietary made use of, viz., peas, beans, and wheat; there seemed to be a necessity for some little admixture of animal food, such as meat or milk. Whether this means a difference in the physiological behavior of the vegetable protein, or whether the animal food contained something essential, which was lacking in the vegetable products, we need not stop to consider.

It is now, I think, perfectly well established that man can maintain, for a time at least, a condition of nitrogen equilibrium on a relatively small amount of protein food, provided carbohydrates and fats are eaten in such amounts as will supply the energy requirements of the body. Less clear, in the minds of many, is the effect on health and efficiency of a low protein diet, when continued for long periods of time. In other words, would not the effect on the race eventually prove disastrous, if a daily dietary was adopted which contained say only 50 to 60 per cent. of the protein called for by the Voit standard? This question I have attempted to answer, so far as a scientific experiment can afford an answer, by a long-continued investigation on a large body of men of different types, different nationalities, and different occupations. The results are all on record, and I may merely summarize by stating that daily analyses of income and output for twenty

individuals during a period of nine months, with careful observations on the health, strength, and endurance, etc., of the subjects, have furnished a fund of information from which definite conclusions seem justified. Further, with several individuals, notably with one, the experiment has continued with some limitations for seven years. I am inclined to believe, on the basis of the results obtained, that the average need for protein food by adults may be fully met by a daily metabolism equal to an exchange of 0.10–0.12 gram of nitrogen per kilogram of body-weight. This means a breaking down of three fourths of a gram of protein daily, per kilogram. Expressing it somewhat differently, the required intake of protein food amounts to say 0.85 gram per kilogram of body-weight. Hence, a man weighing 70 kilograms, or 154 pounds, would require daily 60 grams of protein food; *i.e.*, just one-half the amount called for by the Voit standard, and still further below the quantities implied as essential by the every-day practices of a large proportion of mankind. The facts brought out by this investigation testify to the possibility of maintaining nitrogen equilibrium in man over long periods of time on a daily metabolism of 0.1 to 0.12 gram of nitrogen per kilogram of body-weight, provided sufficient non-nitrogenous foods are eaten to supply the energy needed by the body. As I have said elsewhere, the facts obtained "are seemingly harmonious in indicating that the physiological necessities of the body are fully met by much more temperate use of food than is commonly practised. Dietary standards based on the habits and usages of prosperous communities are not in accord with the data furnished by exact physiological experimentation. Nitrogen equilibrium can be maintained on quantities of protein food fully 50 per cent. less than the every-day habits of mankind imply to be necessary, and this without increasing unduly the consumption of non-nitrogenous food. The long-continued experiments on many individuals, representing different types and degrees of activity, all agree in indicating that equilibrium can be maintained indefinitely on these smaller quantities of food, and that health and strength can be equally well pre-

served, to say nothing of possible improvement. The lifelong experience of individuals and of communities affords sufficient corroborative evidence that there is perfect safety in a closer adherence to physiological needs in the nutrition of the body, and that these needs, so far as protein food is concerned, are in harmony with an endogenous metabolism, or true tissue metabolism, in which the necessary protein exchange is exceedingly limited in quantity. There are many suggestions of improvement in bodily health, of greater efficiency in working power, and of greater freedom from disease, in a system of dietetics which aims to meet the physiological needs of the body without undue waste of energy and unnecessary drain upon the functions of digestion, absorption, excretion, and metabolism in general; a system which recognizes that the smooth running of man's bodily machinery calls for the exercise of reason and intelligence, and is not to be intrusted solely to the dictates of blind instinct, or to the leadings of a capricious appetite.

Recurring once more to some of the objections raised against a daily consumption of smaller amounts of protein food by the human race, it is said that a considerable excess of this type of food is essential, in order to supply a proper variety of the special amino-acids required for the construction of the characteristic proteins of the blood, and of the different organs and tissues of the body. This is an objection that carries some weight and should be given due heed. To be sure, it might be said that since individuals have lived and thrived for long periods of time on small amounts of protein, there cannot be any serious danger, still the objection raised has a good physiological basis. The work of Fischer, Abderhalden, Osborne, Levine, and others, has taught us that the individual proteins, of animal and vegetable origin, differ widely in the character and quantity of the amino-acids of which they are composed. Hence, there is reason in the statement that the body must be supplied with such a variety of amino-acids as will enable the different tissues and organs to construct the specific proteins they require. If the building stones needed are not supplied by the food, how can the body maintain its structure? We are

somewhat in the dark as to the methods by which tissue proteins are repaired. The old-time view that the proteins of the food were simply transformed into the proteins of the blood, and these in turn converted into the proteins of the tissues, has been supplanted by a new conception, viz., synthesis. Note the radical difference in the structure of the individual proteins: Zein of corn meal, for example, contains in its molecule 19.5 per cent. of leucine, 26 per cent. of glutaminic acid, 9.8 per cent. of alanine, no glycocoll, no lysine, and no tryptophane. It is what is known as an incomplete protein. Casein of milk, on the other hand, though lacking glycocoll, contains within its molecule both lysine and tryptophane; 6 per cent. of the former and 1.5 per cent. of the latter. Further, instead of the 26 per cent. of glutaminic acid present in zein, casein contains only 15.5 per cent., and of leucine only 9.3 per cent. These are merely suggestions of the differences which exist in the chemical structure of the individual proteins; differences which imply unlike physiological behavior and raise the question of comparative nutritive values. With such marked variations in composition, especially the complete absence of certain amino-acids from some proteins, there is ground for the assumption that a daily dietary containing only a small amount of protein, and the latter perhaps limited in quality, might prove hazardous. To be sure, even a narrow dietary is pretty liable to contain several varieties of protein, but we may waive this and consider the validity of the suggested danger. It would seem that here is one of the many questions which might be answered by direct experiment, thus allowing facts to supplant opinions. Thanks to the recent work of Osborne and Mendel at New Haven, and of McCollum at Wisconsin, we have some very interesting facts that supply a definite answer to these questions.

Feeding experiments carried out by Osborne and Mendel on white rats, for long periods of time, have shown that a single protein, reinforced by protein-free milk to provide the accessory portions of the diet, is quite sufficient to maintain adequate growth. This was found to be true of the casein of milk, lactalbumin, crystallized egg albumin, crystallized edestin from

hempseed, the glutenin of wheat, and glycinin from the soy bean. McCollum, feeding casein as the sole protein to pigs, found increases of the body protein of 20 to 25 per cent. Further, in the summary of his conclusions, this investigator states, "that the results of experiments in feeding the mixture of proteins occurring in individual grains, in quantity equivalent to the lowest possible level of protein metabolism of which the animal is capable, do not indicate as wide differences in the nutritive values of the protein of the wheat, oat, and corn kernels as would be expected from the known chemical differences in these proteins." But not all proteins are able to promote growth. Thus, as Osborne and Mendel have found, the gliadin of wheat which is notably lacking in the two amino-acids glycocoll and lysine, and the hordein of barley, which closely resembles gliadin, will suffice to maintain an animal, but cannot supply that which is essential for growth. Zein, of maize, which lacks three important amino-acid complexes, viz., glycocoll, lysine, and tryptophane, cannot alone cause growth, neither will it suffice to maintain the animal. Yet, as McCollum has shown, "the animal can utilize the nitrogen of zein very efficiently for repair of the losses due to endogenous or tissue metabolism," the average utilization of zein nitrogen for this purpose being about 80 per cent.

Consider for a moment what results of this character imply regarding the power of the organism to build up from a single dietary protein such diverse nitrogenous tissues as enter into the structure of every animal organism. In the words of Osborne and Mendel, "We have seen rats grow for months with casein—thoroughly purified and glycocoll-free—as the sole source of these amino-acids. During this time, one animal even brought forth two broods of young and secreted milk in sufficient quantity to bring her young to the age when they were able to care for themselves. Another pair of rats maintained 178 days (one-sixth of the average life of an albino rat) on gliadin as the sole protein of the diet produced healthy young and successfully reared them." These facts are strongly suggestive of a power of synthesis possessed by the cells of the organism

far beyond any previous conception. Think what it means for an animal to grow from small size to the adult form, quadrupling its weight, on a diet in which the nitrogen is supplied solely by a simple protein like edestin! What is the character of the process, or processes, by which the tissue cells "perfect the synthesis of purines and nucleoproteins, perchance of phosphoproteins and nitrogenous phosphatides, and of ferruginous proteins (like hæmoglobin) from iron-free protein precursors and inorganic iron"? (Osborne and Mendel.)

Equally suggestive are the results obtained with a so-called incomplete protein, such as gliadin, where health and equilibrium are maintained, with the capacity to produce and rear young, but without the power of growth. As stated by McCollum, "The fact that certain proteins, lacking in one or more cleavage products known to be necessary to the formation of the proteins of the animal body, are of relatively high efficiency in preventing loss of body nitrogen due to endogenous metabolism, yet are insufficient for growth, forces one to the conclusion that the processes of replacing nitrogen degraded in cellular metabolism are not of the same character as the processes of growth. It seems also to be a necessary conclusion that the processes of cellular catabolism and repair do not represent a series of chemical changes involving the destruction and reconstruction of an entire protein molecule." These current views regarding nutrition, and the facts upon which they are based, only serve to strengthen the position that there is no physiological need for a surplus of protein in the daily dietary. The power of synthesis possessed by the animal organism is such that even with a minimal supply of protein, and that perhaps of a character not best adapted for the needs of the body, the tissue cells can be relied upon to make good the deficiency by processes peculiarly their own; a type of a factor of safety which has real physiological significance.

If the newer data, which have been rapidly accumulating, truly represent the protein requirement of the body, would it not be the part of wisdom gradually to adopt dietary practices more nearly in accord with the physiological findings?

To this, however, we hear many objections, some based upon opinions and impressions of varying validity, some so manifestly biased that they carry little weight to an unprejudiced mind, while others are predicated upon findings which are interpreted at least as being opposed to the conclusions I am emphasizing. Opinions and impressions, together with arguments that are more or less visionary, we have not time to consider, but there are certain statements of fact that are deserving of more than passing notice. Take, for example, the interesting observations of Albertoni and Rossi on the nutritive conditions of Italian peasants, who by force of circumstances are compelled to live on a very limited and simple diet, such as is afforded by the immediate products of the land, viz., cornmeal, green vegetables, and olive oil. The diet, which is poorly prepared and unattractive, is low not only in protein, but in all the nutrients; it is exceedingly monotonous, is never reinforced by milk or eggs, and rarely contains any meat. The digestibility of the food is low and it is plainly poorly utilized. The statistics of food intake for thirteen persons, comprising three families, showed an average ingestion of 73 grams of protein per day for the men, with an average body-weight of 57 kilograms, with 8 grams of nitrogen metabolized. The observers state that the social, physiological, and psychical status of these people is anything but satisfactory. If now, without increase in the total calorific value of the day's ration, 100–200 grams of meat are substituted in the diet daily, a marked improvement is to be observed, among other things the digestion and utilization of all the foodstuffs being increased. Albertoni sees in these results convincing evidence of the detrimental effects of a low protein diet when long continued, and by inference at least the lack of stamina and general unsatisfactory status of these people are to be ascribed to their low nitrogen intake. This view is in harmony with a current tendency to ascribe to low protein the responsibility for whatever unsatisfactory feature may show itself whenever a low nitrogen intake is one of the attendant conditions. As a matter of fact, we are dealing here with a people who are through the poverty of their

surroundings manifestly undernourished. They are dependent for their subsistence upon a daily dietary which is inferior, poorly balanced, and difficult of digestion. The fact that the diet is low in protein is merely an incident of minor importance and without any necessary causal relation to the effects which apparently follow its use. What resemblance is there between this narrow, ill-balanced, and difficultly available diet of the Italian peasants and a daily dietary of equal nitrogen content, but made up of a palatable variety of animal and vegetable foods of easy digestibility and ready availability? The real trouble with the dietary of Albertoni's subjects is the *character* of the daily food and not its nitrogen content. The food of man, whether high or low in the proportion of protein, should be of a character readily assimilable if it is to fulfil satisfactorily the requirements of an ideal diet. Further, it must not be lacking in any one essential component; a danger which is greatly enhanced when the daily dietary is constantly limited to a few articles of food. No race or nation can hope to attain a high state of physical or mental development on a diet so manifestly indigestible, so lacking in variety, and so poor in total fuel value as that of these Italian peasants.

Much the same objection must be made to the conclusion drawn by McCay, from the results of his interesting study of the nutrition of the Bengali. This investigator found that the natives of Lower Bengal living on the ordinary diet of the province, viz., rice and a peculiar form of pulse, known as dhall, practically exist all their lives on a metabolism of about 40 grams of protein per man daily. As McCay states, these results confirm the view that it is quite possible for man to subsist throughout his life on a diet containing not more than one-third the amount of protein called for by the generally accepted standards. But the poor physical development of the race, the limited capacity of the individuals for manual labor, their low resistance to disease and infection, the condition of their blood and tissues, all testify to a degree of inferiority as compared with European standards of health and strength which demands explanation. McCay finds the explanation in

the low intake of nitrogen, in the small amount of protein ingested. To use his own words, "The physical development is only such as could be expected from the miserable level of nitrogenous interchanges to which he attains." Here, again, only in more striking fashion than is seen with the Italian peasants, we are dealing with a race which by force of circumstances is compelled to subsist upon a daily dietary utterly unsuited for meeting the needs of the body. The diet is, as already stated, composed almost entirely of rice and dhall; the latter peculiarly undigestible. Full 25 per cent. of the ingested nitrogen passes through the alimentary tract unabsorbed. In the words of McCay, the diets of the Bengali "are one and all bad in every respect, and particularly bad in that the large waste in the alimentary canal allows excessive micro-organismal development and formation of toxic compounds. . . . . A splendid opportunity for the growth of micro-organisms with its attendant intestinal putrefaction and toxæmia is provided, predisposing to numerous pathological conditions, such, for instance, as septic ulceration of the gums, intestinal catarrh and diarrhœa, dysentery, and anæmia. These are all exceedingly common disorders met with in the outpatient department of a general hospital." As I have said in another connection, "What bearing have these results, interesting and important though they are, upon the merits of a proper low protein intake, where the diet is well balanced and with a proper degree of digestibility and availability? There is no difficulty, under most conditions of life, in maintaining a relatively low nitrogen intake with an adequate fuel value, by the use of foodstuffs that are reasonably digestible and available, with freedom from excessive waste in the intestine. Surely then this peculiar, irrational diet of the Bengali, with its large proportion of rice and indigestible dhall, cannot be considered as typifying a true low protein diet. Rather is it an example of an unbalanced, unphysiological ration, the ill effects of which might reasonably be expected." Further, is it not quite likely that in the long-continued use of such a narrow dietary, with its very limited variety of foodstuffs, some one or more essential substances, upon which the

very life of the organism depends, may be omitted and thereby the health of the organism endangered? Is it not quite as plausible to assume that the Bengali owe their poor nutritive condition to the lack of some necessary element which their restricted dietary fails to provide, or to supply in adequate amount, rather than to their low nitrogen metabolism?

How often in our blind search after the truth do we err in the conclusions we draw from the data collected, sometimes magnifying the unimportant at the expense of what is really vital, sometimes overlooking entirely what should attract our attention most markedly. In the disease known as beriberi, so common at one time in Japan, especially among the class of people who subsisted largely upon rice, it was thought that the low protein diet which these people were accustomed to was responsible for the disease. When in connection with the Russian-Japanese War the daily ration of the Japanese sailors and soldiers, through the introduction of American beef and other food products, was reconstructed, raising the protein-content to a level approximating that of the European nations, beriberi began to disappear. These facts have been brought forward repeatedly as evidence of the deleterious effect of a low protein diet, the rice acting as a factor simply because it was poor in protein, and hence a daily diet composed largely of this foodstuff must necessarily be deficient in nitrogen. Now, however, as the work of Eykman and others has shown, it is not rice in general that causes beriberi, but rice that has been prepared in a certain way. It is only the polished rice, *i.e.*, rice that has been cleaned of its cuticle and outer layers by a process of milling that is harmful. In the words of Aron, "We must regard the second process of polishing and milling as that which changes a harmless foodstuff to one harmful under certain circumstances."

Quoting from Heiser, "The advances made during the past year in placing the etiology of beriberi upon a scientific basis have now proceeded sufficiently to warrant the inference that prophylactic medicine has the knowledge at its command to place this scourge among the preventable diseases." It has

now been demonstrated experimentally that beriberi in man and polyneuritis in fowls, when associated with rice as a diet, are due to the removal of the outer portion of the grain of the pericarp. Prior to 1910, beriberi was very common throughout all of the public institutions of the Philippines; also among the Philippine troops of the United States Army. Since that date, when an executive order was issued by the Governor-General of the Philippine Islands prohibiting the use of polished rice in all public civil institutions, beriberi has practically disappeared. To quote again from Dr. Heiser, "In one particular asylum, with 700 inmates, beriberi has almost constantly been present during the past ten years. Since June, 1910, unpolished rice has been used, and a few weeks after its use was begun beriberi disappeared, and since that time no further cases have been reported."

The work of Chamberlain and Vedder, in the Philippines, shows that polyneuritis gallinarum may be prevented by means of an extract of rice polishings, containing only those substances which are soluble in cold water and cold alcohol. Further, the neuritis-preventing substance was found to be capable of dialysis through a parchment membrane, showing that it must be crystalloidal in nature. The recent work by Funk, just published, shows that the essential ingredient in the rice polishings is an organic base; a substance plainly of great physiological importance. A daily diet in which polished rice is the main ingredient may prove deleterious simply because it fails to provide this important compound that resides in the outer layers of the rice berry, or which might be supplied by certain other foods, such a beans, meat, etc. The smaller amount of nitrogen furnished by the rice diet is merely an incident having no connection whatever with the cause of the disease. As illustrating the physiological importance of little things in diet, it is only necessary to state that the amount of this organic, nitrogenous base in rice is probably not more than 0.1 gram per kilogram. Further, as Funk has shown, the curative dose of the active substance is very small; a quantity which contains only 4 milligrams of nitrogen is sufficient to

cure pigeons, in which polyneuritis has been induced by feeding polished rice.

The above facts serve to illustrate and emphasize both the importance and the obscurity of certain nutritive factors which are as yet hardly recognized. Observations and experiment bearing upon the nutritive value of any given foodstuff, or upon any specific dietary, must be carefully safeguarded to avoid possible pitfalls which may lead to error. The inorganic salts which are so variable in character and amount in the different animal and vegetable foods are especially liable to be overlooked or inadequately provided for. These mineral nutrients play a part in the organism which is hardly yet fully recognized or appreciated. "One may, it is true, imitate the 'ash' of milk or blood; but the elements occur here in combinations quite different from those prevailing in the tissue fluids themselves, or in the native foods. The balance of acid and basic groups, the changing need for individual elements like phosphorus, calcium, chlorine, and iron, furnish a series of complex variables which are probably as indispensable to certain aspects of nutrition as they are unappreciated. If to all this is added the uncertain significance of the as yet largely unidentified compounds such as cholesterol and phosphatides which occur in all natural food mixtures, the experimental difficulties begin to appear in their true light" (Osborne and Mendel). This is well illustrated by the recent feeding experiments carried on at New Haven by Osborne and Mendel, where isolated proteins, reinforced by starch, fat, and a salt mixture, were fed to white rats. The young animals given a single protein could be maintained at uniform size and body-weight for long periods of time, but they failed to grow. The natural inference was that the single protein was inadequate, but evidence, gradually accumulated, eventually pointed to something other than the character of the protein, fat, or carbohydrate as the responsible agent. By simply feeding milk from which all protein had been removed, thus leaving only the inorganic salts, milk-sugar and other as yet unknown components of the milk, the necessary accessory elements were

provided and growth at once became possible. In the words of Osborne and Mendel: "Rats which have developed marked symptoms of decline on mixtures of isolated food substances containing a single protein have been revived in a manner little short of marvellous by the substitution of the protein free milk in place of part of the previous (non-protein) food. Instances have occurred where successful realimentation has thus followed in animals practically moribund."

Again, why should herbivorous animals, accustomed to a mixed vegetable diet, show such striking differences in general vigor, rate of growth, strength of offspring, capacity for milk secretion, etc., when fed through a period of three to four years on comparably balanced rations from restricted sources? One reads with interest and surprise the striking results recently presented by Messrs. Hart, McCollum, Steenbock, and Humphrey obtained with young heifers, when fed on nutrients limited to a single plant, namely, corn, wheat, and oats. Although the nitrogen or protein content and fuel values were essentially the same, yet it soon became perfectly evident that the nutritive or physiological value of the different feeds was radically unlike. Animals receiving their nutrients from the corn plant were strong and vigorous, in splendid condition all the time, and reproduced young of great weight and vigor. Those receiving their nutrients from the wheat plant were unable to perform normally and with vigor all the above physiological processes. Animals having their nutrients from the oat plant were able to perform all the physiological processes of growth, reproduction, and milk secretion with a certain degree of vigor, but not in the same degree as manifested by the corn-fed animals. This was the result obtained from the continued use of the specified rations during a period of three years. Wheat-fed animals changed to a corn diet showed marked improvement, both in the size of offspring and in milk secretion. The converse was true when corn-fed animals were transferred to a wheat ration.

How are we to explain such marked differences in the results obtained by the use of rations comparably balanced unless

we assume the presence of various elements, or groups of elements, in these specific foods, "whose proper or improper combination may make for vigor, resistance, and splendid condition, or for weakness, low resistance, and poor condition in the individual"?

Illustrations such as these serve the twofold purpose of emphasizing the paucity of our knowledge regarding all of the nutritive requirements of the body, and the necessity of applying to the study of the problem the same careful and scientific control that should prevail in every physiological inquiry, lest we err in the views we adopt.

AGE, DEATH AND CONJUGATION IN THE LIGHT OF WORK ON LOWER ORGANISMS *

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UNFORTUNATELY we are all interested in the subject of age and death. But the interest is of the kind that my friend Professor Lovejoy calls the interest of the repulsive. If we were free in the matter, we should doubtless prefer neither to hear nor know anything about the subject. But since to continue in that state of blissful ignorance and inexperience is impossible, we are driven to ask certain questions on the matter. What is the reason for our weakening and disappearing, along with all the visible living things that surround us? Why might we not as well continue indefinitely our interesting careers, instead of dropping off just as we become able to do something worth while? And *must* it be so inevitably? Is it grounded in the nature of life that all that live must die?

From the ancient seekers after the fountain of youth to the modern physiologists working toward the preservation of life, the prolongation of its processes, and the suppression of death, there have not lacked men who cherished the bold thought that death may be no essential part of life, that possibly some means may be found for counteracting the process of aging, for excluding death. And these men but express a secret wish of all mankind.

In this condition of affairs, a field of great interest was opened when the microscope revealed to us a world of organ-

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isms which seem at first view not to get old and die. As we follow them from generation to generation, the infusorian, the bacterium, seems not subject to the law of mortality. These creatures live for a time, then divide into two, and continue to live. Death appears, as we watch them, to occupy no place in their life history, save in consequence of accident.

This seemed to settle one of the great questions; whether age and death are inherent in life; inseparable from it. Here apparently was life without death; here was perpetual youth. If this can be in the infusorian, why not in other organisms, why not in man? Or if our thoughts be not so bold as this, may we not by study of the infusorian at least satisfy to a certain degree our understanding, learn perhaps something of the origin, cause and nature of age and death, and of the nature of that kind of life which avoids it? It is because I have devoted some years to a study of these matters in such creatures that I venture to speak to you on this subject.

You remember that one of the famous early essays of Weismann was upon the question I have just raised. He tried to show that death is not at all necessarily involved in living; that natural death originally did not exist, and does not exist now in these lower creatures; with theology he held that death was acquired in the course of time, and the Satan that " brought death into the world and all our woe " was no other than natural selection, acting for the benefit of the race, as distinguished from that of the individual. The body in the course of time becomes worn, battered, crippled. It is well to have at intervals a clearing out of this worn stock; new, fresh bodies replace the battered ones and a race which undergoes regularly this renewal must prevail and perpetuate itself in the place of those that do not; such is the conception of Weismann. Thus, too, the sum of happiness in the world is kept at the highest mark, since the fresh and perfect can enjoy much more than the worn and crippled.

But according to this view, if organisms could but live in such a way as to keep the body fresh and uninjured, there

would be no need for death. And the organisms which have succeeded in doing this are the infusoria and their relatives. These, in the famous phrase of Weismann, are "potentially immortal."

But another fact in the lives of these creatures attracts strongly the attention of the observer. These same unicellular organisms that appear to live forever do likewise go through the same process of sexual union that we find in higher animals. Now this sexual union has proverbially stood as the token of mortality; it is the preparation for the new generation, and prefigures the disappearance of the old one. You will recall the famous remark of Alexander the Great upon this point.

Why then should this take place in these ever-living creatures? The fact that it does was held by many to indicate that to consider these creatures ever-living was a mistake; they predicted that these animals would be found not potentially immortal, but subject to death at the end of a certain term, just as are higher animals. It is interesting to discover here, as in so many other cases, that the diverse possible opinions on the subject were formulated and maintained before investigation had obtained evidence as to the facts in the case.

But men were not content to speculate; and Maupas in one of the great investigations of biology (1883 to 1888) undertook to determine the truth of the matter. We must look briefly at the questions which were raised, and the answers that were obtained by Maupas and by others, for it will help us to understand the present state of the matter.

Maupas took a single individual (a *Stylonychia*), kept it with plenty of food, and allowed it to multiply by repeated division into two; he followed thus its history from generation to generation. The creatures divided every eighteen hours or so, and for about a hundred generations they remained strong and healthy. Then sickly and deformed individuals began to appear here and there; these became more and more numerous, till finally all had degenerated thus; they died out completely

at the end of five months, after 215 generations. Another series, beginning with an animal that had just conjugated, degenerated and died at the end of 316 generations; and other series gave similar results.

Thus, said Maupas, it is clear that these creatures do get old and die, just as higher animals do. The idea that they are potentially immortal is a mistake; death inheres in the process of life.

But why then are not these creatures all dead? How is it that they exist at the present time?

The key to this is found, according to Maupas, and according to the suggestions of many before him, in the process of sexual union. As fertilization saves the life of the egg and permits it to continue dividing for many generations, so does conjugation put new life into the dying infusorian, permitting it also to continue multiplication for many generations. The existence of sexual union in these creatures finds its explanation in the fact that they, like ourselves, are mortal; and their mortality is overcome, like our own, by the process of sexual reproduction. Their lives begin with the strength of youth, and inevitably run down the incline of age, as do our own.

But Maupas was one of those men who are not satisfied with a brilliant hypothesis; if conjugation actually restores vitality, he wanted to see it done. He allowed one of his *Stylonchias* in the 156th generation to conjugate with another that he captured wild. Then he took one from this pair and allowed it to multiply. Most unfortunately he does not say (doubtless he did not know) whether it was the old one or the fresh one that he allowed to continue. But this creature, which had conjugated, propagated itself for 316 generations before it finally died of old age. Meanwhile, the rest of the old stock, which had not been allowed to conjugate with fresh individuals, died out in 59 generations.

Thus it appeared to be demonstrated that conjugation restores vitality, that it rejuvenates. The brilliant hypothesis had seemingly become the demonstrated reality.

But it is interesting to the student of the history of science, and of scientific certainty, to discover that many years before the time of Maupas the function and effect of conjugation had been completely worked out in detail, by the most painstaking investigations, so that in 1862 a statement for it could be made that, according to the competent judgment of Engelmann, had been by a great abundance of observations raised above all doubt.[1] Yet this statement, though it seemed to rest on irrefragable evidence, and agreed with everything else that was known, was quite false, and in Maupas's time had been completely abandoned. Perhaps this was a type of the fate to be met by many other supposed demonstrations as to the function of conjugation, including that of Maupas—and not impossibly the one here presented.

Before leaving the work of Maupas, we must mention certain other observations that he made which are of great importance for understanding the matter. In his experiments, after degeneration had begun, many specimens within the same series (all derived from the same parent) conjugated together. But this did not rejuvenate them. On the contrary they died all the sooner after conjugating with close relatives. This happened in many cases.

So Maupas concluded (1) that conjugation with close relatives does not rejuvenate; (2) that conjugation with related individuals is not merely useless, but destructive; as soon as they do this, says Maupas, their doom is sealed; (3) that rejuvenation is due to conjugation with unrelated individuals.

This work of Maupas had of course tremendous influence; it seemed to be definitive. There appeared to be no escape from his conclusions, and for many years they were hardly seriously questioned.

But in very recent times have come a series of investigations that have shaken the conclusions of Maupas and given the entire matter a new aspect. It appears to me that the time is ripe for a revision of judgment on the whole general

[1] See Engelmann: Zeitschr. f. wiss. Zool., ii (1862), p. 347.

problem of age, death and conjugation in these lower organisms. I shall attempt to give briefly the grounds for such a revision, and the direction which the final judgment must apparently take.

1. The credit for seriously opening the question anew, as well as for getting some of the most important evidence leading to what seem to me the correct conclusions, is due to Calkins in his investigations extending from 1901 to 1904. After cultivating *Paramecium* for about 200 generations (three months) without conjugation, Calkins found that they become depressed; the division rate decreases; many die. As you remember, he found that by changing the diet at these periods, by transferring from hay infusion to beef extract, to pancreas or brain extract—the animals could be revived, and their life and propagation continued. In this way he kept them for 742 generations (23 months), but at the end of that period they finally died, in spite of any changes that were made in their food. This showed that the infusoria could be kept alive without conjugation a much longer time than Maupas had observed. Calkins kept his animals for more than twice as many generations as did Maupas.

The results of Calkins's experiments can evidently be interpreted in two ways:

1. It may be held that the depression was due to a too great uniformity in the food, or to the fact that the food and other conditions were not fully adapted to the animals: what the organisms needed was a change of diet. With frequent changes in diet, perhaps, there would be no degeneration at all. The final death would, on this interpretation, be due to the fact that the injury produced by uniform diet had gone too deep to be remedied by the means which Calkins tried.

2. But Calkins inclined, in view of the evidence then at his command, to another interpretation. This work came shortly after the first portions of Loeb's brilliant investigations on artificial parthenogenesis. Calkins interpreted his results in the light of those experiments. He held that the

infusoria were really in senile degeneration, ready to die of old age. What he had done was essentially to induce artificial parthenogenesis; he had replaced conjugation by chemical means. The final death, he held, was due to the fact that conjugation could not be indefinitely thus replaced; old age finally asserted its power, and in the absence of conjugation produced death.

Now I think it will be apparent at this point that there are two independent questions involved in the investigations; to understand later work it is needful to distinguish them clearly.

1. Does multiplication without conjugation result in degeneration, senility and death? What is the actual cause of the degeneration that has been observed?

2. Does conjugation remedy this degeneration? An affirmative answer to this second question has been generally assumed. If animals degenerate and die without conjugation, then evidently conjugation must be what prevents and remedies this result; such has been the reasoning. But if this is true it must be possible to *observe* this effect of conjugation; we shall do well to follow the example of Maupas, and not rest till a plausible hypothesis has been transformed into an observed fact.

These two questions then suggest two lines for further work, and both of these lines have been followed.

Enriques and Woodruff have followed up the question: What is the cause of the degeneration that has been observed? I myself have pursued mainly the second question, as to the actual effects of conjugation. The results of all these investigations seem to me harmonious and to lead to definite conclusions.

Enriques, in 1903 to 1908, carried out cultural investigations which led him to the following results and conclusions:

1. If he did not take pains to keep his cultures free from the products of bacterial action, the animals degenerated in time, just as observed by Maupas and Calkins.

2. But if he did keep them free from such products, by

changing the fluid every day or oftener, no degeneration took place. He thus kept *Glaucoma* for 683 generations, without a sign of degeneration, and similar results were reached with other species.

Enriques concluded that the results of Maupas and Calkins are explained by these observations. In their experiments, he holds that the continued action of bacterial products was the cause of the degeneration.

Every one with experience in such work must I believe agree with Enriques that bacterial action is a most important factor in producing degeneration and death. But it seems clear that he was in error in holding that this is the only cause. The most significant feature of his results was the fact that he kept his organisms more than twice as long as did Maupas, with no degeneration whatever. He kept them for very nearly the same number of generations as did Calkins, but in the latter's cultures there had been several crises of degeneration, which finally ended in destruction. Enriques' work indicated strongly that this degeneration was not inevitable, though he may not have explained with full adequacy why it occurs. Enriques drew the general conclusion that there is no such thing as senile degeneration in these organisms; they might enjoy perpetual youth and live without end, if only the conditions are kept healthful.

Then came the work of Woodruff, with which you are acquainted; work which appears to be definitive for the part of the problem with which it deals. Woodruff investigated the possibility that the degeneration observed by Maupas and Calkins may have been due to too great uniformity in the cultural conditions; or to the fact that the conditions employed lacked something necessary to the continued health of the animals.

He therefore carried on a set of experiments wherein certain lines were subjected to frequent changes in condition, while others were kept uniform. As you know, this gave the key to the problem. At last accounts, the progeny of a single individual were flourishing in generations subsequent to

the 2,500th, after four years and three months, without conjugation. They had been at that time kept for about four times as many generations as had Calkins's culture when it died out, yet the animals in Woodruff's experiment showed no indication of degeneration. Later work by Woodruff seems to show that if only the culture medium is properly selected, no degeneration occurs even if the conditions are kept uniform.

The work of Woodruff demonstrates that the very limited periods within which Maupas and Calkins observed degeneration has no significance for the question as to whether degeneration is an inevitable result of continued reproduction without conjugation. In other words, it annihilates all the positive evidence for such degeneration, drawn from work on the infusoria. It justifies the statement that the evidence is in favor of the power of these organisms to live indefinitely, if they are kept under healthful conditions. It shows that Weismann was correct in what he meant by speaking of the potential immortality of these organisms.

Thus I believe that we may feel that one of our two main questions has been definitely answered. Old age and death have no necessary place in the life of these creatures, even without conjugation.

But this brings the second question back to us with greater force than ever. What then is the effect of conjugation? What rôle does it play in the life of these creatures. Are we wrong in looking upon sexual union as a token of mortality?

This is the question to which I have addressed my own investigations, and with your permission I will speak next of these.

Before taking up directly the effects of conjugation, I would like to mention two subordinate points. First, in regard to the question that we have just discussed. Five years ago I started cultures from separate single individuals. During all that time there has been no opportunity for conjugation with unrelated animals, such as Maupas held to be necessary

for continued life. Yet these cultures are still alive and flourishing. Thus the progeny of a single individual may certainly continue to multiply for five years without admixture from outside. This then agrees with Woodruff's results, save that Woodruff knows that there has been no conjugation of even related individuals in the line which he follows. But Maupas found, as we saw, that conjugation among the progeny of a single individual does not help, but is actually harmful; if such individuals conjugated, their doom was sealed.

But is this result of Maupas generally true? Is inbreeding among the progeny of a single individual injurious? Or did Maupas's animals die merely because they conjugated when in a dying condition?

To test this point, I caused the progeny of a single individual to conjugate together frequently. There was no evil result whatever from this. To carry the process to an extreme, I caused nine conjugations in succession within a single line, each pair being in every case the progeny of one member of the preceding pair. Thus the forefathers of the existing race have gone through the process of conjugating together nine times. Yet the progeny are as strong and well as ever.

It seems clear therefore that conjugation with close relatives is not harmful in itself, in these creatures, though repeated many times. It is of course possible that there are differences on this point among the infusoria, just as there appear to be among higher organisms. But it is certainly not a principle of general validity that inbreeding is harmful.

But now we come to the main question. What difference does conjugation make in the life of the race?

The way to test this question is to have a set of the animals of the same parentage and history; to divide these into two groups, and to allow one group to conjugate, the other not. Then keeping the two groups under the same conditions, what difference is found to be caused by the conjugation?

In carrying out such experiments, the control set, those that have not conjugated, are fully as necessary as the other;

otherwise we can not tell whether the phenomena shown by those that have conjugated are really due to the conjugation or not. Neglect to have this control set has led to erroneous conclusions in some of the work previously done.

Comparative experiments of this character I have tried many times with large numbers of individuals. As the animals begin to conjugate, they first come in contact and stick together at the anterior end, though the process cannot be consummated till the more posterior regions become united. At this point then I intervened, separated the two before union was complete, and removed each to a drop of water by itself. Other pairs were allowed to complete conjugation, then the members were isolated in the same way. The two sets were then kept under the same conditions and their propagation was followed exactly. The two differ in no other respect save that one set has conjugated, while the other has not. What difference is caused by conjugation?

1. We find that the animals which were ready to conjugate, which were actually attempting to do so, are by no means in a depressed, degenerated condition, unable to multiply further. On the contrary, if they are not allowed to conjugate, each continues to multiply with undiminished vigor. Conjugation is then not necessary for further multiplication. And we can by no means assume that because individuals are ready to conjugate, they are therefore in a degenerate or senile condition. Nor can we assume, as has been done by some authors, that if the animals continue to multiply after conjugation, this shows that conjugation has had a rejuvenating effect, for the same specimens continue equally without conjugation.

This fact, taken in connection with the results of Woodruff, explains Maupas's supposed positive evidence that conjugation produces rejuvenescence, as also the more recent results of Miss Cull.[2] In Maupas's case, which is the one that

[2] Cull, Sara White: Rejuvenescence as a Result of Conjugation, Journ. of Exper. Zool., 1907, 4, 85–89.

has been mainly relied upon as demonstrating rejuvenescence, after the animals had become sickly (this being due, as Woodruff's work shows, to the fact that they had lived long under conditions not fully adapted to them), he tried mating one of them with a wild specimen. He then took one from this pair, and found that it was strong and well, so that it multiplied for 316 generations. Maupas supposed that this was due to the fact that conjugation had occurred. I believe it is fairly clear that the result was not due to the conjugation, but to the fact that he used a wild specimen, which had not been living under unadapted conditions. He apparently used the progeny of this wild individual for the remainder of his study. Now, the results I have just described show that if he had not allowed this animal to conjugate, it would have gone on multiplying just as well. Conjugation had nothing to do with the result, the fact that the specimen came from natural conditions is what counted.

Miss Cull's evidence for rejuvenescence consisted in showing that a considerable part of those that had conjugated continued thereafter to multiply. In the absence of the control experiment, she did not discover that they continue equally if they have not conjugated. There is then in this no evidence for a rejuvenating effect of conjugation.

2. To return to my own investigations, the second important result was to show that the specimens which have been allowed to conjugate multiply much less rapidly than those which have not conjugated. The difference is very marked, and showed itself in every experiment of a great number. The multiplication is slower, in those that have conjugated, for a month or two after conjugation.

This result seems surprising, in view of the widespread impression that multiplication becomes slower and slower, when the animals are kept without conjugation, and that the function of conjugation is to raise the vitality to the pitch where multiplication may continue at the normal rate. It is therefore interesting to note that those sterling investigators, Mau-

pas and Richard Hertwig, knew well that conjugation does not increase the rapidity of multiplication. Maupas emphasizes and insists upon this fact again and again, at much length, in opposition to the prevailing view that conjugation increases the power of multiplication. What Maupas held was that conjugation saves the animals from death, though without increasing their reproductive powers. Richard Hertwig observed, correctly, that conjugation actually decreases the rate of multiplication.

3. A third result of comparing those that have conjugated with those that have not is that many more of the former die or are abnormal than of the latter. In a specially favorable experiment, out of 61 conjugants, eleven lines had died out completely in 33 days, while of 59 lines that had not conjugated, but were otherwise similar, none had died in the same period.

4. Usually a considerable number of the conjugants never divide after conjugation, while all of those that have not conjugated continue dividing.

5. There is much greater variation among the progeny of those that have conjugated than among those that have not. This greater variation shows itself (1) in the rate of multiplication; (2) in dimensions. If we determine the coefficients of variations, we find these much greater in the progeny of those that have been allowed to conjugate.

Thus from these experiments, repeated many times, on an extensive scale, there is no evidence that conjugation causes rejuvenescence. On the contrary, it appears to be a dangerous ordeal, which sets back the rate of reproduction; and results for many individuals in abnormalities and death. What conjugation seems to do positively is to produce a great number of varying combinations, some of which die out, while others continue to exist.

Before attempting to draw more fully the conclusions from these experiments, let us follow the investigations a little further. In conducting an investigation it is necessary not only

to satisfy one's self as to the correctness of a result, but also to meet the objections of those that are firmly of the opposed view. Now, to the results thus far set forth the following objections might be made. Conjugation, it could be said, may indeed be of no use, and even disadvantageous, when organisms are in a strong, healthy condition; they would doubtless do as well without it. Probably they conjugate many times when there is no necessity for it. Yet, it might be urged, if you did not allow them to conjugate at all for many times the usual period, then possibly the need of conjugation might show itself. If you had a race that was in a depressed, degenerate condition, from whatever cause, possibly you might find that conjugation would restore them.

I therefore next carried out experiments to determine whether this objection holds. A certain race of *Paramecium* conjugates as a rule every month or two. A culture of this race was divided into two parts. One part was allowed to conjugate every month, while the other was cultivated on slides and not permited to conjugate. In this way the one set was allowed to conjugate four times in succession, in the course of a number of months, while the other set did not conjugate at all. We have thus a set that had missed four normal conjugations.

Now, as a matter of fact, the set that had missed the conjugations did become depressed; it multiplied slowly and irregularly, and many died. This may have been due, not to lack of conjugation, but to long-continued cultivation on slides; such cultivation does, of itself, produce an unhealthy condition. But in any case, we have now a depressed race and we can test the effect of conjugation upon it. Will conjugation end the depression, rejuvenate the organisms?

The experiment is performed by putting the members of this depressed race under the conditions that induce conjugation. Then, as conjugation begins, we permit one set to complete the process, while another lot is isolated without conjugation. The two sets are then cultivated under identical

conditions. We have now an opportunity to determine the effects of conjugation on a depressed race, not complicated by any other differing factors.

The results were striking, and to a certain degree unexpected. All those that had not conjugated continued to be weak and sickly, and they died out completely in the course of several weeks. Those that had conjugated showed great variation (as usual); some died very quickly; others multiplied very slowly and finally died out; others multiplied more vigorously than any of the non-conjugants. At the end of six weeks, all those that had not conjugated were dead, while certain lines of the others had multiplied and were numerous. The difference between the two sets was in fact very striking. But it is important not to misunderstand the nature of this difference. The lot that had conjugated showed great variation, and many of the lines were not stronger than the non-conjugants, dying out fully as quickly. But a few were stronger, and these multiplied and replaced the rest. Thus after some weeks, all the survivors had come from but three or four among those that had conjugated.

But even in these the depressed condition had not been completely overcome; they were still notably less vigorous than the strain which had been kept throughout under more natural conditions and had conjugated frequently.

Thus what had happened was this: Conjugation had produced much variation; some few of the variants had been more vigorous and had lived, while the rest died.

This result when first reached was unexpected and difficult to interpret. It seems of such importance that one felt it necessary to try it again. I shall not describe to you the long and wearisome process of providing anew the necessary conditions and repeating the experiment. It will suffice to say that the experiment was repeated and gave the same results as before.

Thus I believe that we are in position to make certain positive statements as to the effect of conjugation. Conjugation

does not rejuvenate in any simple, direct way. What it does is to produce variation; to produce a great number of different combinations, having different properties. Some of these are more vigorous, others less vigorous. The latter die, the former survive. This happens equally, whether the animals which conjugate are at the beginning vigorous or weak. If they are vigorous, then one of the most striking effects of conjugation is to produce some lines that are less vigorous than the original ones, so that they die out. If the animals which enter conjugation are weak, then one of the most striking effects of conjugation is to produce certain combinations that are more vigorous than the original ones, so that they survive, while those that did not conjugate die out. In a short time the entire race is replaced by the descendants of a few of those that conjugated.

Now, the relation of all this to certain things that are known in higher organisms seems fairly clear. In higher animals likewise the result of intercrossing is to produce variation. We don't call it variation nowadays, because we know something more about it; we call it Mendelian inheritance. In the crossing of two individuals that resemble each other externally, progeny of many different kinds are produced. In crossing white and cream-colored four o'clocks Correns got eleven kinds of red, white, yellow, and striped offspring among the grandchildren. Heredity, as the Mendelian analysis has revealed it to us, is a process of producing a great number of diverse combinations by the varied intermingling of the characteristics (concealed or apparent) of two indivduals.

Now, it seems clear that this is exactly what is done in the conjugation of the infusoria. We have not yet succeeded in determining the precise rules of recombination, such as have been worked out for many cases in higher organisms; so that for the infusorian we are as yet limited to the statement that conjugation produces variation.

Thus the conjugants apparently have the same relation to each other, so far as inheritance is concerned, as do sperm and egg in the higher organisms. We ought to find that the

progeny inherit from both of the conjugants. What are the positively known facts as to this?

Regarding biparental inheritance in these lower animals, we are as yet in that relatively backward stage of science that is implied by the necessity for the use of statistical methods.

We hear at times the Kantian dictum that any subject is scientific only to the extent that it makes use of mathematics. This dictum is sometimes put before us as an argument for using statistical methods. But for these we could almost reverse the statement, and say that any subject is scientific only to the extent that it can dispense with statistical methods. These are necessary mainly when we cannot understand and control the separate causes that are at work; as soon as we can do this such methods become largely unnecessary.

But the use of statistical methods enables us to show that in conjugation the progeny inherit from both parents. By working out for the rate of fission the coefficient of correlation between the descendants of the two that have conjugated, we find that they have nearly the same closeness of relationship as brothers and sisters; and somewhat closer than cousins. The coefficient of correlation is about .4. This means that if the progeny of one member of a pair have a peculiarity, the progeny of the other member have the same peculiarity, though in a less degree, and this similarity can apparently come only through inheritance from both parents.

Comparing conjugation with the fertilization of higher animals, we find then this state of the case. In higher animals fertilization has two diverse effects, which recent investigation, particularly that of Loeb and his associates, has clearly disentangled. (1) On the one hand, it initiates development; it prevents the egg from dying, as it would do if not fertilized. This function of fertilization is the one that is replaced by the processes which induce artificial parthenogenesis. (2) But, secondly, fertilization brings about in some way inheritance from two parents. When there is inheritance from but one parent, the inheritance is as it were complete; the child as a

rule resembles its parent in all hereditary characteristics; this is the result of the so-called "pure line" work. But when we have biparental inheritance, a great number of different combinations of the characteristics of the two parents are produced, so that the process of fertilization is one that in this respect completely alters the face of organic nature, producing infinite variety in place of relative uniformity.

These two functions of fertilization, the initiation of development, on the one hand, the production of inheritance from two parents, on the other, are logically independent; they might conceivably be performed at different times and by different mechanisms. The fact that in many organisms the same mechanism that brings about biparental inheritance is likewise the one that initiates development might from certain points of view be called an adaptation. Its result is to insure that in *all* the organisms that develop there shall be inheritance from two parents, not from one. In the work on artificial parthenogenesis these two functions have been separated experimentally; the initiation of development takes place alone.

Now, in endeavoring to understand conjugation, attention has been given hitherto almost exclusively to the first of these two functions. It was held that the function of conjugation must be to make possible life and development where it was otherwise impossible, just as fertilization arouses the egg to further life and development. But it turns out that conjugation, instead of having this one of the two functions of fertilization, has the other. The two functions are in the infusorian separated, just as they are in artificial parthenogenesis, but it is the second, not the first, that we have before us. Conjugation is not necessary in order that life and reproduction shall continue; they continue without it.

But the life which thus continues is uniform and unchanging. To give biparental inheritance, with varying mixtures of the characteristics of the two parents; to produce these new combinations in great variety, conjugation is necessary. And when this happens under such conditions that the original

combinations were not adapted to survival, then some of the new combinations produced often are adapted to the conditions; conjugation then results in a survival of an organism that would have been completely destroyed without it. It is most interesting in this connection to observe that conjugation is usually induced by an unfavorable change of conditions, a change of such a nature that the organisms begin to decline. Thereupon conjugation occurs, so that new combinations are produced, adapted to varied conditions, some of which may survive.

Thus it appears to me that the whole series of investigations on old age and on conjugation leads to a unified result, and one that is in most respects in consonance with what we observe in higher animals. But in one respect there is a difference, and this brings us back to the question with which we began. Is death a necessary accompaniment of life? Do the life processes necessarily take such a course that they must lead to death?

To this question the work on the infusoria answers *No!* The evidence that was supposed to show that the life processes must gradually run down and end in death had been shown by the work of Woodruff not to lead to any such conclusion. Woodruff appears to be clearly justified in his recent statement that these organisms "have the potentiality to perpetuate themselves indefinitely by division," and my own studies on the effects of conjugation furnish the complement to this result, agreeing with it fundamentally.

All that Weismann meant by saying that such creatures are potentially immortal has shown itself correct. Death is not necessarily involved in life.

But why, then, in higher animals and in ourselves, even when there is no accident and conditions are good, do we find death coming as a natural end to life? Why should there be this tremendous difference in such an essential point between the lower organisms and the higher ones? Is there any possibility of mistake as to the necessity in the case of higher organisms?

To find a ground for this difference, we shall do well to follow the usual procedure in science, and examine other differences between these lower creatures and the higher ones, to see if these may not give us the clue. And here I touch upon a matter that had been fully developed by Minot and others; it is worth while to speak of it briefly, because work bearing upon the matter has recently appeared.

The most striking other difference between these lower organisms and the higher ones is evidently the fact that in the higher organisms the body becomes large, complex and differentiated into a number of diverse parts; different cells of the body have taken on themselves different functions and different structures. This appears to involve a correlative loss of the power of carrying on the fundamental vital processes; the cell that has become filled with lime, or that has transformed into muscle, no longer retains the vital elasticity of the cell in which the diverse functions remain well balanced. Products of metabolism are no longer perfectly removed; other processes necessary to life become clogged. The final result of this is a complete cessation of the processes; age and death follow upon differentiation. This, as you know, is the theory of Minot. According to it, the welfare of the individual cell is as it were sacrificed to that of the body as a whole, and this in turn involves the final destruction of the body itself, so that a period of higher diversified life is purchased at the price of ultimate death.

Minot has added to this fundamental idea certain views as to quantitative relations of nuclear and cytoplasmic material in the cell. Relative increase of cytoplasm is taken to be the beginning of the process of aging, while relative increase in nuclear material is considered a process of rejuvenation. Such rejuvenation was held therefore to occur in the early cleavage of the egg, since here the amount of nuclear material was supposed to increase greatly in proportion to the amount of cytoplasm.

The recent important paper of Conklin has shown that in

the cleavage of many animals this increase of nuclear material relative to the cytoplasm does not occur. Conklin's results will apparently go far in rendering untenable or modifying all theories in which great significance is attached to the precise quantitative relations between nucleus and cytoplasm. But what is important to realize is that this has no bearing on the fundamental feature of the theory that aging and death are due to differentiation. The grafting of the theory that the quantitative relation between nuclear and cytoplasmic material is an essential point upon this general theory was unfortunate from the beginning.

Everything points, it appears to me, to the essential correctness of the view which holds age and death to be the result of the greatly increased differentiation of larger organisms. Is there then any probability that we shall some time find that in the higher animals, as in the lower ones, death need not occur?

Evidently not. If death is the price of differentiation, then after the goods have been delivered the price must be paid. To prevent a higher organism from undergoing death would at the same time prevent him from becoming a higher organism. And the cell which remains in the embryonic condition—the cell of the germ glands—is even now as immortal as the cell of the infusorian. Death, as Minot says, is the price we pay for our more complex life. Age and death, though not inherent in life itself, are inherent in the differentiation which makes life worth living.

ON MALARIAL FEVER, WITH SPECIAL REFERENCE TO PROPHYLAXIS *

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IT is now over thirty years since that patient and careful student Laveran discovered parasites in the blood of sufferers from malarial fever, and recognized their significance; it is over twenty-five years since Golgi pointed out the relations between the life history of the parasites in their human host and the manifestations of the malady; it is nearly fifteen years since Ross's discovery of the development of the microörganisms in the body of the mosquito, which, along with the studies of the Italian school, revealed the manner in which the disease is spread and the way in which infection takes place. In the ten or twelve years which have followed these discoveries, the advances in our knowledge of the ætiology, prophylaxis, and treatment of various other infectious diseases, such as yellow fever, cerebro-spinal meningitis, syphilis, poliomyelitis, have been so rapid and so absorbing, that here in America, at least, the lessons which we have learned with regard to the nature of malarial fevers and the methods of prophylaxis and treatment by which they may be controlled, have not been taken to heart as they have been in some other parts of the world.

A brief consideration, therefore, of the present state of our knowledge concerning malaria, and of some of the problems which concern us, as a profession and as a people, with regard to questions of prophylaxis and treatment, may be worthy of consideration before this society.

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ÆTIOLOGY. NATURE OF INFECTIOUS AGENT. MANNER OF INFECTION

The infectious agent we now know to be a sporozoön of the order Hæmosporidia, sub-order, Acystosporea, genus, Plasmodium.

These hæmosporidia have two cycles of existence—one, asexual (schizogonia), takes place in the blood of vertebrates; the second, sexual (sporogonia), in the viscera of certain insects. The vertebrates appear to represent the intermediate hosts, the insects the definitive hosts. In the case of Plasmodium, the definitive hosts are various mosquitoes belonging to the subfamily Anophelinæ.

The genus Plasmodium is represented by three distinct species, differing not only in their morphological and biological characteristics but in the character of the manifestations to which they give rise in the infected individual. These species are:

Plasmodium vivax (Grassi and Feletti, 1890), the parasite of tertian fever.

Plasmodium malariæ (Laveran, 1881), the parasite of quartan fever.

Plasmodium falciparum (Welch, 1897), the parasite of æstivo-autumnal or tropical fever.

In the human being, the parasite passes through its asexual cycle (schizogonia) in the substance of the red blood-corpuscle, dividing, at maturity, by segmentation, into a fresh brood of young parasites, merozoïtes, which in turn attack new corpuscles, and pursue again their cycle of existence, a process which may be continued for an indefinite period of time. Alongside of the parasites pursuing this asexual cycle of development, there appear, however, in most cases, other organisms—distinguishable, in the younger tertian and quartan parasites, mainly by differences in their nuclear structure, but in the æstivo-autumnal parasite, by gross differences of form—which early begin to take on sexual characters. These *gametocytes* show, in all forms of malaria, a resistance to quinine, greater than members of the asexual cycle, but slightly greater in *P. vivax* and *P. malariæ*, very markedly so in *Plasmodium falciparum*.

Immediately after the removal of the parasites from the human host by the anopheline mosquito, actively motile filaments (*microgametes*) escape from the male element (*microgametocytes*) and penetrate the female organism. The fecundated female element (*oökinete*) develops then the power of active locomotion, penetrates the wall of the stomach of the mosquito, and there becomes an *oöcyst*, from which, after about eight days, at maturity, escapes a brood of newly formed *sporozoïtes* (*sporonts*) which collect in the salivary glands of the mosquito, from which they are discharged into the succeeding human host.

On entering the blood of the human being, the sporont attacks a red blood-corpuscle, enters it, and thenceforth becomes indistinguishable from the product of asexual division (schizont). In the red blood-corpuscle it enters immediately upon the ordinary cycle of asexual development (schizogonia). The length of the sexual cycle of development in the mosquito host depends upon the conditions under which the insect is placed, amounting, under favorable circumstances, to about eight days.

The anophelines which may act as definitive hosts for the parasite belong to several genera and a variety of species. In the United States, two genera and eight species have been recognized, namely: *Anopheles punctipennis* (Say); *Anopheles pseudopunctipennis* (Theobald); *Anopheles crucians* (Wiedemann); *Anopheles occidentalis* (Dyar and Knab); *Anopheles atropos* (Dyar and Knab); *Anopheles walkeri* (Theobald); *Anopheles maculipennis* (Meigen); *Cœlodiazesis barberi* (Coquillet).

In Panama, the commonest hosts of the malarial parasite are: *Anopheles albimanus* and *Anopheles tarsimaculata* *Anopheles pseudopunctipennis* is apparently but slightly concerned in the transmission of malaria, and it has not yet been proven that *Anopheles malefactor* transmits the disease.[1]

[1] Darling: Transmission of Malarial Fever in the Canal Zone by Anopheles Mosquitoes. J. Am. Med. Ass., Chicago, 1909, liii, 2051–2052.

It is a question whether, in the temperate parts of this country, the common *Anopheles punctipennis* plays any part in the transmission of malaria, and in temperate Europe and in America the main agent of transmission is *Anopheles maculipennis.*

The anophelines are essentially country mosquitoes, breeding by preference in shallow pools, especially those containing a growth of algæ; they rarely develop in water standing in tubs or about houses as do Culices, the common house mosquitoes of the city. Several species, however, breed in marshes with brackish water. The anophelines are, as a rule, night-biting mosquitoes, that is, they bite only at night or at dusk, morning or evening. In daytime, they retire to dark places, behind curtains or clothes or even into holes in the ground. This has led to the construction of rather interesting mosquito traps. The simplest of these are boxes lined with black or dark blue cloth. The mosquitoes seek the dark recesses and are suddenly shut in by a lid—and later destroyed. Blin,[2] who noticed that mosquitoes often repaired to crab holes by day, dug small holes in the ground about 16 inches deep at an acute angle to the surface. The holes, protected from direct light, are soon filled with mosquitoes which are burned by torches.

The oöcysts will not develop in their mosquito host at all temperatures and under all conditions; they grow best at a temperature from 20° to 30° C. They are killed in temperatures steadily under 16°. Exposure, however, to a temperature as low as 10° or 13° for an hour will not kill the oöcyst if the insect later be placed under favorable surroundings. Anophelinæ may bite at a season considerably earlier or later than that which is suitable for the complete development of oöcysts (Jancsó)[3].

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[2] Blin: Destruction des moustiques par le procédé des trous-pièges. Caducée, Par., 1909, ix, 163.

[3] Jancsó: Der Einfluss der Temperatur auf die geschlechtliche Generationsentwickelung der Malariaparasiten und auf die experimentelle Malariaerkrankung. Centralbl. f. Bakt., etc., I Abt., Orig., 1905, xxxviii, 650.

The parasite is not transmitted to the offspring of the mosquito. The average length of life of the anopheline mosquito is difficult to determine. Artificially cultivated, they have been kept alive for 56 days.[4] Ross calculates that the average natural life of an anopheline is of about three weeks' duration. During the cold weather, a certain number of adults, especially females, hibernate in lofts, cellars or dark rooms, coming out again with the return of warm weather. The length of time during which a mosquito may contain viable sporozoïtes in the salivary glands cannot be stated with positive certainty. The observations of Jancsó above mentioned would tend to suggest that in temperate climates few mosquitoes can be infectious at the beginning of the succeeding season.

Among mosquitoes collected at the beginning of the malarial season, the number of infected insects is extremely small. It cannot, then, be regarded as proven that the hibernating mosquito may be a carrier of infection.

SEASONAL INCIDENCE OF MALARIA; RELAPSES; LATENT INFECTIONS

Relapses.—Although the infection of a human being can occur only as a result of a bite by an infected mosquito, yet the curve of seasonal prevalence of the disease is remarkably modified by the fact that relapses, which are apparently commonest in tertian malaria, have a definite seasonal relation, being especially frequent in all climates at the onset of warm weather in spring, and notably preceding the appearance of anophelines, which initiates the annual epidemic.

The seasonal occurrence of malaria in Baltimore, which corresponds very closely with the figures reported by the observers in Rome, may be illustrated by the following table:

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[4] Nuttall and Shipley: Studies in Relation to Malaria—The Structure and Biology of Anopheles (*Anopheles maculipennis*). J. Hygiene, Cambridge, 1902, ii, 58-84.

SEASONAL DISTRIBUTION OF MALARIA IN BALTIMORE

	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Tertian.....	12	12	28	51	76	68	131	161	153	168	54	17	931
Quartan.....	3	1	0	1	0	0	3	0	2	1	4	2	17
Æstivo-autumnal	5	1	2	5	2	3	37	99	191	203	63	22	633
Combined.....	0	1	1	0	0	1	3	3	4	11	6	2	32
	20	15	31	57	78	72	174	263	350	383	127	43	1613

It was further found on questioning these patients, who, for the most part, were ordinary ward patients, people who might well have forgotten a previous malarial attack, that about two-thirds of the individuals who had consulted us during the first half year had had previous attacks, and might therefore be suffering from a relapse, while only about one-third of those suffering with malaria during the second half year could remember a preceding affection of the same sort.

It would thus appear that the greater part, if, indeed, not all of the cases occurring early in the season in temperate climates, are relapses from previous attacks.

The causes of relapses have been much discussed. Untreated malaria often disappears spontaneously, but these disappearances are usually followed by recrudescences and relapses at varying intervals through months and years. Caccini [5] finds that in tertian fever, relapses and rallies alternate in periods of from two to three weeks. In æstivo-autumnal fever, the relapses and rallies in untreated cases occur at rather shorter intervals, amounting usually, according to Carducci,[6] to about seven days. Often, however, spontaneous recoveries may occur, particularly in tertian fever, followed by relapses after intervals of months or indeed even years. The condition here is indistinguishable from that which occurs after more or

[5] Caccini: Duration of the Latency of Malaria after Primary Infection, etc. J. Trop. Med., Lond., 1902, v, 119; 137; 159; 172; 186.

[6] Carducci (A.): Sulla cura e sulla causa delle recidive nella malaria. Atti d. Soc. per gli stud. d. malaria, Roma, 1905, vi, 27.

less incomplete treatment by quinine. From a seasonal standpoint, as has been said, relapses occur with beginning warm weather, or, in the tropics, after the onset of the rainy season; but in any individual with latent malarial infection and sometimes after it has apparently been eradicated by long continued and careful treatment, a relapse may occur following sudden changes of climate, exposure, fatigue, emotional excitement, or infectious disease.

The cause of such relapses is still uncertain. No evidence exists in support of the old assumption that the parasite persists somewhere in the organism in the shape of encapsulated spores. Ross [7] believes that it is, on the whole, more probable that certain more resistant parasites of the asexual cycle may persist for very long periods of time, in numbers so small as to produce no definite symptoms, but ever ready to multiply under circumstances which lower the resistance of their hosts.

Bignami [8] is inclined to believe that the persistent relapses in some cases may be due to the acquisition, by certain strains of the parasites, of a tolerance for quinine such as has been observed, for instance, in the case of trypanosomes toward preparations of arsenic.

Others have suggested, however, as a possible cause of relapses, the parthenogenetic sporulation of the more resistant gametocytes. Grassi,[9] Schaudinn,[10] and others describe pictures which they interpret as a parthenogenetic sporulation of macrogametes. It is well known that gametocytes are more resistant against treatment with quinine than organisms of the asexual cycle, and it is suggested by these observers that the parthenogenetic sporulation of macrogametes which have persisted for a long time after treatment may well be the cause of the reawak-

[7] Ross: The Prevention of Malaria. 8° London (Murray), 1910, 115.

[8] Bignami: Sulla patogenesi delle recidive nelle febbre malariche. Riv. ospedal., Roma, 1911, i, 305–317.

[9] Grassi (B.): Die Malaria. Studien eines Zoölogen. 2 ed., Jena, 1901.

[10] Schaudinn (F.): Studien über krankheitserregende Protozoen. II, Plasmodium Vivax, etc. Arbeit. a. d. K. Gesndhtsamt., 1903, xix, 169.

ening of latent infections. Similar pictures of segmentation in crescents were described many years ago by Canalis.[11] This process, though apparently confirmed by good observers, is still doubted by a student so reliable as Bignami.[12]

Craig [13] contends that these so-called parthenogenetic sporulating forms are, in reality, more resistant elements, resulting from the early conjugation of two young parasites. This conjugation, first described by Mannaberg,[14] who, as is well known, has long believed that it is a regular step in the formation of crescents, and Ewing [15] in young forms of the tertian parasite, has been repeatedly observed by Craig, who regards the resultant zygote as a more resistant body destined to remain in the human organism after other forms of parasite have disappeared as the result of treatment or of the natural destructive powers of the blood. It is to the reawakening and segmentation of such bodies, he believes, that the relapses are due.

Mary Rowley-Lawson [16] has recently described and pictured that which suggests a process of impregnation of macrogametes within the body of the human host in æstivo-autumnal infections, and has apparently followed every intermediate stage from impregnation to segmentation (schizogonia). Such a diversion of the usual process of development might well account for some relapses. The recent remarkable studies of Bass,[17] who asserts that he has succeeded in cultivating the

[11] Canalis (P.): Studi sull' infezione malarica, etc. Arch. per le sc. med., Torino, 1890, xiv, 73.

[12] Bignami: op. cit.

[13] Craig (C. F.): Intracorpuscular Conjugation in the Malarial Parasite and its Significance. Am. Med., Phila., 1905, x, 982; 1029.

[14] Mannaberg (J.): Beiträge z. Kenntniss der Malariaparasiten. Verhandl. d. Cong. f. innere Med., Wiesb., 1892, xi, 437–449.

[15] Ewing (J.): On a Form of Conjugation of the Malarial Parasite. J. Hopkins Hosp. Bull., 1900, xi, 94. Also, Malarial Parasitology. J. Exper. M., N. Y., 1901, v, 475.

[16] Rowley-Lawson: The Æstivo-autumnal Parasite, etc. J. Exper. M., N. Y., 1911, xiii, 263–289.

[17] Bass (C. C.): A New Conception of Immunity, etc. J. Am. M. Ass., Chicago, 1911, lvii, 1534.

malarial parasites outside the human body, should, if confirmed and extended, shed a flood of light upon the development of the organism.

However this may be, the malarial season in all countries is almost invariably preceded by an outbreak of relapses. These relapses, at the beginning, occur at a time when the anophelines are not yet active. The true epidemic follows shortly after the appearance of anophelines. But it is not necessary that there should be an active outbreak of relapses, for it has been shown that latent malaria is by no means uncommon. This was brought out especially by Koch [18] in his malaria expedition to the East. Koch called attention particularly to the fact, which has been confirmed by many other observers in all parts of the world since that time, that in malarious localities the proportion of children who are infected is very large, but more than this, a large proportion of these children carry the infection without signs so striking as to be recognized by the ordinary individual. It is not an uncommon thing for a child to be playing about, apparently in reasonably good condition, with active parasites demonstrable in the circulation.

But children are not the only malaria carriers, and the number of adults who may keep at work with considerable numbers of malarial parasites, especially of æstivo-autumnal gametocytes, in the blood is, in malarious districts, very large. For instance, in the Panama Canal Zone, where so much has been done, Darling,[19] a few years ago, reported that in several

[18] Koch (R.): Erster Bericht über die Thätigkeit der Malariaexpedition. Deutsche med. Wchnschr., 1899, xxv, 601. Zweiter Bericht über die Thätigkeit der Malariaexpedition. Ibid., 1900, xxvi, 88. Dritter Bericht über die Thätigkeit der Malariaexpedition. Ibid., 1900, xxvi, 296. Vierter Bericht über die Thätigkeit der Malariaexpedition. Ibid., 1900, xxvi, 397. Fünfter Bericht über die Thätigkeit der Malariaexpedition. Ibid., 1900, xxvi, 541. Schlussbericht über die Thätigkeit der Malariaexpedition des geh. med. Raths. Prof. Dr. Koch. Deutsche med. Wchnschr., 1900, xxvi, 733. Zusammenfassende Darstellung der Ergebnisse der Malariaexpedition. Deutsche med. Wchnschr., 1900, xxvi, 781; 801.

[19] Darling: op. cit.

regions where the malarial sick rate did not fall to zero and where no anophelines were breeding, 10 per cent. of the men who were at work without symptoms had parasites in the blood. Thirty per cent. of these were æstivo-autumnal, 70 per cent. tertian. Among the Spanish and West Indian families, the latent malarias amounted to 30 per cent. Darling observes: "It is this latent malaria in every tropical community that contributes largely to the preservation of malarial parasites, and to the infection of anopheles when, after the rainy season, mosquitoes have begun to breed in numbers."

Craig,[20] who had previously made important observations tending to show that the proportion of malarial carriers among adults is nearly as high as that among children, has recently brought together in one table the observations as to latent malaria made by a variety of observers in different parts of the world (Koch, New Guinea; Thomas, Maños, North Brazil; Annett, Dutton and Elliott, Nigeria, Africa; Craig, Philippines; Ollwig, Dutch, East Africa; Panse, Tongo, East Africa; Sergent, Algeria; Plehn, Kameruns, W. Africa.

TABLE I (From Craig).

PREVALENCE OF LATENT INFECTION AT VARIOUS AGES. CONSOLIDATED TABLE.

Age.	No. Examined.	No. Infected.	Per cent. Infected.
1 to 5 years.....	1684	502	29.8
5 to 10 years.....	1645	463	28.1
10 to 15 years.....	1390	437	31.4
adults.....	4931	1139	23.
Totals.....	9650	2541	26.3

These figures appear to indicate that there is no great difference between the number of malarial carriers among children and adults.

[20] Craig: Important Factors in the Prophylaxis of the Malarial Fevers. Southern M. J., Nashville and Mobile, 1912, v, 50–57.

Craig estimates that about 50 per cent. of latent cases are gamete carriers. The existence of these latent infections, especially among individuals who have lived long in infected districts, is generally regarded as evidence of a certain acquired immunity. But the fact that parasites are to be discovered in the blood opens the question as to how far the immunity is to the parasite or to its toxic products. Some have assumed that the latter alone is the case, and true it is that the number of parasites found in these individuals is sometimes no less, apparently, than that associated in other instances with severe symptoms. On the other hand, the number is usually rather small, and the immunity may well consist, in part at least, in the power of the organism to destroy the parasites so as to keep them always at a minimum below that necessary to produce symptoms. Although all efforts artificially to produce immunity have failed, yet there would seem to be a certain acquired immunity in some individuals who have lived long in malarious regions.

TREATMENT AND PROPHYLACTIC METHODS

From this summary of our knowledge concerning the nature and manner of spread of malarial fever, it is quite clear that the prevention of the malady is possible, theoretically, by breaking the chain of existence of the infectious agent at any point in its cycle in mosquito or in man. Abundant proof of this proposition has been afforded by a series of practical experiments.

1. Various Italian [21] and English [22] observers have shown that thoroughly carried out mechanical protection against the bites of mosquitoes will permit individuals to remain for in-

[21] Crassi: op. cit.
Di Mattei. La profilassi della malaria colla protezione dell' uomo dalle Zanzare. Atti d. Soc. per gli stud. d. malaria. Roma, 1901, ii, 24–32.

[22] Sambon and Low: British Med. Jour., Lond., 1900, ii, 1679.

definite periods in regions where the infection is extremely prevalent.

2. Ross [23] and others in Ismaïlia, Port Said, and elsewhere have shown that by thorough drainage and removal of the breeding places of anophelines, together with measures such as oiling the surface of pools which cannot be drained, the development of the larvæ may be prevented and the mosquitoes thus entirely removed from certain localities. And this results, as might be expected, in the immediate disappearance of the disease.

3. Koch and his students [24] in New Guinea and elsewhere have further shown that by carefully seeking out the relapses before the outbreak of the malarial season and by thorough treatment of these, together with any new cases that may break out, the parasites may be so far destroyed in their human hosts that when the season characterized by the prevalence of anophelines comes on, the malarial epidemic remains absent.

With these practical demonstrations, why, then, is not the eradication of malaria an easy problem? Why have we not taken our malaria in hand as we have yellow fever? Why can we not, by isolating and thoroughly treating infected individuals, while protecting them from the bites of mosquitoes—why can we not by these methods easily eradicate the disease?

The reasons are obvious. The mildness of the manifestations in many cases, the frequency of latent infections, the length of time during which treatment and precautions must be continued, make it very difficult to carry out such measures ex-

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[23] Ross: The Prevention of Malaria. 8°, London (Murray), 1910, 496 et seq.

[24] Koch (R.): Berichte über die Thätigkeit der Malariaexpedition. Op. cit.

Frosch, P.: Die malaria bekämpfung in Brioni (Istrien). Ztschr. f. Hyg. u. Infectionskrankh., Leipz., 1903, xliii, 5–66.

Schilling: In Ross: The Prevention of Malaria, 8°, London (Murray), 1910, 496 et seq.

cepting in small communities and under practically military surveillance.

There have been ardent partisans of each individual method of prophylaxis, and many interesting experiments on larger or smaller scales have been carried out. From these experiences several conclusions may definitely be drawn:

1. The methods by which malaria may be attacked, may be divided into: (*a*) individual prophylaxis—that relating to the patient himself; (*b*) public prophylaxis—those general measures for the protection of the inhabitants which should be adopted by countries, states, counties, cities, and towns.

2. There is no one sovereign method of malarial prophylaxis. Different methods vary in their applicability according to the physical geography and climate of the locality, according to the denseness and nature of the population, and according to the form of government.

At the base of the prophylaxis of malaria, in a civilized country, stands the individual practitioner. If every practitioner of medicine should recognize and treat thoroughly every case of malaria that came to him, and should take precautions so that relapses might early be recognized and treated in their turn; if, in other words, each practitioner sterilized each individual patient, much of the work would be done.

What does thorough treatment mean? How are we to recognize the early relapses and the latent cases of malaria?

Much of the prevalence of malaria depends upon insufficient and incomplete treatment of the disease, and the very brilliancy of the specific action of quinine is indirectly the cause of much carelessness in treatment, based upon the lack of general knowledge as to the best method of giving the drug and as to its effect upon the parasites.

Different salts of quinine vary greatly in their solubility in water, with regard to which also the statements of different authors vary extraordinarily. The following table compiled from several works will give some idea as to these points:

TABLE SHOWING EQUIVALENTS OF QUININE, SOLUBILITY, AND RATE OF ELIMINATION OF DIFFERENT SALTS OF QUININE.

Salt.	Equivalent of quinine.	Solubility.	Appearance of Urine.
	Per cent.		*Minutes.*
Bihydrochlorate	72.0	1/1	15
Hydrochlorate	81.8	1/40	15
Hydrobromate	76.6	1/45	
Bihydrobromate	60.0	1/7	
Acetate	84.0		30
Citrate	67.0	1/820	30
Bisulphate	59.1	1/11	30
Sulphate	73.5	1/800	45
Tannate	20.0	slight	180
Euquinine	81.0	1/12,500	
Phosphate	76.2	1/420	
Valerianate	73.0	1/120°	
Lactate	78.2	1/110	
Salicylate	70.1	1/225	
Arseniate	69.4	very slight	

The rapidity and completeness of absorption of quinine vary greatly according (1) to the salt used; (2) to the form in which it is administered; (3) to the method in which it is introduced into the body. Most quinine (MacGilchrist)[25] is absorbed by the small intestine; a very small amount by the stomach, when the drug is introduced during fasting and in an easily soluble form; and a relatively smaller amount yet from the large intestine. The absorption is somewhat retarded when quinine is given with or after food, and also if the less soluble forms of the salt are used.

Rapid action is best obtained by administration of the soluble salts while fasting; gradual and prolonged action by the less soluble salts given during or after meals. Under the latter circumstances the quinine in the circulation may be maintained at a considerable level for as much as eight hours.

As a rule, from two-thirds to three-quarters of the quinine introduced into the organism is destroyed by the metabolic processes of the body, and, through them, is probably deprived

[25] MacGilchrist (A. C.): Quinine and its salts; their solubility and absorbability. Paludism, Simla, 1911, No. 2, 27–30.

of most if not all of its activity. It has generally been assumed that one may estimate fairly well the efficacity of our methods of giving quinine by the amount eliminated as such by the urine and fæces. Giemsa and Schaumann [26] appear to have shown that a given quantity of quinine administered daily in several fractional doses is eliminated more completely than a similar amount administered as a single dose (23.8 per cent.: 27.8 per cent.). MacGilchrist, however, asserts that larger doses administered three times a day give better results in treatment than fractional doses administered at two-hour intervals. The same observer, estimating the absorbability of quinine by the study of the minimal lethal dose in guinea pigs, arrives at essentially the same conclusions as Mariani [27] and Giemsa and Schaumann, who studied only the urinary elimination. According to MacGilchrist quinine is absorbed best: (1) subcutaneously, in solutions of a dilution not less than 1 to 150; (2) in soluble form by the mouth on an empty stomach; (3) by the mouth with or just after a meal; (4) subcutaneously in the ordinary dilutions 1: 2—1: 8.

The first method is, of course, impossible. Subcutaneously in the ordinary dose, the absorption of quinine is not very complete, for a large proportion of the salt is precipitated in combination with proteid substances. But, practically, this method of administration is often necessary to obtain immediate action in individuals with pernicious malaria, where the drug cannot be administered by the mouth.

Here one is obliged to resort to subcutaneous or better deep intramuscular injections of soluble salts, of which the dihydrochlorate is unquestionably the best, in doses no larger than 1 Gm. diluted in the proportion of 1 to 10.

The most rapid method of introduction of quinine is, un-

[26] Giemsa and Schaumann: Pharmakologische und chemische Studien über Chinin. Arch. f. Schiffs u. Tropenhyg., Leipz., 1907, xl, 1–83.

[27] Mariani: L'assorbimento e l'eliminazione della chinina e de' suoi sali, etc. Atti d. soc. per gli stud. d. malaria. Roma, 1904, v, 211. Sull' assorbimento e sull' eliminazione della chinina e dei suoi sali, etc., ibid., 1905, vi, 72.

doubtedly, the intravenous injection. I have seen cinchonism produced within a few moments after the injection, while yet standing by the bedside. But the intravenous injection of quinine in the ordinary doses and dilutions is not devoid of danger, and MacGilchrist insists that it should never be given in dilutions less than 1 to 150. This, however, is perfectly possible and easy to do in an emergency.

By the mouth, it is better to give the salts of quinine in solution rather than in capsules, and the salt most fitting for this method of administration is the dihydrochlorate, which is soluble in less than its own volume of water. The salt most commonly used in this country, the sulphate of quinine, may however easily be administered in solutions to which a little diluted hydrochlorate or sulphuric acid is added.

The objections raised by MacGilchrist to the administration of soluble salts in tablet or capsule form, that they may cause gastric disturbances, is, as a matter of fact, more theoretical than real, and except in urgent cases quinine may be given in this fashion with wholly satisfactory results.

From these considerations it is easy to see that the form and manner in which one gives quinine should vary according to the conditions existing in the patient. It has been a time-honored custom in intermittent fever to administer quinine in an intermittent manner. Torti advised large doses in the period immediately preceding the paroxysm. Sydenham gave large doses immediately after the paroxysm. Experience shows that to obtain the most rapid action it is well to have quinine in the system at the time of the paroxysm, namely, at that period when the fresh young brood of merozoïtes is present in the circulation. Practically, however, excepting in pernicious cases, experience to-day favors the administration of quinine in regular, daily, broken doses at frequent intervals. As Mariani and Giemsa and Schaumann have pointed out, a steady quantity of quinine may then be maintained in the circulation without the discomfort often following individual large doses.

Single doses of more than 1 Gm. (gr. xv) are never neces-

sary, and in all excepting pernicious cases, 2 Gm. (gr. xxx), in fractional doses of 0.32 Gm. (gr. v) every four hours, are quite sufficient.

The length of time under which treatment should be continued varies materially with the case. For ordinary tertian fever in temperate climates, the dose may soon be reduced to 1 Gm. a day, and, in the course of a few days, to one-half that amount. But in this quantity it should be continued for long periods of time, not less than three months. In this way alone may we hope to avoid a large percentage of relapses.

In æstivo-autumnal fever it is often necessary to continue treatment with as much as 2 Gm. (gr. xxx) a day for a week, and the diminution of doses thereafter will depend largely upon the appearance or non-appearance of crescents. Darling [28] appears to have shown that 2 Gm. a day will reduce the gametes of æstivo-autumnal parasites to a non-infective minimum* in two or three weeks.

To one who has not observed it, the difference in the efficacity of treatment in an individual on his feet and attending to his affairs, and in one who is kept at rest in bed is incredible.

It is *always* desirable that a patient with malarial fever should be kept in his bed until all symptoms of fever have gone. It is highly desirable that the patient with æstivo-autumnal fever should be kept in his room until gametocytes have been reduced to a non-infective minimum. The recent observations of Thompson [29] emphasize the importance of vigor-

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* Darling concludes from experimental studies, that patients with more than one crescent to every 500 leucocytes, or 12 to a cu. mm. of blood, are infective. If the crescents are scantier than this there is little chance of their developing in the mosquito.

[28] Darling: Transmission of Malarial Fever in the Canal Zone by Anopheles Mosquitoes. J. Am. M. Ass., Chicago, 1909, liii, 2051–2053.

[29] Thompson (D.): I. Research into the production, life, and death of crescents in malignant tertian malaria, in treated and untreated cases, by an enumerative method. Annals of Trop. Med. and Parasitol., Liverp., 1911, Series T. M., v, 57.

ous initial treatment of a patient with æstivo-autumnal gametocytes in his blood.

The patient with fever or with demonstrable malarial parasites in his blood should always be isolated and protected with a net. A regular daily search for mosquitoes should be made in the house, and every method for their extermination by traps and fumigation should be employed.

All evidence goes to show that it is only by treatment continued through long periods of time, that relapses can be prevented, and even then a certain percentage of cases, especially of tertian malaria, reawaken with the succeeding season.

How are we to recognize the early relapses and latent infections? Only by careful observation of the patient, by the study of the temperature, by frequent examination of the blood, and by determining the presence or absence of splenic enlargement. This latter method has been much employed, following the investigations of Koch, and it is of very considerable value in the carrying out of large public measures of prophylaxis. It is, however, obviously a much more uncertain procedure than that of careful examination of the blood.

A very remarkable observation has recently been made by David Thompson,[30] which, if confirmed, may be of real assistance in the recognition of latent cases. Ordinarily in acute malaria there is a leucopenia, but in latent malaria, where the number of parasites sporulating is small, there is a leucocytosis which increases, at the time of sporulation, to a very remarkable degree. Thompson has found often from 30,000 to 50,000 leucocytes, and once even 125,000, a leucocytosis which rapidly falls after the period of sporulation. In acute malaria the relative proportion of mononuclear leucocytes is low at the time of the paroxysm, becoming high with the fall of temperature and apyrexia; this same fluctuation persists without regard to the total number of leucocytes for months, even years, after apparent cure.

[30] Thompson (D.): II. The leucocytes in malarial fever. A method of diagnosing malaria long after it is apparently cured. Ann. Trop. Med. and Parasitol., Liverp., 1911, Series T. M., v, 83.

As has been said before, the corner-stone of the edifice of malarial prophylaxis is the work of the individual practitioner in protecting his patients and in detecting and properly disinfecting the affected individual. But while nearly every case of typhoid fever, yellow fever, or cholera falls into the hands of a physician, and while in most of these diseases the danger is over with the disappearance of the acute symptoms of the malady, in malaria the condition is radically different. Immense numbers of patients in rural districts never consult a physician, and many more, imperfectly treated, are carriers of the disease through long periods of time.

The question, therefore, is not purely one of thorough treatment; in every malarious district the healthy must be protected from the dangers of infection, which are always more or less present. The duties of the individual practitioner toward the patient and the general public are therefore greatly complicated.

Let us consider, first, the question of the measures of *individual prophylaxis* which one should adopt when in a malarious region.

A. The first principle is the avoidance, so far as possible, of infected houses or infected individuals. The hunter or traveller in the wilds should, when possible, avoid sleeping in recently inhabited houses. A tent so far removed as possible from the infected population is the safest place.

B. The house and the bed should be thoroughly netted, the house, if possible, with wire netting. The bed net should be strong and should never be allowed to fall to the floor, but should always be tucked under the mattress. Loose folds shut out the air. The meshes should not be too large. Eighteen threads to the inch (seven to the cubic millimetre) are sufficient. There should be no slit for entering. The substance should be white, so that the insects may readily be detected. Holes are fatal.

C. The thoroughly netted house should be searched daily for mosquitoes. This should be the regular duty of some member of the household. These may be killed by hand and may be caught from ceilings or walls by a small butterfly net on a

pole. In some instances fumigation may be desirable. This may be carried out as follows:[31]

"To fumigate a room thoroughly for mosquitoes all the chinks in the doors and windows should be closed by pasting paper over them. Then burn the culicide as follows (Sir Rubert Boyce):

"1. *Sulphur.* Allow 2 lbs. of sulphur to 1,000 cubic feet. Use two pots, place them in a pan containing 1 inch of water to prevent damage, and set fire to the sulphur by means of spirit.

"*Duration,* Three hours.

"2. *Pyrethrum.* Allow 3 lbs. to 1,000 cubic feet, and divide amongst two or three pots, using the same precautions as with sulphur.

"*Duration,* Three hours.

"3. *Camphor and Carbolic Acid.* Equal parts camphor and crystallised carbolic acid are fused together into a liquid by gentle heat. Vaporise 4 ozs. of mixture to each 1,000 cubic feet; this can be done by placing the liquid in a wide shallow pan over a spirit or petroleum lamp; white fumes are given off. To avoid the mixture burning, the fumes should not come in close contact with the flame of the lamp.

"*Duration,* Two hours.

"Few of these methods actually kill the insect. After fumigation, floors should be thoroughly swept and all stupefied insects burned."

D. One should look out for all stagnant water on ground and plants, in any receptacle in the neighborhood of the house, "in cisterns, drains, gutters, tubs, jugs, flower-pots, gourds, broken bottles and crockery, old tins, or other rubbish, or holes in trees or in certain plants, such as the wild pineapple." As Ross suggests, an inspection of the premises once a week is an admirable plan. Cisterns should be screened so that mosquitoes cannot lay eggs on the surface.

E. For those obliged to work in the neighborhood of in-

[31] Ross: op. cit., 59.

fected localities at dusk and by night, personal protection by means of nets hanging from the hat and bound about the neck, thick gloves, etc., have been shown to be of great value, especially by the Italians, in the case of employees on the State railways, and by the Japanese army in Formosa.

These methods, however, are most uncomfortable and trying, and very difficult to enforce. Ross points out the considerable value of the ordinary hand fan consistently agitated by an intelligent individual.

F. Protection by medicinal substances applied to the skin, such as oil of lavender, oil of citronelle, oil of eucalyptus, familiar to all fishermen in this country, is of considerable value where one cannot carry out other precautions. He, however, who has used these substances by night, knows well their inconveniences. They soil the bed, and usually give out to such an extent as to need at least one re-application before morning.

G. Finally, the method of quinine prophylaxis is of really great importance. There is abundant proof that the regular ingestion of small quantities of quinine is an excellent protection against infection. Koch,[32] as a result of his East Indian and African experiences, advised 1 Gm. (gr. xv) every seventh and eighth day. Such intermittent treatment is, however, easy to forget, and large doses often cause unpleasant symptoms. Mariani [33] has shown that small divided daily doses accomplish as much and are easier to take. From 0.4 to 0.6 Gm. (gr. vi to gr. x) daily in divided doses is usually advised, and in most cases this prevents infection, particularly if associated with other measures of protection.

If such methods as these be carried out by the individual and in the household, there is little fear, even in the worst regions, of other than occasional mild and easily treated infections.

It is especially interesting to note that regularly carried out quinine prophylaxis is as valuable in combating malarial

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[32] Koch: Berichte über die Thätigkeit d. Malariaexpedition. Op. cit.
[33] Mariani: op. cit.

hæmoglobinuria as it is in the case of any other manifestation of the disease (Reynaud).[34]

But the important point in connection with prophylaxis of malaria is the question of public measures of protection. Here, as has already been said, we in America have so far made a poor showing in comparison to what has been done in other countries and in our own colonial possessions. Let us for a moment consider some of that which may be done and has been done elsewhere.

The measures of *public prophylaxis* which should be adopted in a malarious district are many, but unquestionably the most fundamental are those directed toward the extermination of mosquitoes. These measures consist:

1. In the removal, so far as possible, of all breeding places, namely, collections of stagnant water.

2. In the treatment of those collections of water which cannot be removed in such manner that they are no longer suitable for the complete development of the larvæ and pupæ of the mosquito.

3. In the removal of all underbrush, grass, etc., which might serve as resting or hiding places for the insects, from considerable areas surrounding all human habitations.

In some localities these procedures alone may suffice to eradicate the disease.

ISMAÏLIA

One of the most brilliant examples of the eradication of malaria as a result of mosquito destruction is the achievement of Ross[35] at Ismaïlia.

The mosquitoes here all came from a canal which conducts the water of the Nile to the town, and from the standing water associated with it. The country surrounding the town is a desert. The climate is rainless. The canal company is all-powerful in the government of the town. The flow of water in

[34] Reynaud (G.): La quinine préventive contre le paludisme et la fièvre bilieuse hémoglobinurique. Marseille méd., 1911, xlviii, 49; 81; 126; 151; 177.

[35] Ross: The Prevention of Malaria. 8° Lond. (Murray), 1910, 499.

the canal was regulated; leaks were stopped. The marsh was drained. Irrigation canals and channels were cleared of weeds and the water made to run swiftly. "When a certain garden had received its proper supply of water, the flow was stopped and the water allowed to soak in." All receptacles for standing water were emptied. A regular mosquito brigade visited each house once a week and treated the cesspools with petroleum. In September, 1902, this work was begun. By 1906 the disease was eradicated, as may be appreciated by reference to the following table:[36]

MALARIA AT ISMAILIA.

Years	Cases.
1899	1,545
1900	2,284
1901	1,990
1902	1,551—antimosquito war begun.
1903	214
1904	90
1905	37
1906	No fresh cases.
1907	No fresh cases.
1908	No malaria contracted in Ismailia.

HAVANA

With the American occupation of Havana in 1909, a general cleaning up of the city was undertaken under military direction, and in February, 1901, Gorgas began his famous campaign against yellow fever, a campaign the essential feature of which was extensive mosquito destruction. This work has been continued since then by the Cuban authorities. As is well known, yellow fever disappeared from Havana seven months after the initiation of this work.

The striking effect of these measures on the malarial mortality of Havana may be seen by reference to the following table:

[36] Ross: op. cit., 503.

Deaths From Malaria at Havana.

1890	170
1891	203
1892	202
1893	240
1894	201
1895	207
1896	250
1897	811
1898	910
1899	909
1900	325
1901	151
1902	87
1903	51
1904	44
1905	32
1906	26
1907	23
1908	119
1909	6
1910	15

This is unquestionably the ideal method of prophylaxis, and it may often be carried out successfully, especially in cities and centres of population. But in large areas of swampy, uncultivated, sparsely populated land such as exist in some of our Southern States, these measures are difficult in their application and do not suffice. Here we must combine and concentrate all known methods of prophylaxis.

PANAMA

The great example of what may be done under such conditions is afforded by the work of Gorgas at Panama. Here conditions were as difficult as may well be imagined. The whole district was terribly infected, not only with yellow fever but with the gravest forms of malaria. The death rate had baffled even those enterprising Frenchmen through whose foresight and energy the waters of Europe had been married to those of the Indies. The population to be dealt with was a large body of workmen living in the country within half a mile of the railroad, in small villages and camps and sometimes in isolated dwellings. Fresh from his work in Havana, Gorgas was given sanitary control of the Canal Zone in 1904. The results of his campaign are remarkable. The last case of yellow fever occurred in 1906. The death rate has steadily fallen

until it compares most favorably with that of the cleanest of civilized nations, as may be seen by reference to the following table:

Death Rate per 1000 Inhabitants in Panama Canal Zone.

1905	49.94
1906	48.37
1907	33.63
1908	24.83
1909	18.19
1910	21.18
1911	21.46

The deaths from malaria have fallen from 16.21 per thousand in July, 1906, to 2.58 per thousand in December, 1909.

Among employees the deaths have fallen from 11.59 per thousand in November, 1906, to 0.99 per thousand in November, 1911.

The admission rate per thousand among employees to the hospitals for malaria has fallen also in a most encouraging manner.

Admission Rate to Hospitals for Malaria.
(Per Thousand) Canal Zone.

1904	125
1905	514
1906	821
1907	424
1908	282
1909	215
1910	187
1911	184

The cost of this sanitary work in the canal for a population amounting to something over 100,000 inhabitants is $3.50 a head, of which about $2.00 is spent on anti-malarial work.

And this work is but a beginning. A sure and steady improvement must follow its continuance. A certain relapse to the old conditions will follow its abandonment.

A word as to the nature of this work perhaps is worth while. The 47 miles of the Panama strip are divided into 18 districts, each under the control of an inspector, under whom are employed 50 men.

Drainage.—All pools within 100 yards of individual dwellings or within 200 yards of villages are done away with either by subsoil or open (concrete if possible) ditches.

Brush and Grass Cutting.—Within the same areas all tropical undergrowth is cut. Brush and grass shelter adult mosquitoes, while anophelines will not as a rule cross a clear area of 100 yards.

Oiling is used where drainage is impracticable. Where oil will not spread, a poison which is called "larvicide" is used. This consists of crude carbolic acid, resin, and caustic soda.

Quinine in prophylactic doses is offered to all employees.

Screening is carefully carried out on all government buildings.

Killing Mosquitoes.—Each morning all mosquitoes found in buildings are killed by special men.

ITALY

Conditions not dissimilar to those in the United States exist in Italy, where the problem has been approached in a somewhat different manner. Here, as everywhere, the main mortality occurs among the peasants, especially on rice plantations and in the fields, in the army, and among the employees of the railways, who are obliged to live in infected and unhealthy localities. In 1890, a Society for the Study of Malaria was founded, supported by contributions of generous citizens headed by the Queen.

Inspired by the activities of this society presided over by one whose name has long and honorably been identified with the study of this disease,* a most important and active campaign has been conducted.

While endeavoring in every way to educate the public and to encourage all measures directed toward the destruction of mosquitoes, their larvæ, and the breeding places, the society at the outset directed its attention especially to personal and household protection from the bites of mosquitoes, and later toward quinine prophylaxis.

The experimental demonstration of the value of the netting

* Prof. Angelo Celli. The work done by this society is presented annually in the admirable Atti della Soc. per gli studi della Malaria, and is summed up at the end of each volume by Prof. Celli.

of dwellings and the personal protection against the bites of mosquitoes, carried out by this society, has already been mentioned. Its impracticability, however, on a large scale in rural communities, was early recognized, and the great value of quinine prophylaxis under such circumstances has been admirably brought out by the Italian campaign.

By means of lectures and demonstrations and publications widely distributed, and with the help of many district physicians and school masters, and through the formation of local anti-malarial committees, a campaign of education has been steadily conducted for over ten years.

In 1902, at the instigation of the society, the State began the manufacture of quinine, which is placed on sale at every tobacco store in Italy. The price is nominal. The preparations are pure and easy to take, and are supplied gratuitously to the needy, partly through the funds of the society and partly as a result of laws recently passed by the government, through which the profits from the manufacture of the drug, already considerable, are employed in furthering the anti-malarial campaign. The results as set forth by the following table are most striking:

ITALY:* STATE QUININE AND MORTALITY FROM MALARIA.

Consumption of State Quinine		Mortality from Malaria.		Net profits of Adminstration of State Quinine in Lire.
Financial Year	Kilograms Sold	Solar Year	Total Death	
.....	.....	1895	16,464	.....
.....	.....	1896	14,017	.....
.....	.....	1897	11,947	.....
.....	.....	1898	11,378	.....
.....	.....	1899	10,811	.....
.....	.....	1900	15,865	.....
.....	.....	1901	13,861	.....
1902–3	2,242	1902	9,908	34,270
1903–4	7,234	1903	8,513	183,039
1904–5	14,071	1904	8,501	183,382
1905–6	18,712	1905	7,838	293,395
1906–7	20,723	1906	4,871	462,290
1907–8	24,351	1907	4,160	700,062
1908–9	23,635	1908	3,463	769,809
1909–10	21,656	1909	3,535	720,000

*Compiled from Atti della Soc. per gli stud. della Malaria.

An especially valuable part of the work of the Italian Society for the Study of Malaria has been the preparation of chocolate confections of tannate of quinine. The tannate, a salt but slightly soluble and rather slow of absorption, is nevertheless absorbed in the end nearly, if not quite, as completely as the more soluble preparations. The *cioccolatini,* agreeable to the taste and practically free from the bitterness of quinine, are peculiarly valuable in connection with large general measures of prophylaxis, as they are well taken by children. The objection that the constitution of the preparation is subject to some variations in its quinine content has little importance in the light of the Italian experiences.

The work in Italy to-day has opened up to agriculture regions which had previously been practically abandoned, and is saving, as may be seen from the chart, thousands of lives every year.

GREECE [37]

In Greece, in 1903, a similar league was formed which is doing good work. The studies on the Plain of Marathon emphasize the value of small, daily, prophylactic doses of quinine in association with other measures, while other studies in the same region have furnished an excellent demonstration of what may be accomplished by careful diagnosis and thorough treatment alone.

INDIA [38]

The British Government in India has recently started a campaign of a similar sort, the results of which must soon be apparent. A conference was held in October, 1909, at Simla, at which there was founded a committee for the study of

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[37] Savas (C.): Le paludisme en Grèce, etc. Atti d. Soc. per gli stud. della Malaria. Roma, 1907, viii, 136–170. Also, similar communications in the same publication: 1908, ix, 95–105; 1909, x, 291–298; 1910, xi, 129–136.

[38] Paludism, being the Transactions of the Committee for the Study of Malaria in India. Simla, No. I, July, 1910.

malaria in India. The organization of the campaign in abstract was as follows:[39]

1. A committee in each province of three or more members, personally interested in the malaria problem, enjoying the confidence of the local government and prepared to obtain and supervise local inquiries. They should perhaps control the agency for the distribution of quinine. One of their first duties would be (in association with provincial sanitary department) to ascertain the real causes of death in different localities, and to set in motion an inquiry in each district regarding the relation of the fever season to the drainage and rainfall.

2. Every autumn each provincial community would delegate, under the orders of the local government, one of their members to attend a meeting of a general committee in Simla. This general committee would consist of the provincial delegates, the sanitary commissioner representing the Governor of India, with Major James as Secretary. The Government of India would appoint a general scientific committee. . . . . .

A class of instruction was held in March, 1910, presided over by one of the members of this general committee, which was attended by various medical officers and subordinates from each province. This work has been most valuable. At the first meeting, a series of special subjects to be inquired into was settled upon and the reports which are appearing in a publication entitled "Paludism," edited by the scientific committee, already contain much valuable material.

There can be little doubt that this movement will bring great results in India.

In many other regions, especially in Algiers and in British and German Colonial possessions, enlightened campaigns against malaria have been conducted with excellent results.

AMERICAN CONDITIONS

When, however, we turn to our own country, we find, alas, that but little has been done. Local anti-mosquito campaigns undertaken here and there, of which those in the neighborhood

[39] Abstracted from Paludism, op. cit.

of this city have been notable, have had good results. Local attempts at educational movements, of which that conducted by Dr. Lankford [40] in San Antonio, Texas, is a striking example, have been of great interest and are most creditable.

In Pennsylvania [41] and Florida [42] special bulletins have been issued by the State societies and, in the latter State, a most creditable beginning has been made toward a thorough State campaign. Nowhere, however, have systematic anti-malarial measures been taken on any large scale.

The first problem which confronts us when we consider the steps which should be taken is as to the determination of the prevalence and distribution of the disease. Here, immediately, we meet with a difficulty. We know that malaria exists in certain parts of New England and New York; that it increases in prevalence along the coast, southward; that it prevails with particular virulence in the Mississippi Valley and in the valleys of its tributaries; that it occurs to a certain extent on the Pacific Coast and about the great lakes. The conditions associated with registration of morbidity and mortality are, however, so imperfect that it is a difficult matter to form an adequate idea as to the malarial mortality, not to speak of the morbidity.

In the interesting study by the Florida State Board of Health, it is estimated that the rural malarial death rate for the South for 1908 was approximately 54.52 per 100,000 inhabitants, or 11,326 deaths. The registration of the deaths in this area is so imperfect that this is but an estimate. But if this estimate even approaches the truth, it is probably safe to say that the actual mortality in this country is as high as 10,000 a year, and probably considerably greater. And beside these fatal cases, there is an enormous number of individ-

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[40] Lankford (J. S.): Public School Children and Preventive Medicine. N. York M. J. (etc.), 1904, lxxx, 1124–1126.

[41] Malaria: How it is Caused and How to Get Rid of It. Pa. Health Bull., Harrisburg, March, 1911, No. 21.

[42] Malaria: Its Prevention and Control. State Board of Health of Florida. Publication 84, Jacksonville, June, 1911, pp. 1–43.

uals, hundreds of thousands certainly, whose lives are made miserable and whose physical and moral development are retarded and perverted by a preventable and easily treated disease; and we, as a people, with just pride in what we have done in Havana and Panama, sit complacently and allow this to go on.

A few years ago, it was discovered that much of what had been called malaria in the South was in reality due to infection with the hookworm—*Necator Americanus*—and straightway, through the philanthropy of Mr. Rockefeller, a commission was established, which, working in unison with State boards of health through the South, is doing a great work in the eradication of this plague.

But the old plague, that which calls for a greater toll of human lives every year, a malady easily prevented and easily treated, still holds its sway practically unattacked. It is the old story that "familiarity breeds contempt."

That no more general measures are taken in this country for the study and control of malaria is a national disgrace.

The problem is one which demands national consideration. Although the actual prophylactic measures must, under our form of government, be undertaken by State and local authorities, the first step should be a wide-spread and general study of conditions as they exist in the various localities.

Harris of Mobile and recently Craig [43] of the Army have suggested the formation of a national commission for the study of the disease. The creation of such a commission would be an admirable plan.

Just such measures as this would be rendered possible by the establishment of that National Bureau of Health so urgently necessary and so long struggled for by all who have the health and welfare of the community truly at heart. Such a commission working in harmony with the health authorities of the

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[43] Craig (C. F.): Important Factors in the Prophylaxis of the Malarial Fevers. Southern M. J., Nashville and Mobile, 1912, 50–57.

various States could rapidly accomplish results of inestimable value.

For the accomplishment of much that is to be desired in the attempt to control malaria in this country, the initiation of a popular campaign, a campaign of education, is absolutely necessary.

This might be accomplished through the establishment of a National Society for the Study and Prevention of Malaria, a society analogous to that existing in Italy. Such a society might be formed as an adjunct to a national or endowed commission. It would, in the beginning, have to depend upon individual subscriptions as in the case of the Italian organization, and these would have to amount to an appreciable sum, if it were hoped to enter immediately upon valuable work. But if a foundation could be established, such as that which exists for the study of the hookworm problem, it would be safe to prophesy that within a few years the results in the saving of human lives would be very appreciable. Such an organization should have its central office somewhere in the midst of a malarious country, *i.e.,* in the South. An excellent place would be in New Orleans, a great centre in the immediate neighborhood and within easy access of gravely malarious districts. Moreover, New Orleans is already the seat of a school of tropical medicine. The campaign should be deliberately planned under the direction of a carefully chosen and well qualified and salaried director. The first point for study would be the distribution of malaria in one State after another. This work should be undertaken in connection with the local health authorities, as is being done by the hookworm commission. Through the foundation of a central Society for the Study and Prevention of Malaria, with branch organizations in each State analogous to the anti-tuberculous leagues or to the excellent organization in India, a vigorous campaign of education should be conducted.

It is especially important to instruct, to interest, and to enlist the support of school teachers and later to arrange for systematic instruction of the children. In this connection one

cannot do better than quote the words of Craig:[44] "The teachings of the essentials of malarial prophylaxis in public schools, in regions in which these fevers are endemic, is a most useful method of public education. The young are receptive and there is no better way of interesting the parent than by instruction of the children. Not only is this true, but what one learns in youth becomes a matter of habit and will be practiced throughout life. The adage that 'You cannot teach an old dog new tricks,' is often exemplified when attempts are made to instruct the adult population in modern views of the ætiology and prophylaxis of disease, and for this reason it is most important that the young be thoroughly taught regarding the prophylaxis of malaria."

Above all, it should not be forgotten that an educational campaign of this nature has a far wider effect than the influence upon the specific malady against which it is directed. It should and would lead to the more general instruction in public schools as to matters of general and personal hygiene, and such instruction, if given in the proper manner, not by dry lectures and recitations but by practical demonstration, cannot fail to go far toward making this country a better and safer place in which to live.

By such a campaign the interests of the community would soon be awakened, and active public support would be gained for measures insuring proper registration of the malarial mortality and morbidity, as well as for active prophylactic procedures.

But it is not only in spreading the propaganda that children may be of use in an active anti-malarial campaign. They may at times be employed in putting into effect some of the fundamental measures of malarial prophylaxis. School children, in the course of their instruction, may be of real assistance in detecting the breeding places of anophelines—as is testified to by the interesting results obtained in San Antonio under the leadership of Lankford.[45]

[44] Craig: op. cit.
[45] Lankford: op. cit.

There is another interesting manner in which a good deal might be accomplished. The organization of Boy Scouts is spreading rapidly through the country. But no part of the instruction of the soldier is more important than that which relates to the hygiene of the encampment. The employment of boy scouts in the course of their instruction in the detection of the breeding places of anophelines, as has already been attempted in Pensacola,[46] perhaps, indeed, in the actual treatment of these localities, might well be of great assistance in local anti-malarial campaigns.

Exactly how the work of such a society alone, or better as an adjunct to a central commission, might best be accomplished could be determined only as the investigation continued. In some regions, the main prophylactic effort would probably be directed toward drainage and mosquito destruction; in others, toward measures of personal protection and quinine prophylaxis. It is, however, quite certain that the first and principal work would be one of investigation and education. So soon as our legislators—and that means the people—understand the true conditions, just so soon may they be counted upon to lend a hand and assist in the good work. It is the belief of the speaker that the establishment of a scientific commission, appointed by the Government or established through private endowment, for the study and prevention of malaria, supported by an active popular campaign conducted by national or State anti-malarial leagues, would bear results of no less brilliancy than those which have been accomplished in other parts of the world. And this means the annual saving of thousands of human lives and the restoration to health of hundreds of thousands of suffering human beings, with all the influence that this has on the physical and moral character of the race and on the efficiency and prosperity of the community.

I have said before, and I wish to repeat it now, that no more measures are taken in this community for the study and

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[46] Malaria: Its Prevention and Control. State Board of Health of Florida, Publication 84, June, 1911, 30.

control of malaria is a national disgrace. Such a condition could not long exist with an efficient National Bureau of Health, through which the initiative in the necessary statistical investigations and suggestions as to the proper prophylactic steps should come. That no such body should exist in our country to-day is a sad reflection on the general intelligence and education of the public. But if we are not as a community sufficiently intelligent to realize that the health of our fellows approaches in importance that of the sheep and the hog so dear to our representatives in Congress—that is to us—it is well at least for us as physicians to recognize the fact and to do what we can to show the way.

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