SCIENCE

FRIDAY, AUGUST 6, 1920

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MSS. intended for publication and books, etc., intended for review should be sent to The Editor of Science, Garrison-on-Hudson, N. Y.

MEDICAL RESEARCH[1]

I HAVE said that I would not plunge with you this evening into the ocean of science; but if you are a little tired of hearing of the dependence of medicine upon science you may find refreshment or diversion in contemplating the debts of science to medicine. My old medical friend Mr. Meade, of Bradford, was almost the only man who knew much about flies at the time when Manson and Ross began to watch these little pests. Without medicine, bacteriology and the study of the cell would have made slow way; yet it is the study of the cells of bacteria, of algæ, of protozoa—not of mandarins—which has brought us nearer to the secret of life. On the wonderful world of the cell I have spoken before. Professor Hopkins has lately described to us the almost incredible coexistence in it of different constitutions, phases, and events; though every change in any phase affects the equilibrium of the whole cell system. And every one of these is essential to the whole; "so long, for example, as a liver cell remains alive its glycogen constituent can not be wholly removed." If a cell be so ground up as to become more homogeneous, its reactions fall out at haphazard, and the cell dies by mutual destruction of its parts. This process of nature is illustrated on a mighty scale to-day in the disintegration of the Russian social organism.

Some of the apparently simple cell constituents, hæmoglobin for instance, are incredibly complex; this substance is specific for every kind of animal; in allied species, if concordant, it is not identical. Of the chromosomes I need say nothing; except to hope that as X rays have analyzed crystalline structure some such rays may analyze nuclear constitutions.

By another way, medicine has promoted research on organic syntheses; and conversely on

[1] From the address of the president of the British Medical Association at the Cambridge meeting.

the reduction of foods into the more complex amino-acids before being rewoven into the tissues of life. From medicine began our recognition of the plowman as the first parent of animals and man, and our fuller knowledge of "the green plant as the fundamental capitalist."

> Herbs gladly cure our flesh, because that they
> Finde their acquaintance there.

In the dark soil the nitrifying bacteria live on inorganic matter; so in the light some inorganic colloidal systems can build up formaldehyde (B. Moore). Medicine has introduced the chemist to the domain of the hormones and chalones, themselves also bodies of the simpler chemical constitution—some crystallizable, all able to resist prolonged boiling—blended into a wonderful physico-chemical coordinating system, secretly at work all the time under the diagrams of the innocent neurologist. We may suppose indeed that every active tissue of the body, or every cell, even of bone and skin, or of the substrate of mind itself, like every individual of a social organism, contributes some element to the organic whole, some inward production necessary for growths, or for signals.[2] There may be a world of pathological (alien or perverted) hormones as yet unexplored. May the dive inwards of epithelial cells in cancer be due to some inversion of chemotaxis, possibly under the influence of an alien (parasitic?) enzyme? Within the body then all parts are the "environment" of each—so that we have both an inner and an outer "climate," an aspect of the microcosm not to be forgotten in the field of mental disease. Thus it is that "Each part may call the farthest, brother." And these agents have a field of action far beyond the body, as we see for example in the sexual hormones. If there be a "migration hormone" its sphere is the world.

Again, is it not largely by medicine that the study of enzymes has thrown light upon the operations of catalysis which, like the rollers under a log or, as we now think, more by engagement and disengagement like rack and pinion, is incessantly forwarding, by various intermediate series, and by reversible actions at points of concentrative equilibrium, the processes of nature? The vitamines may be of this kind, agents which have upset our cruder calculations of nutritive values; for instance, in the feeding of children, we no longer take cane sugar to be the vital equivalent of lactose, nor margarine of butter; not all the nitrogen of nutrition is included in protein, nor are phospho- and amino-lipins, nucleic acid, amino-acids, and so on, mutually convertible in the body. We must admit that the fundamental principles of nutrition have yet to be redetermined. Moreover the war has forced us to remember the mutual dependence of food kinds; that of course fats and carbohydrates are not wholly independent or equivalent; the carbohydrates can not make up any great lack of fats, nor can oxidation of fats proceed in the absence of carbohydrates.

Another system of balances in the body, as of the reciprocal functions of lung and kidney, is more obviously chemical. Medicine has taught us how the lung deals with the CO_2 ions, the kidneys with sundry other acids, so that the blood reaction is maintained with extreme nicety; and that other systems—for example, the vasomotor—are probably little less sensitive, and that there are other subtle causes of anoxaemia besides the cardio-pulmonary (Haldane); so that in medicine it is of the first importance that in all abnormal conditions the oxygen tension of bloods should be systematically ascertained and compared. The hydrogen ion concentration is consistently higher upon flesh diet, lower upon vegetable diet; but I think we have not yet learned to discriminate so subtly as Charles Kean who is said to have chosen his viands according to the parts he had to play—pork for tyrants, beef for murderers, mutton for lovers.

Next after the origin of life itself, from ancient times to this day no enigma has attracted and baffled the curious mind of man more than that of living "form." Many of our keenest minds—Haldane, D'Arcy Thompson, Osborn, Dendy, McBride, I mention a few

[2] Mathews, "Physiological Chemistry," second edition, p. 835.

names as they occur to me—are still chasing this will-o'-the-wisp; and moth-like I can not but flutter after them. Of the nitrifying bacteria which assimilate inorganic matter, of the synthetic amines of animal nutrition, of the properties of colloids, I have spoken already to-day and last year; but "how," says Dr. Haldane, "is constant form maintained amid the continuous changes of our changing matter?" and—I may add—of variations of parts. Is "form" something after the manner of seal, which is impressed upon matter? or is it, in Aristotle's sense, a kind of soul (entelechy) which shapes the potential, or capacity, into integral being? Here we hover between metaphysical or ontological concepts and natural law, or the properties of matter. A few years ago all notion of self-shaping was dismissed, and the animal regarded merely as a diagram of incident forces; to-day there is some harkback, if not to moulding entities, at any rate to some phases which partake both of germ and matrix. We had been taught that for development functional stimuli were all that was necessary; for instance, that the heart grew, even beyond the normal, only in response to demand for its work and by increased supply of blood to its tissues. But is there any functional adaptation from within? If a limb be not used the bone will still grow more or less; but why does the bone grow *round?* And an eye will grow, from a germ of it, in the dark (Loeb). Is there such a property in living matter as "functional adaptation"? Is function in its effect upon form adaptive or purposive? Is environment met by adaptive variation—for instance in a germ cell? Again, if so, can specific properties of such a kind be acquired? Biologists seem to have proved that evolution of form may go on continuously when environmental change is suspended, or remains constant; and conversely that environmental change does not necessarily induce evolution. On a broad view, says Professor Osborn,[3] during the infinite variety of the widely diverging forms of the Mammalian period of the earth, the reptiles have shown very little change. We perceive that these questions arise in some contrast with the hypothesis of the selection of "chance" variations.

On the other hand, we find reason to marvel at the constancy of bacterial species; humble and embryonic beings that we should not expect to have become fixed in their habits. Yet they and their enzymes are very exacting about it; as we find, for example, with the several enteric bacteria, or with the meningococcic or pneumococcic varieties, of which each has its own serous or agglutinin test, and is indifferent to the rest. And there is more still to be said: when the microbe finds itself in the host's body it may be wholly out of tune, or wholly in tune, with any or all cells that it approaches; in either case presumably nothing morbid would happen, perhaps, by a kind of zygosis, a benefit; morbid happenings would lie between this microbe and body cells within its range but not in tune with it. Now there seems to be reason to suppose that a microbe, on its approach to a body cell only just out of its range, may try this way and that to get a hitch on. If so, the microbe, at first innocuous, would become noxious. So on the other hand body cells may educate themselves to vibrate in harmony with a microbe before dissonant; or there may be mutual interchange and co-adaptation. Such considerations arise out of many known phenomena at phase boundaries, of sympathetic vibrations, of acquired immunity, of new virulences, and so forth; the cells out of tune getting nearer and nearer into consonance with each other.

But, if things be so, surely we are face to face with a marvelous and far-reaching faculty, *the faculty of choice,* and this rising from the utter bottom of biology to the summit—formative faculty—"auto-determination," or, if you please, "mind." Can the microbe do as the retriever does when with a hare in his mouth he comes to a gate; he tries this way and that, then thrusts the hare under the gate, leaps over and pulls the hare through? So the microbe tries it on, this way or that, till it succeeds, by self-education in the school of experience—*Bildungstrieb.* This is far more —radically more—than *"élan vital";* not

[3] Osborn, "Origin and Evolution of Life," p. 137.

merely energy but *choice*—plasticity driven to choose or fail; thus new devices are tried and new habits established. So likewise Dr. Topley has dwelt upon a microbe acquiring a capacity to bring about certain fermentations,[4] an ability, as he says, "to be regarded as something inherent in the organism itself." We may be reminded also of Professor Stanley Gardiner's "education" of his oysters—a very curious observation.

So far as I can think upon it there seems to be but one alternative hypothesis, but this does not cover so many phenomena. As I have said, if the vibrations of an alien cell are out of range of a certain body cell so as just to be indifferent but yet not far out of range, the vibrations of the one might induce like vibrations in the other, and meanwhile interference waves would arise in the field; thus disturbances—symptoms—would begin and continue until the two sets of waves should blend into unison; and this would mean acquired immunity. If a number of wag-at-the-wall clocks are hung near each other, in a calculable time they will get to swing in unison. But this hypothesis does not lead on, as does the trial and error hypothesis, to larger and larger gains. We see only a discord and a mode of requiescence; no line of development. What we apprehend is something more than orderliness of chemical reaction; that *cells are teachable;* a key to illimitable progress. Was not Coleridge right when he said

> For I had found
> That outward forms, the loftiest, still receive
> Their final influence from the Life within.

I am not for one moment forgetting that the physical modes of energy—adsorption, surface tension, and so forth—may count for much in these advances, arrests, immunities, and disintegrations. Adsorption, or other physical condition, may put up a block. How remarkable are the effects of anesthesia and palsy which may follow injections of sodium oxalate and magnesium sulphate, and of their quick removal by calcium salts; indeed the whole influence of calcium on metabolism—probably all of them surface (interface) actions, as of any radio-active element upon cell function.[5] Indeed, as in the relation of foodstuffs to amines, so in the physics of the cell we may discover a comparative accessibility and intelligibility of the processes of life—Poincaré's "*simplicité caché.*" It seems that God has more "respect to the measure and ease of the human understanding" than Boyle supposed.

Thus we are led to the thaumaturgic word "Research" which, for some of us, means remote and rather unreal speculations; for others the discovery of short cuts to making more money; for others again the ideal of pure knowledge. Research may be regarded as of two kinds, as natural observation and as artificial experiment; the one yielding more and more to the other as investigation penetrates from the more superficial to the deeper processes. Still, if we are to surprise and "capture wild nature in her secret paths," the two ways are strictly inseparable. Indeed the infinitely little does man more harm than the enormously great. War may bring with it some redemptive virtues; pestilence only raw superstitions. The advance of the last half century from the deadhouse pathology to more refined and penetrating methods we have witnessed in our time, and yet more intimate methods, those of biochemistry for instance, are being rapidly unfolded. Research, as it is working to-day, advances from fixed and measured bases; as observation it watches nature's march past; then as experiment it puts events to test under artificial conditions of separation or isolation, and measures their phases. But the laboratory can not, as nature does, contrive the unexpected; so we must "gear up our tiny machines to the vast wheel of nature," and try for a first roughing out of an idea or concept. If we are to select our facts to any considerable purpose as crucial, we must first have an idea in our minds; and for this a certain kind of imagination is needed, one of general concepts rather than of the concrete individualizing imagination of the artist. Thus there

[4] *Lancet,* May 22, 1920, where he quotes "Penfold and others."

[5] Gates and Meltzer, Rockf. St., Vol. XXV., and *Jour. of Physiol.,* February 20, 1920.

are two kinds of discoverers, whose comparative outlines we have not yet well discerned. Of scientific discovery Henri Poincaré gives an interesting appreciation; he says that discovery consists of three stages: the first stage is of laborious work at the problem on all sides; the next is not one of conscious occupation with the subject, but of unconscious cerebration, during which a promising hypothesis may unexpectedly arise in the mind; the third is deliberate verification and completion of form. Thus out of an unlimited number of possible combinations, and by many speculations, the discoverer at length divines the true one. In medicine this has been clearly the course of surgery, the side of medicine which is closer to nature.[6] The surgery of my young days was only too "observational"; the friendly fingers of curious colleagues were popped in and out of an operative incision with no apprehensions about "the infinitely little." Now the observer is sadly pushed aside; the ritual of surgery is become like the magic rites of old of which, if a point were dropped or a word changed, the virtue went out. But the rite could be done over again by the penitent; unluckily in surgical rites there is little room for repentances.

A new scheme of research into the origin of diseases, lately instituted at St. Andrews, claims our respectful attention. And may I be forgiven if here I pay a tribute to the rare devotion which inspired Sir James Mackenzie to forsake place and honor to follow after knowledge; indifferent whither he were led so long as truth was the leader. Sir James argues that the man in charge of the first deviations from health is the general practitioner; and that, if we are to detect diseases in their incipience, he must be the detective. One evening about the year 1879, when staying with Sir George Humphrey, he and I sat into the small hours devising a method by which we hoped to engage the general practitioner in scientific investigation. We secured the cooperation of this association and of many coadjutors;[7] Dr. Mahomed joined us as secretary. We hoped by gathering in large numbers of observations to eliminate error; and several series of questionnaires were distributed. Four volumes of reports were issued, under such editors as Humphry himself (on Old Age), Butlin (on Cancer), Whipham (on Rheumatic Fever), and Isambard Owen (on Intemperance). But the effort was premature; the data were too rickety, the reports too often irregular, dilatory and imperfect, and the reporters untrained in observation, punctuality and precision. As things are, few of our colleagues remember to let us know the issues of cases seen in consultation. We may hope now for better material and more accurate workers; not only so, but Sir James Mackenzie is developing another and no doubt better method; he is working with intense culture, on a small holding, and on a more intimate clinical plan.

In exploring a country the great watersheds and rivers are first laid down; to map out these and their valleys and tributaries is the first great work. These main features known, bearings are obtained whence to discover the contours of the hills, and to track up to the hidden sources of the streams. This is Sir James's mission—to track out the nascent rivulets, and with his divining rod to dig for the springs which feed the streams of disease.

Let us not suppose that this research will be but a matter of cleverness, sagacity, or even of intensive observation; nor flatter ourselves that because Mackenzie produced his great work on the *Pulse* while a general practitioner that he achieved this by ordinary clinical observation, however acute The progress of medicine must in large part be endogenous. While our pathologists in balloons were working on morbid phenomena without ever seeing a sick man, Mackenzie was bringing laboratory equipment, and exquisite laboratory methods, to the bedside. The polygraph, no easy instrument to handle even now, was the grandchild of the kymograph; and by it was

[6] See C. A., "Hist. Relations of Medicine and Survey."

[7] See Sir G. Humphry's presidential address at Cambridge, 1880.

proved again that science consists—as Plato said five centuries before Christ—*in measurement.* So in the St. Andrews research, not only have the initial warpings to be discovered, in their many ways and tides, but their volumes and their curves also to be measured as precisely as were those of the circulation by the polygraph. The physicist and the biochemist will need all their expertness in valuing molecular motions, analyzing secretions, recording blood tests and morphologies, and so forth, in their earliest and subtlest phases. For it is in molecular dynamics that the first deviations will arise; massive visible changes come later, and happily are now in large part calculated, or calculable. Mere observation—Nature's march past—will not count for much now; and as to family histories—well, they vary with each historian. And we practitioners will need a more searching discipline before we can occupy ourselves with problems so subtle.

The laws of inheritance must, I think, be sought out, at any rate at first, on animals; the generations of man are too long for comprehension; besides, something else seems lacking in this study of the genetics of man? . . . Is it a sense of humor?

And there is something more to be said. If light is to be thrown upon the generation of diseases in man it must be in part also by study in a far larger field; we must discover and compare the elements and phases of disease in animals and in plants. Sir James Paget, in his admirable address to the Pathological Section of this Association at Cambridge in 1880, reflected on the difficulties of human pathology because of its great complexity. He had "long and often felt that in this difficulty we might gain help from studying the consequences of injury and disease in the structure of plants" as less complex and under simpler conditions. To this field of pathology he devoted almost the whole of the address. A large part of my address in medicine to this association in Glasgow in 1888 was given to this appeal; it has found no response, hardly an echo. Yet what would anatomy be without comparative anatomy; language without comparative philology; anthropology, law, history, and even religion, without a like comprehension? Without an *Institute of Comparative Pathology* in Cambridge our range of vision and work is contracted. In the "Field Laboratories," it is true, Professors Woodhead and Nuttall, ably seconded by Dr. Stanley Griffith, are doing as much as lies in the power of a few individuals; but any such effort is puny beside the sphere of observation and research awaiting us. The comparative survey must cover the diseases of plants as well as of animals; of the lowest of living things up to the highest. The money loss year after year caused by the depredations and the diseases of animals and plants is enormous; and many of the methods of dealing with them—as with foot and mouth disease and swine fever—barbarous; if at present imperative.

Yet no one stirs, save to gyrate each in his own little circle. There is no integration, no organization of research, no cross light from school to school, no mutual enlightenment among investigators, no big outlook. The destruction by insects in forestry and agriculture alone in Great Britain is put at £30,000,000 per annum.[8] An Institute of Comparative Pathology in Cambridge with the endowment of professorial chairs and subordinate workers would cost no doubt a quarter of a million, a big sum; but what is this to the wastage of disease throughout the world of life!—to swine fever, diseases of cattle and horses, of crops, of forests, and so forth—utilitarian ends it is true, but to be followed on paths of discovery which would illuminate the whole field of nosology. Diseases are not "entities," nor even recurrent phases of independent events, but partial aspects of a universal series. The young graduates we have, many of them of great capacity; but every day we are losing them because they are not taken up at once into scientific teams; so they slacken, or drift into some other means of livelihood, and things muddle on as before. How blind we are!

T. Clifford Allbutt

[8] Mr. L. Scott, M.P., in the House of Commons.