SCIENCE

VOL. 89 | FRIDAY, JANUARY 20, 1939 | No. 2299

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS
New York City: Grand Central Terminal
Lancaster, Pa. Garrison, N. Y.
Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary in the Smithsonian Institution Building, Washington, D. C.

THE CELL AND THE PROBLEM OF ORGANIZATION[1]

By Professor EDMUND W. SINNOTT
COLUMBIA UNIVERSITY

THE third decade of the nineteenth century may well be regarded as the period in which the science of biology began to assume its modern form. The great conceptions of protoplasm as the physical basis of life, of the cell as the unit of plant and animal structure and of the nucleus as an integral part of the cell were then taking shape in the minds of biologists and were beginning to receive their first published expression. My predecessor of seven years ago celebrated the discovery of the nucleus by Robert Brown in 1831. The present year is generally accepted as marking the centennial of a still more important biological idea, that the cell is the unit of structure in all organisms. It was just one hundred years ago that Schleiden's famous paper was published. We need not attempt here to determine what part of the credit for the formulation of the cell theory should be given to Schleiden and Schwann and how much to earlier students of the minute structure of living things. The year 1838 is at least a convenient point from which to measure a century, and 1938 thus provides a natural occasion on which to evaluate the theory in terms of present-day biology. Such is the purpose of a number of scientific programs, at this meeting of the American Association and elsewhere.

It is not my intention here to undertake the ambitious task of reviewing the significant part which the cell theory has played in the history of morphology, physiology, genetics and indeed of every biological discipline. I do propose, however, to discuss briefly with you certain of its implications for one particular field—that most baffling of biological enigmas, the problem of the organized development of living things. An organism is not static. It continually changes, but in such a regular and orderly fashion

[1] Address of the retiring president of the Botanical Society of America at Richmond, Virginia, December 29, 1938.

that we must recognize in this developmental process the operation of a constant control. The wealth of knowledge which biologists have acquired about plants and animals has thrown surprisingly little light on what this control is or how it is exercised. To watch a fertilized egg or a tiny primordium march unfalteringly onward until the ultimate form of complex organ or body has been attained is an experience common enough among biologists, but it can not fail to impress the thoughtful observer with a sense of his ignorance. Until we shall discover what is really happening in this mass of developing protoplasm, what molding and morphogenetic processes are here so subtly at work, our knowledge of living things will still be merely superficial. This is the biologist's frontier. Beyond is undiscovered country into whose borders a few explorers have penetrated here and there just far enough to see how broad and fertile the land is and how well protected against those who seek to enter it.

It is to this problem of organic development, of course, that the cell theory has made one of its major contributions. To understand that growth is accomplished chiefly by the multiplication of essentially uniform cellular elements and that changes in external form and internal structure are related to differences in the rate and plane of cell division and in modification of the characters of the cells themselves, is evidently to take a long and hopeful step along the road toward a knowledge of the process of development. But we must sadly admit that the hopes raised by this first triumph have not been altogether realized. The developmental relations between cells and the higher structures which they compose are still unknown. The extreme proponents of the cell theory regard the organism essentially as a colony of cellular individuals and attribute the phenomena of development to complex interactions between these units. At the other extreme are the organismalists, who agree that "the cells do not make the body but the body makes the cells." Both admit the significance of cellular organization as either a primary or a secondary factor, but neither has been able to interpret the phenomena of development in any simple or comprehensible terms. The body admittedly is built of cellular units, but the mechanism which controls the multiplication of these units and builds from them before our eyes the amazingly complex organic edifice entirely eludes observation. The most enthusiastic proponent of the cell theory must admit as much.

In an attempt to solve this problem biologists have carried still further the methods of analysis which led to the great generalization which we celebrate to-day. The rather nebulous genetic factors postulated by Mendel have taken material form as genes, and the intensive study which has been given to these new units has yielded much exact knowledge as to their location, and even some idea of their number, size and other characteristics. It is not too much to say that the theory of the gene will play as important a part in the development of our science as did the theory of the cell. Indeed, for many the gene has supplanted the cell as *the* biological unit.

But the geneticist is now beginning to turn his attention to problems of development and encounters here the same difficulty which faces the cellular embryologist. He has learned much about the gene as it occurs in the fertilized egg, primarily through a study of gene-controlled differences in the adult organism; but how the gene is actually related to the development of these traits is still unknown. The spectacular analysis of the cell and thus of the entire organism into an aggregation of genic units has thus far proved no more helpful in solving the basic problems of development than was the earlier analysis into an aggregation of cellular units.

But perhaps the process of subdivision should be carried still further. Students of cytogenetics hopefully discuss the possibility of an analysis of the gene into even smaller units and thus of bringing their problem to the very door of the biochemist. Those who feel content only when their problems can be stated in terms of atoms and molecules look to such an analysis for a final solution, but it is permissible to wonder whether, even if the molecular constitution of every gene were known, we should not still be confronted with the problem of exactly how this elaborate series of units actually gets itself built into what we so well have named an organism.

The repeated failure of these various attempts to solve the problem of organized development by cutting up the individual into smaller and smaller unitary elements breeds the uneasy suspicion that here again, as in so many other scientific problems, we have been confusing analysis with solution. The scientific temperament feels much more comfortable when it is breaking down a complex phenomenon into simpler parts than when it is trying to pull together a series of diverse facts into a unity of relationship. For a solution of the ultimate riddles, however, synthesis is more important than analysis. It is far less easy to come by, and often requires the intuition of genius itself. Thus the progress of chemistry has been marked by an analysis of the material universe into a series of ninety-two different kinds of atoms, which arrange themselves into units of a higher order, the molecules, and are themselves further resolvable into unitary charges of electricity. This was an accomplishment of supreme importance, but Mendelejeff's recognition of orderly relationships between these elements at once made it possible to bring together a wide range of diverse and hitherto unrelated facts into a single integrated system and thus to achieve a far deeper insight into the nature of matter. Similarly, the chief purpose of biology for a long time was to analyze the plant and animal kingdoms into a series of orders, families, genera and species, which seemed to be as arbitrarily arranged as the letters of the alphabet; but Darwin's great synthesis at once made clear that the organic world was not a series of unrelated units but was knit together in the ultimate unity of a common descent. The genius of another Darwin is needed to-day to discover how the complex of molecules, genes and cells are integrated to form a living organism. It is not an understanding of units which we now seek, but of unity. We are like the small boy who takes the clock apart to discover the secret of its running, but after he has dissected the works into an impressive array of wheels, gears and springs is unable to put them together again successfully and is still as far as ever from an understanding of synthetic horology. Like him, we need to know the principles underlying the construction and operation of our machine. Analysis is not enough.

I do not wish in any way to disparage the usefulness of the analytic method or to minimize the very great value of the discoveries which have been made by its means. An understanding of the relations which the products of an analysis bear to each other, however, is quite as essential as the analysis itself. It is important to know that a molecule of water may be resolved into two atoms of hydrogen and one of oxygen, but still more important to know what are the properties and relationships of hydrogen and oxygen which result in the production of a molecule of water when they unite. The analysis has long since been made, but an understanding of the synthesis is still beyond our powers. It is important to know that a living plant is composed of cellular units, but it is even more important to understand how, through the multiplication and interrelations of these units, the orderly development of an organism is assured. The analysis is more than a century old; the synthesis is still far from consummation.

But if the synthetic approach to problems of development is so much to be desired, why in practice has it proven relatively unfruitful? The inherent difficulties of the method and the intractability of the materials to which it is to be applied have doubtless been chiefly responsible. Many biologists have been deterred by these difficulties from attacking the problems or organization at all. Others, despairing of finding a solution through the familiar techniques of their science, have begun to explore the possibilities of ideas and postulates foreign to the familiar biological idiom. The more tender-minded among them have needed little encouragement to run after the strange gods of mysticism and metaphysics and have set up in their midst the golden calf of entelechy. Even those who remain in the ranks of the orthodox speak the unfamiliar language of holism, organicism, metabolic gradients, allometry, organizers, morphogenetic fields, gestalten and other words outlandish in the ear of analytical biology and which for the most part are merely the terminology of enlightened ignorance.

It is not strange, therefore, that many students of development have ceased to concern themselves with what seem to be the fruitless and often demoralizing problems of the synthesis, organization and integration of living things. This defeatist attitude is hard to defend. Granted that the mechanics of development may be among the most recondite of problems, we surely can not admit that it is not open to scientific approach. Granted that it lends itself to fantastic and unsupported speculation and has always attracted the lunatic fringe of our science, yet surely this should not prevent the serious student from applying to its solution the sound and tested methods of biological research. Granted that to coordinate the data of biochemistry, biophysics, cytology, morphology and genetics requires a breadth of training and catholicity of view-point almost impossible to gain to-day, yet the job must be done. My plea is for more laborers in this vineyard. Difficult the task surely is, but by no means hopeless. It should be our chief ultimate concern, for the very autonomy of biology rests upon the phenomenon of organization. Whatever distinguishes the life sciences from the physical sciences lies here, and here we must ultimately succeed or surrender our birthright.

But how can we lay hold of such an elusive and difficult problem? The failure of the cell theory to explain development has at least shown that "Divide and conquer" is a futile strategy to follow in this particular campaign. The easy philosophy that the ultimate task is simply to resolve an organism into its constituent genic or chemical elements and that all else will follow is clearly not enough. Biology is more than biochemistry. Something more profound is required. We must discover the relationships between developmental units and thus the manner in which organized syntheses arise. This task may well be too much for biology alone, and we must nourish no false pride which would disdain the help of any branch of knowledge. The chemist, with his hormones, organizers and other morphogenetic substances, must certainly be our constant companion. The physicist should more often be consulted, especially when he can speak with certainty of polarity, gradients, potential differences and fields of force in an organism. The mathematician, with his curves and coordinates, his beautifully precise methods of describing relationships and his remarkable science of topology, is evidently a friend to be closely cultivated. Since the climax of the integrative process seems to be the development of conscious personality, the student of organization should not fail to examine the findings of the psychologist, inexact and subjective as these often appear to an outsider; for, after all, the most intimate knowledge we can ever possess of any living organism is yielded through our unique point of vantage within one of them. Our problem may reach out so far that it transcends the more familiar categories of scientific thought so that ultimately we can not shirk the necessity of facing the problems of biological philosophy, and here the professional philosopher, especially if he has the advantage of understanding the results of modern biology, will be an indispensable guide. These all must be our allies. Let us never grow so pedantic that we shall frown on any brother who occasionally goes off the reservation of biological orthodoxy to refresh himself in other fields. He may well bring back from his excursion a treasure which those who stay at home can never find.

To all this, I am sure that most of you will readily agree; but you will point out that for years many of the best minds in biology have been devoted to just this problem; that the literature of Entwicklungsmechanik is enormous; that I am offering but a counsel of perfection in a field the difficulties of which I seriously underestimate, and that unless I have some constructive suggestions to offer, this would be a very appropriate time for me to sit down. I admit the validity of much of this indictment and hasten to offer here my own very slender contribution toward the solution of our problem. It is a development of two simple ideas, namely, that the process of biological organization takes place at various essentially independent levels and may be studied at any of them, and that one of these levels, the development of the multiple, determinate organ of the higher plants, provides exceptionally favorable material for such a study. These suggestions I propose to discuss briefly here.

Following the lead of the zoologists, we have been accustomed to look for developmental relations between the cell and the body as a whole. In plants, with their much looser organization, the problem is simpler than this, for there is clearly a level of organization between cell and body, the multiple organ, repeated indefinitely in a single individual and bearing somewhat the same unitary relation to the body as a whole that the cell bears to it. The nodes and internodes, leaves, flowers and fruits of the higher plants are examples of this sort of unit. The fruit, for various reasons, is especially favorable for study, and it is evidence from fruit development in the family Cucurbitaceae which I wish first to present.

That the fruit here is a distinct developmental entity, essentially independent of the cell below it and of the entire body above, is indicated by a number of facts. In any given race, the fruit has a very definite developmental history, both as to its size and form and as to its internal differentiation. This history is altered little or not at all by the size or character of growth of the plant as a whole. Environmental factors which markedly influence plant size have little or no effect on fruit size unless they are extremely unfavorable. Conditions which greatly increase total growth of the plant will increase the number of fruits it bears but not their size. The plant body is an indeterminate series of such multiple structures, their number depending on environmental factors but their particular characteristics being essentially autonomous.

Evidence is now available that the organ is equally independent of the next lower unit, the cell. If the growth of a cucurbit fruit from a tiny ovary primordium until several days after fertilization is measured, the rate of increase is found to be constant, there being a uniform daily percentage increment which is characteristic for a given race. Investigation shows that cell multiplication is occurring abundantly during the early part of this exponential growth period but then ceases, and that all subsequent growth results from cell expansion. The rate of growth, however, is exactly the same whether the cells are dividing or not. Furthermore, even while cell division is still going on, cell size is slowly increasing and the rate of division slowly decreasing. Thus the mass of material being poured into the young fruit is growing at a constant rate regardless of whether this mass is being cut up into new cells rapidly, slowly or not at all. Dry weight follows the same procedure, for it increases at a constant rate both before and after cell division ceases. Differentiation, too, proceeds independently of cell division, for the rate of division is found to be the same in all regions (axis, inner, middle and outer wall, and epidermis) but the relative proportions of these various regions change markedly along a gradient from the inside of the fruit outward. This evidence all suggests that the mechanisms controlling growth and differentiation in the fruit are concerned with the entire organ and not with the behavior and interrelationships of the individual cells of which it is composed. The unity of behavior, and thus presumably the unity of organization, inheres in the whole and not in its elements.

On its own level the cell also displays a unity of organization independent of the organ above or of smaller units below. Biologists have long recognized that cell size, for a given tissue, is relatively constant as compared with organ and body size. Every cell also seems to possess a uniform complement of genes.

These are not arranged at random but in a very definite order in each chromosome, and this constancy of position seems important in determining the rôle which a gene plays in development. Nor are the chromosomes entirely independent, for events in one have been shown to have effects on the others. The essential elements in the cell seem clearly to be the genes, for it is known that if one or at most a few of these are lacking, the cell will die. So far as can be determined the genes are of the same general order of magnitude and seem to be fundamentally similar units. It is in accord with the facts to regard the cell as an organized group of equivalent but somewhat differentiated genic units, just as we regard the organ as an organized group of equivalent but somewhat differentiated cells.

Of course one can speculate on the possibility that the gene itself is an organized aggregation, at a lower level, of still smaller units, perhaps protein molecules or simpler chemical entities, but our knowledge of genic constitution can go no further than to suggest that such may be the case. What is the ultimate living unit, if there is one, and of what it is composed are questions for the future to answer.

It should be noted that this process of organization is not a mere building up of similar units into an amorphous mass. Their arrangement and interrelations produce specific patterns which are evidently the result of a control more precise than one which would merely bring them together. Hence arises the problem of the development of organic form, which makes dynamic morphology a fundamental biological discipline.

The problem of organization thus presents itself as one which is concerned not with the entire organism alone but with a hierarchy of successively more advanced and essentially independent levels, from the gene or a still smaller unit to the body as a whole. It can be studied profitably at any level, for evidently the same process is at work in all of them, namely, the integration of a group of essentially similar units into a unity of a different and higher order with a specific pattern of its own. The primitive units of life, whatever they were—possibly something akin to genes or to virus particles—may have become organized into the systems which we now recognize as cells. Groups of cells remaining together in a multicellular mass may then have organized themselves into some higher entity, such as the metamere in animals or the multiple organ or perhaps the "phyton" in plants. From a series of these units is built up, in turn, the most complex entity of all, the body of the individual organism. In plants and many lower animals, like the annelids, this is still rather loosely organized and consists of an indeterminate number of essentially similar units. In most animals, however, integration is much more complete and the body has become a closely knit and highly differentiated entity. Throughout all these levels, the process is thus the same. So long as a mass of living material is continuous there is manifest in it this persistent urge to pull all parts together into a unity. Protoplasm seems inherently integrative in its activity, and only in certain tissue cultures and in clearly pathological conditions does this propensity for organization disappear. From this point of view, then, the cell is to be regarded not as a unique unit, but simply as one member of a series of units.

A recognition of the fact that organization is not a single event but proceeds from level to level is but a short step forward on a long and difficult path. How these units are pulled together and molded into a higher patterned synthesis is still beyond our knowledge. At least it is encouraging to know that the problem may be attacked at any level along the series and that we therefore possess the advantage so much esteemed by good generalship of being able to choose our battle-ground. The cell is too small for easy investigation, the whole body too complex. The multiple organs of the higher plants, however, offer ideal material for such studies. Of these organs the fruit is particularly favorable. It is large enough for easy investigation. Its form is relatively simple. It rarely becomes highly differentiated. Its structure is not closely involved with the function which it performs, as is that of the leaf. It has a relatively long developmental history. It is available in large numbers in the same individual, so that genetic identity is assured even under very diverse conditions. Developmental studies of such organs should yield much information as to the facts of growth and organization and should prove even more significant than have the more familiar studies on the early animal embryo. These structures, it seems to me, offer to botanists a notable opportunity for productive work on the problems of development.

In conclusion you will doubtless expect at least a word of concrete suggestion as to procedure. How can we lay hold of the elusive problem of organization, even with the best of material? The advice I have to offer will seem prosaic enough. It is to begin by describing with the utmost detail the phenomenon of organized development. Before the Darwin of morphogenesis can profitably indulge in synthesis, coordination and generalization, he must be provided with a far greater body of facts than are now available as to what actually happens in all stages of the developmental process. Our immediate task is to state as fully and exactly as possible, in terms of number, size, rate and position, just what occurs when an organized whole builds itself by multiplication of its parts. A vast amount of spade work of this careful but uninspiring sort must be done, tedious in execution but fruitful in results, in order to provide a basis of facts sufficiently rich and varied so that among them some thoughtful student may begin to perceive those significant relationships which will finally lead him into the heart of the problem.

Those early biologists who established the cell theory made the first great contribution to such a descriptive study of development, and under the stimulus of their idea, biological analysis has gained many triumphs in the century that is past. We can best honor these pioneers of yesterday, however, not by pushing indefinitely onward over the path they first began to blaze and which now seems destined to end blindly in discouragement and frustration, but rather to follow the pioneers of to-day along the far more difficult path which will lead, however distantly, to an understanding of biological syntheses. Life is integration. Life is the knitting together of units into patterned wholes. Many of the units we know, thanks to the labors of a hundred years. An understanding of how these units are built into the fabric of an organism is the task for the hundred years that are to come.

MATHEMATICIANS, AND POETRY AND DRAMA. II*

By Professor RAYMOND CLARE ARCHIBALD
BROWN UNIVERSITY

I have referred to Hamilton as a youthful prodigy able successfully to compete with the American mental calculator, Zerah Colburn. But among many gifted mental calculators who gave public exhibitions of their prowess, no one could compare with Zacharias Dase, who was born at Hamburg in 1824 and died in 1861. He is known to have extracted the square root of a 100-figure number in 52 minutes, and to have multiplied two 100-figure numbers in $8\frac{3}{4}$ hours; there is reason to believe that this last-mentioned multiplication was no great tax upon his powers of mental arithmetic. Gauss, the greatest living mathematician of his time, got him to work on calculating mathematical tables of value, and as a result four important volumes were published. A few years before his death Dase published a volume of material about himself, extracted from his scrapbook.[53] In this material are 69 stanzas or poems in a variety of forms and by as many different authors. So far as I am aware this is the largest number of so-called poems on any single mathematician. But these measure rather the popular appeal of his peculiar gift.

No such acclaim awaited two men of superlative genius who died in their twenties about the time that Dase was born, but whose names are constantly mentioned wherever mathematical research is now carried on. The one was Evariste Galois, a Frenchman, killed in a duel when 21 years of age. The other, probably the greater genius, was Niels Henrik Abel[54] (1802-29), of whom Norway was later so proud. After the articulation of far-reaching mathematical discoveries and a gallant struggle with poverty, he died of tuberculosis at the age of 27, just as his achievements had brought high recognition, which would have filled his later life with ease and content and given him untrammeled opportunity to draw back curtains hiding eternal truths. At the centenary of his birth in 1902 a great international celebration was held in Oslo,[55] and a long French poem on "Abel" was read by Bjørnstjerne Bjørnson.[56] Happy indeed was the expression of thought in two lines of this poem:—

> Là où il a été
> on ne pense plus sans lui.

Several other poems about him include one engraved on his tomb. The centenary of Abel's death was internationally celebrated in 1929, and four Norwegian postage stamps bearing his portrait were then issued.[57]

Let us turn now to a British centenary. Nearly seven years ago throughout the English-speaking world there were elaborate celebrations of the centenary of the birth of Charles Lutwidge Dodgson[58] (1832–1898), familiarly known by the pen name Lewis Carroll, which he first used in connection with a poem he published shortly after he graduated from Oxford. No other mathematician in the writing of nonsense produced such an effect on his country's literature[59] or became

* Concluded from the issue of SCIENCE for January 13.

53 "Zacharias Dase. Aufschlüsse und Proben seiner Leistungen als Rechenkünstler. Mitgetheilt von ihm selbst aus seinem Album," Berlin, 1856, vi + 122 pp.

54 G. Mittag-Leffler, *Revue du Mois*, 4: 5–26, 207–229, 1907; E. T. Bell, "Men of Mathematics," New York, 1937, pp. 307–326; G. Prasad, "Some Great Mathematicians of the Nineteenth Century," Benares, v. 1, 1933, pp. 111–165.

55 "Niels Henrik Abel. Memorial publié à l'Occasion du Centenaire de sa Naissance," Christiania, 1902.

56 See footnote 54.

57 *Scripta Mathematica*, 1: 183, 1932.

58 E. V. Lucas, "Dict. Nat. Biog," Suppl., v. 2, 1901. W. De La Mare, "Lewis Carroll," London, 1932; the best appreciation of Alice and her creator. S. H. Williams and F. Madan, "A Handbook of the Literature of the Rev. C. L. Dodgson (Lewis Carroll)," and Supplement, Oxford, 1931, 1935; invaluable work. F. Madan, ed., "The Lewis Carroll Centenary in London, 1932, including a Catalogue of the Exhibition, with Notes," London, 1932. *Scripta Mathematica*, 1: 172–175, 349, 1932; 4: 318, 1936. "Catalogue of an Exhibition at Columbia University to Commemorate the One Hundredth Anniversary of the Birth of Lewis Carroll," New York, 1932.

59 F. J. H. Darton, "Children's Books in England," Cambridge, England, 1932, pp. 263–269.