GUYER

DEFICIENCIES OF CHROMOSOME THEORY OF HEREDITY

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I should like in the present paper to discuss the evidence upon which inordinate importance has been attributed to the chromosomes as vehicles of heredity, and to inquire into how far this theory agrees or fails to agree with some of the known facts of protoplasmic activity and of heredity. By chromosome theory is meant, in this connection, the original theory which regards the various morphological parts of an adult as specifically predetermined by corresponding anticipatory units which reside in the chromosomes of germ-cells. While many present-day workers, I am aware, do not hold rigidly to this conception, nevertheless, for purposes of criticism it seems best to adhere to a consideration of the theory as expressed and still largely maintained by its founders. To get at the matter satisfactorily it will be best to examine, point by point, the evidence upon which the theory is founded.

1. Roux's ('83) dictum that mitosis is meaningless unless it is for the precise halving of qualities serially arranged, so that, qualitatively, each daughter-cell will resemble the other, is historically, perhaps, the first specification of the chromosomes as centers of series of qualities.

As the case then stood, no evidence had been adduced to show that chromatin is qualitatively differentiated, but theoretical considerations, based chiefly upon the phenomena of what is commonly termed particulate inheritance, had led several biological workers to the assumption that a multitude of particles bearing incipient hereditary qualities must exist in the germ cells. In mitosis was found a mechanism seemingly designed for halving a series of differential particles; consequently, to the chromatin masses which make up the in-

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dividual chromosomes was assigned the rôle of being the actual bearers of the so-called hereditary qualities. As to Roux's avowal that, unless we postulate in the chromosomes discrete qualitative particles which require to be accurately halved, direct division would suffice and mitosis would be superfluous, we know that direct division does sometimes suffice, even for the production of cells which ultimately give rise to germ-cells. In 1894 Meves showed that apparently normal development of spermatozoa may follow amitosis in the salamander. More recently Child ('07) has brought forward what appears to be unmistakable proof of the fact in Cestodes. These cases, of course, neither prove nor disprove the qualitative nature of chromatin, but if chromatin is qualitatively differentiated, the results of these investigators show that the qualities can be distributed without the elaborate structures seen in mitosis, and Roux's argument, therefore, based as it is upon the significance of mitosis, is invalid.

2. The fact that the nucleus is apparently an important center of chemical synthesis has been construed as a proof that it is therefore the vehicle of heredity.

Judging from the results of physiological chemists, it seems probable that the synthetic chemical changes wrought by the nucleus result in part in the construction of incitive or activating materials, in part, presumably, in the further elaboration of nutritive substances; but, to my knowledge, there is no evidence which will warrant us in assuming that the nucleus bears or makes, as it were, self-sufficient morphological units which at just the right time pass out and take up their proper position in the cytoplasm and with the more or less passive cooperation of the latter expand into the structures required.

Everyone will admit, I think, that the cytoplasm of a given species of plant or animal is distinctive of that species in all cells of the organism, and there is no conceivable reason why it, any more than the nucleus, must be made so anew in the germ-cells of each generation. So distinctive of its kind is a given protoplasm, in fact, that there is great probability that in higher animals digested proteids, either in transit through the digestive epithelium or immediately upon entering the blood, are synthesized into a new proteid specifically characteristic of the animal in which it is present. Here, then, we have a degree of specificity initiated before the proteid in question has ever become cellular in nature.

Of all cells in the body, those which show nuclei of enormous size in proportion to their cytoplasm are not cells which have a large number of morphological structures to establish, but gland-cells characterized by intense secretory activity in which chiefly one kind of product is elaborated.

The death of denucleated, and the regeneration of nucleated, fragments of protozoa are phenomena sometimes cited as demonstrating the fact that the nucleus is the center of morphological synthesis. But may they not indicate only that some general substance elaborated or controlled by the nucleus is wanting? Loeb ('99) has shown that possibly in such cases failure to regenerate may be due largely to a lack of oxygen, and that the nucleus is apparently the chief source of the oxygen supply of the cell. Spitzer ('97) has established the fact, moreover, that certain "oxidation ferments" are nuclear in origin. In these experiments on protozoa the rapidity of regeneration seems to be in direct proportion to the amount of nuclear matter left in the piece—a question of quantity rather than quality. Indeed, if the nucleus is an aggregate of qualitatively different morphological units, one would expect parts to be missing in the regenerated protozoa in proportion to the amount of nuclear matter removed, but the evidence does not bear this out. The regeneration is seemingly complete, only a longer time is required if but a small fragment of the nucleus is left in the piece.

3. Another evidence that is commonly cited may be expressed as follows: Offspring inherit equally from each parent; only one spermatozoon enters the egg normally, and this spermatozoon, though exceedingly smaller than the egg, contributes the same number of chromosomes that are present in the egg. Since only the chromosomes are contributed equally by sperm and egg-cell to the fertilized egg, it is argued that they must be the physical bearers of the equal contributions of qualities from the respective parents.

However, I think we may legitimately question the alleged fact of parental equality in inheritance. While it is true, apparently, that individual or specific characters may be derived equally from either parent, the fundamental characters that go to make up an organism—such, for example, as make it an animal and a vertebrate of a given family or genus—are characters that are common to both parents; and from a consideration of adult forms alone, therefore, we have no means of definitely determining whether such characters are transmitted by one or by both parent germ-cells. When we come to consider embryological stages, however, the evidence at our command, meager though it be, plainly indicates that we do not inherit equally from each, but more from the maternal parent.

Since I have discussed this matter at some length in a former paper (Guyer, '07), I shall cite but a single instance in this connection. Both Conklin ('05) and Lillie ('06), if I do not misinterpret their results, find that in certain forms, before the spermatozoon enters, the fundamental organology is already roughly indicated in the egg by the distribution of so-called "formative substances." The egg then passes on to cleavage without waiting for a duplicate set of "formative substances" to pass out from the male pronucleus. Since there is evidently no biparental mechanism present in these early and more fundamental stages, we are not justified in maintaining that offspring inherit equally from each parent. Consequently, if we insist on restricting *all* of the mechanism of heredity to the chromosomes, the argument from the striking parity between the chromosomes of male and female germ-cells loses its force.

It is true that in these cases cleavage is not inaugurated until the spermatozoon enters the egg, but here we must discriminate between simply the stimulating effect of the sperm and its capacity for conveying hereditary qualities. That this is a valid distinction is evidenced by the facts of artificial parthenogenesis, where by various artificial means the mere stimulus to cleavage may be brought about.

It may be urged that although "organ-forming substances" are present in the cytoplasm of certain eggs before fertilization, these substances have originated from the nucleus during the earlier history of the egg-cell. There is good evidence, in fact, to show that the cytoplasm of the egg is more homogeneous in appearance in earlier stages than later, and that substances are ejected into it from the nucleus. However, this does not prove that these nuclear emanations are morphological entities, and I see no sufficient reason for not regarding them simply as nuclear products which cooperate with cytoplasmic substance of equal importance in the construction of materials which may serve as a basis for further differentiation. In any event, the disparity between maternal and paternal inheritance would remain.

Inasmuch as the bulk of the egg, even after fertilization, is cytoplasm chiefly of maternal origin, it is clear that the developing organism is more maternal than paternal in its derivation. Nevertheless, we can see how the veneer of individual traits may be equally of maternal and paternal origin if, to express it crudely, we look upon cytoplasm and chromatin respectively as responsive mechanism and inciting agent—the character of the response depending upon both the constitution of the cytoplasm and the materials (enzymes? nutritive substances?) emanating from the nucleus—subject, of course, to the restrictive influences of the environment. We know, furthermore, that individual parental characteristics appear for the most part as modifications of characters held in common, rather than in the presence or absence of special characters.

So it seems not improbable that, as the proper stages in development are reached, the secretions or emanations from the chromosomes of paternal and maternal origin can produce in combination or interaction with the cytoplasm and the general environment the ultimate characters peculiar to the respective parents. From what we already know of physiological chemistry we can but conclude that before the final adult organism is evolved there must ensue numerous reactions between the nuclear material and the cytoplasm, and probably many highly complex interactions would follow, both among the products of these reactions and between them and other nuclear and cytoplasmic materials which had been developed in the meantime, or which had remained quiescent because of the want of proper material with which to react.

By way of rough analogy, the writer has always thought of the process of specific organogeny as possibly somewhat similar to the production of galls on plants. Any one of several species of insects may produce galls on a given plant, but each kind of insect always produces its own specific type of gall. Here is an actual case of living protoplasm producing a specific character through the activity of a specific exciting agent. That is, the reaction between certain secretions of the insect and the living substance of the plant produces new and definite structures. Change either factor and the resulting structure must be modified.

Likewise, in the germ-cell, alterations in the constitution of either chromosomes or cytoplasm must undoubtedly produce structural changes in the adult. It would seem that one might expect to find in the chromosomes the greater source of variability because they are derived in much greater proportions from two sources—the two parents—than is the cytoplasm, and this very mingling of the two materials could afford an adequate basis of both quantitative and qualitative changes. The changeable nature of chromosomes is evidenced, furthermore, by their marked differences in structure and appearance under different conditions of activity, and their instability is shown in the pronounced irregularities which may arise through hybridizing or from such external influence as drugging, etc.

In so far as the cytoplasmic constitution is altered before the germ-cells are specifically set aside, we might reasonably expect this constitution to persist as such in the cytoplasm of these cells. We can readily see, moreover, if persistence of such a cytoplasmic constitution is possible, how changes of chromosomal constitution (or, indirectly, even the effects of physical environment) might be reflected onto the cytoplasm from time to time, and there conserved.

A pursuit of this line of thought is tempting, but it would lead us far astray from our subject-matter. Nevertheless, it is well to remember that from the very fact that racial evolution is possible we must concede an accumulative capacity of some kind to the germ-cell. However our respective judgments may balance the factors of preformation or epigenesis in ontogeny, the fact confronts us that phylogenetic development has been largely an epigenesis, since in the first living matter there could not have been specific organ-forming substances for all the later organisms which have evolved from it. If organ-forming substances are necessary for the ontogeny of present forms, it is a necessity which has been acquired hand in hand with the evolution of the race, and the problem which confronts us is to solve the riddle of how it has been cumulatively grafted onto the pristine protoplasm.

4. The presumed necessity of a reduction in the number of qualities which arise as the result of dual ancestry, together with the fact that there are reduction divisions strikingly similar in appearance and results in the germ-cells of both male and female, is also regarded as a proof that the chromosomes are the bearers of the hereditary characters. As a consequence of these reduction divisions, the male and female germ-cells each come to have only half the number of chromosomes characteristic of the ordinary tissue-cells, a fact which is interpreted by Weismann and his school as indicating that half the hereditary qualities have been eliminated in each germ-cell. The total number of chromosomes is restored again through the act of fertilization.

Even ignoring the fact that reduction divisions of chromosomes do not occur in a number of seemingly well-authenticated cases, the theoretical necessity for qualitative reduction is by no means obvious. In the first place, it is improbable that the number of qualities are doubled at conjugation because, for the most part, leaving out of consideration superficial individual differences, probably like protoplasm is added to like protoplasm; or possibly, as already suggested, the male brings in materials which can participate in the construction of a more limited number of characters. As to the difficulty regarding the ultimate accumulation of individual qualities, there is evidence that they may often blend in time, or that certain ones become dominant. Finally, as far as probability is concerned, it is just as likely that inactive qualities, if represented materially, might be resorbed by the protoplasm (just as we have resorption of visible morphological structures, such as the tail of the tadpole) as that a complicated mechanism for throwing out half the qualities of each germ-cell is necessary.

Weismann himself has shown, in fact, how, according to his theory of heredity, through panmixia (cessation of natural selection) and the battling of "determinants" for nutriment, a useless part "must grow smaller and smaller until finally it disappears altogether." (*Germinal Selection*; second edition, p. 42.) If one accepts this view of the elimination of superfluous qualities, it is difficult to see the necessity of postulating a second method of elimination by reduction divisions, or how, indeed, in the course of evolution the enormous supply of accessory or reserve characters which are attributed to the germ-plasm, could have arisen.

5. The perpetuation through successive cell-generations of a fixed number of chromosomes, each apparently of distinct individuality, together with their final seeming accordance with the idea of "pure" germ-cells as demanded by Mendelian principles, is regarded by many as one of the strongest supports of the chromosome theory of heredity.

That there is at least a kind of individuality (recurrence of form) of the chromosome is clearly demonstrated in the results of such investigators as Herla ('93), Zoja ('95), or Moenkhaus ('04), who have studied the chromosomes of hybrids from widely separated forms which have noticeably different chromosomes. And the same thing is shown almost as conclusively, I think, in the researches of Montgomery ('01), Sutton ('02), Wilson ('06), and others who, working upon non-hybrid forms which have chromosomes of varying size, have accumulated much evidence to the effect that in somatic and early germ-cells pairs of homologous chromosomes exist, one member of each pair being maternal, the other paternal, in origin. Persistency of form, however, does not necessarily imply persistency of constitution. This is evident when we consider that a chromosome is a complex made up of at least two substances, viz., an apparently more homogeneous linin substratum, encasing innumerable granules of chromatin. Whether any exchange of individual granules occurs, or whether any permanent changes are wrought in the chemical constitution of these granules or of the surrounding cytoplasm, we have at present no direct means of ascertaining. It is certain that abundant opportunity for such alterations is afforded when chromosomes are resolved into their ordinary diffuse condition in the nucleus.

Granted that in hybrid offspring there are such things as germ-cells "pure" with respect to a given character—and there are some who would dispute this—it would seem, if we assume that the chromosomes determine certain hereditary characters, that in the separation of homologous chromosomes of different parentage an adequate mechanism exists for the segregation of these qualities, as has recently been advocated by various cytologists. Doubt is cast upon this interpretation, however, by such facts of non-Mendelian inheritance as blending, the persistence of hybrid mosaics, and the lingering of certain influences in gametes which theoretically should have been purged of such characters.

The very fact, however, that constant types of visibly different chromosomes recur time after time in cell divisions shows, at least, that under certain conditions they possess different physical properties, and that in some respects, therefore, they are qualitatively different. But there are no sufficient reasons, I think, why we may not look upon their differences as differences of more elemental chemical and physical constitution rather than as differences among systems of determinate morphological units. Because when the two are brought together under certain conditions water (H_2O) is the result, we do not postulate a "determinant" of "aquosity" in hydrogen or in oxygen. It is true that in view of certain properties possessed by each of the two gases, the formation of water is possible, but bring them together under other conditions and the same two elements yield an entirely different "character," viz., hydrogen peroxide (H_2O_2). Or, again, let chlorine act upon benzene (C_6H_6) and, depending upon purely quantitative relations and other physical conditions, any one of six different substitution products ranging from C_6H_5Cl to C_6Cl_6 can be secured. No quasi-teleological conception of anticipatory units is found necessary in a consideration of such cases of chemical configuration, and it seems to me that its necessity, as implied in the conception of determinants or pangenes, is yet to be demonstrated in phenomena of heredity. Even in case of the divorcement of paired parental chromosomes in gametes—and I think this is strongly evidenced in a number of Tracheata—it would seem that we might account for the so-called Mendelian phenomena by attributing to the chromosomes simply chemical and physical differences without endowing them with morphological entities. And, moreover, on such a basis, looking to the reactions of nucleus and cytoplasmic materials for the establishment of ultimate "characters," we can more readily see how non-Mendelian gradations and "contaminations" of characters might arise, because we might then attribute more importance to purely quantitative relations and chance mixture of the chemical substances. In short, there can be a "qualitative" basis, or a series of qualitative bases, without these being at the same time specific "determinants," and until such a more neutral qualitative basis for the phenomena of heredity is shown to be untenable there is no valid reason for postulating a series of morphogenic entities.

But such considerations as these open up another important question, viz., as to just how we are to regard heritable qualities. One great difficulty here lies in the vagueness which enshrouds the term "quality" or "character." It is obvious that many so-called characters are in reality only the expression of the relations of a number of parts and can have no individual basis of their own.

In all our systematic zoology *stability* is the fundamental principle used in selecting characters for purposes of classification. For example, the features chosen as characteristic of genera have shown themselves to be more constant than those which are selected to indicate species, otherwise they would have been discarded as generic characters; specific characters, in turn, are less fluctuating than varietal traits. The qualities which stamp a given animal as a vertebrate or a mammal are certainly more stable and definitely coordinated than those which mark it as a particular variety or species. Our whole scheme of natural classification, which is, when correct, but an expression of the evolutionary status of the forms classified, is based necessarily upon the facts of heredity—that is, of community of descent. Does not the very fact itself that certain character relations are uniform and others fluctuating through successive generations show that in seeking for a physical-unit basis of inheritance we cannot expect to find it wholly in a series of equipotent units, but that unmistakably we have to deal with groupings of characters, some groups of which are more stable than others? This, in turn, can mean only that any such group must be a unit in itself, and that we are dealing, therefore, with units of a higher and of a lower order; or, in other words, with series of coordinations built upon broader coordinations.

To some, such an admission may seem inevitably to demand as a consequence some kind of morphological basis or organization in the germ-cell, some coordinating influence, to which the more restricted chemical processes are subordinated. However this may be, it assuredly does not make an accompanying demand that such controlling factor or factors shall reside wholly or predominantly in the chromosomes. The so-called "organism" standpoint, indeed, which as new facts come to light is appealing to more and more minds, would seem to tend rather toward conclusions just the reverse of this or of any that would seek to localize the adult morphology of a living organism in any special part of its antecedent germ-cell. A germ-cell, in fact, should need no special units to generate the peculiar *genre* equilibrium or idiosyncrasy of protoplasm which is distinctive of a particular kind of individual, since such a germ-cell not only is itself already an individual, but from the very fact of having had the same racial history as other individuals of its peculiar kind (be they germ-cell, embryo, or adult) it must likewise as a whole already possess this distinctive idiosyncracy.

The results of recent experiments on regeneration and regulation tend, in so far as they have bearing on ultimate organogeny, to emphasize the significance of an organism as a whole to its environment, together with its physiological coordination or interaction of parts. The results of such work seem to indicate clearly, as ably maintained by Child ('06), a fundamental physiological unity of the entire organism to account for which any purely "unit-character" basis of transmission is inadequate.

To express the phenomena of organic characters, it would seem that we must turn to a condition somewhat analogous to that with which we meet in chemistry in many organic compounds; and while the comparison is only an analogy, we might well remember that it is an analogy drawn from organic matter itself. For example, in many organic compounds we have certain fundamental groups of comparatively great stability, well illustrated in the so-called benzene ring. We can substitute for the hydrogens of this ring one, two, or many alkyl or other groups, thus producing different compounds. Yet these compounds have certain fundamental properties in common, due to the benzene ring.

While in living beings qualities must be looked upon as more or less flexible rather than absolutely static, with certain possibilities of blending, of gradational and of cumulative effects, still we must recognize more and less stable coordinations. But even in this matter of flexibility chemical and physical analogy does not forsake us, for we find many analogous examples of similar flexible or gradational combinations, in which the components may establish any proportional relation one to another, depending upon external factors. This is best evidenced in solutions, and especially in certain solid solutions. Moreover, in phenomena of "dynamic isomerism," in changing substances of the same chemical composition but of different structure one into another, we can get a condition of equilibrium between the two at any point, the condition of this equilibrium depending upon temperature, pressure, and concentration. Again, in allotropic forms of such substances as sulphur, phosphorus, tin, etc., various conditions of stability can be brought about in different ways.

6. Boveri's demonstration ('89, '95), that the denucleated egg of one species of sea urchin when fertilized with the spermatozoon of another species shows purely paternal characters, has been numbered among the proofs of the exclusive control by the nucleus of matters of heredity.

Both Seeliger ('95, '96) and Morgan ('95), however, have shown that even when the egg is not denucleated, still, in hybrids between the forms with which Boveri worked, the paternal type may occasionally predominate, to the apparent exclusion of the maternal type; that, in fact, Boveri's experiments may mean simply that in such cross fertilization the characters of the male species are prepotent over those of the female species. Furthermore, as just the converse of Boveri's results, we have Godlewski's ('05) observations that non-nucleated pieces of sea-urchin eggs, fertilized by sperm from a crinoid, produced larvae *exclusively of the maternal type.*

7. The apparent association of specific qualities of the adult with specific chromosomes is regarded as another support of the chromosome theory of heredity. The most noted example of this is the finding of a chromosome that is regarded as a possible sex determinant in certain tracheata.

We cannot enter here into a review of this intricate matter, a detailed discussion of which will be found in Professor Wilson's ('06) paper. While the whole question of whether sex is predetermined, or whether it may be determined after development has begun, remains almost as much of a puzzle as ever; still, if there is any truth in the latter alternative, the trend of experiment points mainly to the conclusion that nutrition is the chief factor in determining sex. Consequently, since of the insects exhibiting the "accessory chromosome" the females are characterized by the presence of an extra chromosome (or by a greater bulk of active chromatin in case idiochromosomes are present), we seem justified in asking that it be shown untenable that the production of females is due, not necessarily to special sex-determinants in the chromosome, but to the presence of more chromatin which has meant increased chemical activity on the part of the nucleus. In the few cases where the idiochromosomes are of equal size, however, purely quantitative relations are apparently inadequate as an explanation. But even here there may be a difference in intensity of chemical activity between the two chromosomes, since, in this group of insects, according to Wilson, there are indications of a tendency of one of the idiochromosomes to disappear ultimately.

The observations of Boveri ('02) on echinoid eggs which have been fertilized by two spermatozoa is also regarded by some as strong evidence that the nucleus is the real bearer of hereditary qualities. We must recognize, however, that in such cases as the production of three cells by means of a tri-polar spindle, for example, the cytoplasm of the sperm, scant as it may be, is also distributed among the three cells, as is also the substance of the spindles; so that the result is not three different series and combinations of chromosomes in three cells of similar protoplasm, but a series of chromosomes in cytoplasm, which itself differs in the three cells. Again, if the individual chromosomes differ only in that they produce different nutritive materials, or enzymes, then we might expect different and abnormal results from different blastomeres, since the cytoplasmic mechanism could only react on or be stimulated by the substances distributed to it. Thus absence of parts in a portion of the body developed from a blastomere in which an insufficient number of chromosomes is present might well be expected, and the whole phenomenon is as easily interpreted to mean that, considering nucleus and cytoplasm as of coordinate importance in inheritance, a proper reaction has been prevented or that insufficient material was present. as to regard it as a demonstration of the exclusive importance of the nucleus in heredity.

Lastly, inconstancy in the number of chromosomes in closely allied forms argues against the idea that we shall ultimately be able to associate specific characters of the adult with individual chromosomes. The numerical differences would seem to be out of all proportion to the actual differences between the adults of the species or genera showing such discrepancies.

On the other hand, if we find closely allied genera or species with chromosomes very constant in number and appearance, even should they have no causal connection with the phenomena of heredity, one need be no more surprised than at finding close similarity among any other organs in closely related species. It might be argued, indeed, with some plausibility, that the number and arrangement of the chromosomes in a given species are the effects of the fundamental constitution of a given kind of living matter, rather than that they stand in a specifically casual relation to such constitution.

By way of final summary with regard to the proposition that the chromosomes are the exclusive vehicles of heredity, we may, I think, deny that a satisfactory case has as yet been proven. While the jumble of facts which have been determined so far may not negate the theory, still we are not justified for that reason in maintaining that they substantiate it, especially when most of the facts are so Janus-faced as to be of equal utility in confirming other hypotheses.

The important fact always confronts us that a given kind of protoplasm is a protoplasm peculiar to the organism of which it forms a part, whether the latter be amoeba or man, and the egg as a whole, both cytoplasm and nucleus, therefore, has its own individuality. Hence no special formative force has to change it into a specific kind of protoplasm before the more obvious morphological entities can become manifest. Heredity is a problem of the handing on of metabolic energies already established, rather than of the transmission of a series of determinative units which create a wholly new organism. We can see that in so far as the substances constructed by the nucleus are peculiar or individual, the number of structures the cytoplasm can shape from such material or form in combination with it has been restricted, and in this sense the nucleus has conditioned heredity. But because the three elements, carbon, oxygen, and hydrogen, condition substances of which they are components, we do not postulate a specifically determinative substance in any of them for each of the numerous carbohydrates and carbohydrate products that result from their various combinations and arrangements. What the chemist seeks to determine are the quantitative and other physical relations necessary to the establishment of a certain molecular configuration. Likewise, what we seek in heredity are the shaping and controlling factors which bring materials into place that they may combine in the proper way and at the proper time. This much is certain: no chemical, physiological, or morphological evidence is yet extant which places these factors wholly within the chromosomes.

I do not desire to minimize the importance of the chromosomes in heredity, and I think no one would deny that they may stand in definite causal relationship to adult characters. On the other hand, I see no sufficient reasons for denying that other germ-cell constituents may, in the same sense, stand in causal relationship to such characters. In these initial substances, however, I see no more necessity for postulating specific anticipatory characters (beyond the properties which makes a given substance a substance *per se*, irrespective of the structures into which it may ultimately be builded) than I do of regarding yeast, or flour, or milk as in itself a specific determinant of a loaf of bread. While the net results may be in large measure the same, whether we accept the rigid "determinant" idea or whether we adhere to a more neutral qualitative basis, there are certain elements of freedom in the latter conception, I think, which render it a safer foundation for unbiased investigation of the problems of heredity. I would plead, therefore, not for the abandonment but for the maintainance of other working hypotheses as our greatest safeguard.

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