THE ELECTRICAL FORCES OF MITOSIS AND THE ORIGIN OF CANCER

BY A. E. AND A. C. JESSUP, E. C. C. BALY, F.R.S., *Fellow of University College, London*, F. W. GOODBODY, M.D., M.R.C.P., AND E. PRIDEAUX, M.R.C.S., L.R.C.P.

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Professor Hartog has recently brought forward the interesting suggestion that the phenomena of mitosis, that is to say the well-known mitotic figures, are due to the existence of a dual force, as for example, a magnetic or, better, electrical type. Without pre-judging its nature, he calls this force mitokinetism. He introduces the conception of relative permeability in elucidating the behaviour of this dual force in comparison with the phenomena of magnetism. He goes on to say that as the cell structures are all material the conception of geometrical lines of force is adequate to explain them. He says that the effect of stresses within a mixture of substances which are of different permeability and free to arrange themselves will be to segregate out the more permeable material in strands along the lines of force. While the idea of an opposite polarity is reasonable, it is difficult to accept the polarity as being magnetic in any way, because there does not seem to be present any mechanism whereby magnetic stresses are to be produced. On the other hand, the substitution of an electrostatic difference of potential for the magnetic removes these difficulties, for it would appear that in the configuration of the protein material we have at hand all the necessary conditions for the establishment of such charges. The -NH-CO- linking which, from a physico-chemical point of view, is both acid and basic in character, or, as usually called, amphoteric, possesses residual affinity of two opposite types, and it is in the existence of these two types that we can obtain the mechanism for the establishment of electrostatic difference of potential. Although in the cytoplasm and centrosome we can find an analogy with the solvent and the dissolved and ionised salt in inorganic chemistry, yet it must be remembered that in the organic cell the phenomena must be those of colloids, and for this reason we are somewhat hampered by ignorance of the nature of colloidal substances. It is possible, however, to develop a theory that electrically charged colloids play a very important rôle in mitosis, a theory which leads to some very interesting results. When a crystalline salt, as, for example, sodium chloride, is dissolved in

water the residual affinity of the water molecules causes them to condense round and form loose hydrate compounds with one or both of the sodium and chlorine portions. The lines of force due to the chemical combination of the sodium and chlorine are thereby weakened, and by virtue of their velocity of movement by diffusion the two ions get separated, becoming at the same time seats of positive and negative charges respectively. In an analogous fashion the cytoplasm can resolve a discrete molecule or complex of molecules of amphoteric type into two oppositely charged portions. The cytoplasmic mass can, by virtue of its two types of residual affinity, form loose compounds with the two portions of the simpler compound. The lines of force between the two will be weakened, and the two portions can be separated and become seats of positive and negative charges respectively. It appears, therefore, a justifiable assumption that electrostatic differences of potential are established during mitosis and that the two centrosomes represent the location of two of these charges. Very much the same reasoning may be applied to the chromosomes or chromatin granules; these, by the same process as detailed above, can become resolved into two oppositely charged portions. Without in any way assuming that these differences of potential cause the phenomena of mitosis to occur, it is very difficult to believe that they are not produced when mitosis does occur. How far they act as the *causae causantes* is not determinable with any certainty in the present state of our knowledge of the vital processes, but our knowledge of the chemical and physical properties of the protein configuration leads us to the standpoint that the resolution of the centrosomes and chromatin granules must be accompanied by the establishment of definite electrostatic differences of potential.

If now we consider the probable influence of the lines of force between two oppositely charged bodies upon a colloidal mass it will be seen that the colloid will tend to coagulate. The well-known coagulation of colloids in the presence of an ionised salt is now attributed to the alteration in their surface tension by the lines of force between the ions passing through the surface. If the view be accepted that a colloidal solution is due to the existence of a negative surface tension, that is to say, a tendency to form as great a surface as possible, the penetration of that surface by the lines of force between the ions becomes at once comprehensible when a colloidal and ionised solution are mixed together. Applying this view to the prophase of mitosis, the penetration of the nucleus by the lines of force between the centrosomes will cause the coagulation or partial coagulation of the chromatin in the chromosomes,

a coagulation which will increase, the greater the number the lines of force which pass through the nucleus. This perhaps gives a reason for the condensation of the reticular structure in the chromosomes in the earliest prophase of mitosis.

To deal next with the chromosomes themselves. There is little doubt that these consist of discrete particles or granules of chromatin, and, in all probability, each of these is resolved into two daughter particles charged with positive and negative electricity respectively. The chromosome, by virtue of the splitting of each of its particles into two, forms two daughter chromosomes, one charged with negative and the other with positive electricity. It may be argued here that the splitting of the chromosomes occurs at a much later stage than the commencement of separation of the centrosomes. This, however, would be the result of the fact that during the earlier phases the chromosomes are coagulating; for it is not likely that the resolution of the material can occur until the coagulation of the granule into a discrete particle with a definite surface has taken place.

FIG. 1.

The first stage of somatic mitosis would, therefore, appear to be the resolution and separation of the centrosomes with their definite, equal and opposite charges of electricity. The lines of force between the two centrosomes as these lines penetrate the nucleus cause the coagulation or condensation of the chromosomes. The next stage is the resolution of the chromatin granules, each into two daughter particles of equal and opposite charge, and this is eventually followed by the splitting of the chromosomes. The first evidence of an incipient splitting of the chromosomes will be their polarisation; that is to say, each chromosome will be half positively and half negatively electrified and will tend, therefore, to move and take up its position in the equatorial plane of the mitotic figure (as in fig. 1).

The next change in the mitosis will be the actual parting of the

chromosomes into two daughter chromosomes, which by reason of the electrostatic attraction will migrate to the oppositely charged centrosome. When the daughter chromosomes arrive at the centrosomes the electrical charges will be neutralised. It is necessary to assume that the charges are entirely neutralised, for if there remain a balance of positive or negative electricity, this will tend to mount up in successive divisions—a condition which it is quite impossible to accept. We are, therefore, bound to take the view that the sum of all the charges on one set of daughter chromosomes is equal and opposite to that upon one centrosome, and that perfect neutrality of charge is established at the end of each somatic mitosis. When the lines of force cease to exist, each chromosome tends to become again de-coagulated. It at once begins to increase its surface, which it does by means of growing processes which extend until the whole nucleus appears to all intents and purposes structureless. The chromosomes, however, must preserve their individuality, although their processes appear inextricably intermingled. The application of the lines of force due to the commencement of a new mitosis will at once cause each chromosome to contract and condense until it exists once again as a dense individual, capable of being highly stained.

We have not considered as yet several of the attendant phenomena of mitosis; for example, no reason has been advanced for the separation of the centrosomes, the formation of the spindle figure, and also the disappearance and the reappearance of the nuclear wall.

Considering first the separation of the centrosomes, which appears to us to be the most important feature of mitosis, it must be remembered that in the analogous case of ion formation in aqueous solution the separation of the ions is due to diffusion. But this is quite inapplicable to the present case. It is equally necessary, however, to postulate some definite influence which separates the centrosomes—an influence which is stronger than and quite apart from the electrical forces: for these would naturally tend to draw the two centrosomes together. In other words, the electrical force cannot be the *causa causans* of mitosis, but must be a concomitant phenomenon. This fact cannot be too strongly insisted upon, for although the conditions of a living cell would seem to be such that the vital units must become resolved into two oppositely charged masses, yet unless some definite and separate stress were present, the two oppositely charged masses would lie side by side without any electrical influence on their surroundings. As stated above, the resolution into oppositely charged masses is the natural result of loose combination between the vital unit

and surrounding medium, and, again, these loose combinations are themselves the result of the chemical structure of the cell materials. These loose compounds must play a very important part in the general life of the cell, as, for example, in the growth of the chromatin. There is no doubt a strong separative force at work—a force which would appear to be connected with the mass division of the cytoplasm. It would seem that this mass division is an inherent vital property of living cytoplasm; and we incline to the view that it is the real *causa causans* of mitosis, and that the phenomena described above are produced by the mass division taking place. There is a sound foundation for our view, for it has been shown that the periodic activity of cytoplasm is independent of both nucleus and centrosome. For example, in the case of a fertilized egg divided into two portions, one of which contains the nucleus and the other not, the behaviour of the enucleated portion is most remarkable. It forms three times in succession a polar lobe at the same time that the nuclear half is dividing, becoming spherical after each period without dividing. At the fourth cleavage a fourth lobe is formed, which is not re-absorbed but grows steadily larger, so that the fragment appears finally to be divided into two. The activity of the enucleated half is thus not merely rhythmic in character but changes in character at the fourth cleavage when in normal development the polar lobe no longer forms a temporary structure but is permanently cut off by cell division. The cytoplasm, therefore, would seem to possess a power of mass division—a power which is also periodic in its action, its periodicity no doubt depending upon the cytoplasm reaching a certain stage of development during the vegetative period of the cell. The existence of this power of mass division possessed by the cytoplasm gives a reasonable explanation for the separation of the centrosomes. When the period has been reached, the first feature of the phenomenon is the resolution of the centrosome from the previous division into two oppositely charged centrosomes. When the mass division begins the axis is determined by the position of the centrosomes, so that they are drawn apart. The electrical forces brought into play cause the condensation or coagulation of the chromosomes, their resolution and migration, and, finally, when the mass division of the cytoplasm is finished the formation of two daughter cells. By the statement that the axis of mass division is determined by the centrosomes we mean that the two daughter centrosomes are separated, because one must be in each daughter mass of cytoplasm. This fact cannot be a matter of chance, for if it were so, many more divisions of cytoplasm

would occur than mitoses of the nucleus, which is absurd. It is a natural sequence that the line of cleavage of the cytoplasm is determined by the centrosomes. This would seem to be the normal order of events in any mitosis, but there is no reason why certain minor details should not be altered either as regards their character or their position in the scale of operations. Such variations need not, and do not, militate against the electrical theory in any way. For example, in many cases the centrosome in the daughter cell divides immediately after the mitosis is finished in readiness for the next division. All that the theory demands is that the centrosome divide into two; the period at which this occurs is not of any moment, but the fact that is of the greatest importance is that the two new centrosomes never get separated except during mitosis, and then only with the formation of the spindle figure.

In reference to the statement that the axis of the mass division is determined by the centrosomes, O. and R. Hertwig¹ and also Roux² have noticed that as a rule the plane of division of a non-spherical cell is at right angles with the direction of the greatest diameter or extension, and Driesch has shown that if the newly fertilized egg of the sea urchin be gently pressed under a cover glass, so that it is slightly flattened, the plane of division is at right angles to the slide. The position of the plane of cleavage is determined by the position of the nuclear spindle, and this depends upon the position of the centrosomes. Moreover, in the process of cell division the egg of some animals becomes elliptic with the long axis falling in the direction of the common diameter of the amphiaster. This has given rise to the idea that it is the spindle itself which elongates the egg, but Loeb³ has often noticed that the elongation, though in the direction of the spindle, always occurs immediately before the cell division.

Again, the possession by the cytoplasm of a power of mass division will give an explanation of the phenomenon of streaming which is observed during mitosis, for the streaming will merely be the flowing of the cytoplasm from the cleavage plane into two daughter masses. Inasmuch as the sum of the masses of the cytoplasm of the two daughter cells is less than that of the mother cell, it at once suggests itself that the mass division is caused in the first place by a loss of water from the periphery of the cell by osmosis.

1. *Untersuch. zur Morphol. und Physiol. der Zelle*, V, 1887.

2. *Breslauer Arzt. Zeit.*, 1885.

3. Loeb, *Dynamics of Living Matter*, p. 64. Columbia University Press, 1906.

To give an explanation of the formation of the asters and spindle figure of mitosis is not easy. The natural view to take would be that these are due to the coagulation or condensation of the cytoplasm along paths parallel to the lines of force, using the same argument as in the case of the chromosomes above. Furthermore, it is quite true that in many cases the mitotic diagrams present great similarity with the lines of force between oppositely charged bodies. This view has been previously advanced by A. Fischer.¹ In certain cases, however, the rays from the two asters appear to cross one another—an effect which is impossible if they are simply due to lines of force. But it may be that this is only an apparent effect due to the point of view of the phenomenon. If this be a real crossing it is clear that the rays cannot be due to threads of coagulated cytoplasm; although it might be possible to look upon them as direct growths from the centrosomes, yet the former explanation would seem far more reasonable, provided that the difficulty as regards their crossing one another be surmounted. Of course it must not be forgotten that the separation of the centrosomes by the mass division of the cytoplasm will induce stresses which may disturb the position of the threads. On the whole the evidence would appear to support the view that the mitotic figures are due to the coagulation of the cytoplasm under the influence of the lines of force.

In the present state of our knowledge of the chemistry of cell physiology it is impossible to account for the disappearance of the nuclear membrane during mitosis and its reappearance after the process is finished. We might say that the membrane is due to a definite chemical reaction between the nucleic acid and the cytoplasm, and that this reaction is reversed under the stimulus of the lines of force, so that the membrane disappears only to reappear when the force lines die away; but this can only be pure hypothesis.

We may next turn our attention to the maturation divisions of the germ cells, and investigate the relations which exist between the electric charges in these cases. The results obtained are peculiarly interesting, inasmuch as it seems absolutely certain that complete electrical neutrality does not, and cannot, result from these divisions.

The first fact which we are met with in these divisions is the fusion together of the chromosomes in pairs to give the meiotic gemini. In order to account for this and bring it into line with the other phenomena it is necessary to assume the existence of some form of polarity difference

1. *Fixierung, Färbung und Bau des Protoplasmas*, 1899.

between each of the two individual chromosomes, which fuse together to form the gemini. All recent cytological research leads to the view that in each case it is one paternal and one maternal chromosome which fuse together, producing a bi-polar twin; and, moreover, that it is not any chance pair which fuse together, but there exists some type of selective pairing between paternal and maternal chromosomes. For this pairing there must exist in the cell some opposite polarity between the two members of each twin—a polarity which may well be of electrical type. This would point to the existence of some difference in electrical charge between the paternal and maternal chromosomes which comes into play during the long resting period of the germ cell. That an electrical attraction can be produced between paternal and maternal chromatin in the germ cell follows readily from the general theory, but its consideration may be postponed for the moment. It must be confessed that the phases of the phenomena of maturation divisions differ so much according to various observers that it is impossible to deal with more than what appear to be the most typical cases; and we must content ourselves with pointing out how the general relation between the charges is not altered in any of the cases observed.

The simplest case to deal with is when no tetrads are formed and when the first maturation division takes place between the split halves of the meiotic gemini, while the second division is a somatic division of the reduced number of chromosomes. It is necessary, in order to follow out the distribution of the charges in the maturation divisions, that the relative values of the charges upon the centrosome and chromosome be considered. Beyond the bare statement that it is essential that at the end of each somatic mitosis the charges upon the centrosomes must be neutralised by the chromosomes nothing has been stated as to the relative values of the charges. The establishment of electrical neutrality at the close of each somatic mitosis is of a very great importance, for if by some means or other the charges were not neutralised entirely and a small amount were left over in the daughter cells, clearly this would go on mounting up steadily in successive divisions without any apparent limit. This is, of course, impossible of acceptance, and therefore we are driven to the conclusion, which is indeed the simplest, that complete neutrality obtains at the end of every somatic mitosis. We must therefore equate the charge upon each centrosome to the sum of the charges upon the daughter chromosomes, and in doing this it will be convenient to speak of the charge upon each centrosome as a unit-charge of positive or

negative electricity respectively. In the case, for example, of an individual with four somatic chromosomes, the sum of the charges upon the four daughter chromosomes which migrate to one daughter cell must equal the unit charge upon the corresponding centrosome. We therefore in this would expect the average charge upon each of the chromosomes to be one quarter of the unit charge, but it may be pointed out that there is no *à priori* reason why the charges on all the chromosomes should be equal in amount, the essential condition only being that the sum of the charges on them be equal to the unit charge.

Turning now to the germ cells we may say, as above, that a definite difference of potential is developed between paternal and maternal chromosomes; and let us say, merely for purposes of argument, that this difference of potential is half that carried by the chromosomes in somatic mitosis. If we continue to deal with the case of an individual with four somatic chromosomes, then we will assume the difference between paternal and maternal chromosomes in the germ cells as one-eighth of the unit-charge. This difference of potential will cause the fusion of the paternal and maternal chromosomes in pairs, which will be polarised, and carry at each end a one-eighth unit-charge of positive and negative electricity respectively. The result will be that the gemini will carry themselves across the equatorial plane of the spindle figure, with their ends turned towards the centrosomes, as in fig. 2.

FIG. 2.

When the gemini split again, and the two chromosomes migrate to the centrosomes, the charges will not be neutralised, but in each daughter cell there will be left a residue of electricity. When the meiotic gemini split they each give two halves carrying an eighth positive and negative charge respectively, and in fig. 2 the two positive halves migrate to the centrosome on the right and the two negative ones migrate to the centrosome on the left. When the two positive halves arrive at the negative centrosome they each bring a one-eighth unit, that is to say, one-quarter unit positive electricity altogether. Since the centrosome

carries a whole unit of negative electricity, we have one unit negative and one-quarter unit of positive electricity, which leaves a balance of three-quarter positive electricity. Similarly at the other side there will be left a residue of three-quarter unit negative electricity. On these lines it is clearly impossible for the charges to be neutralised in the daughter cells, for the only condition under which this could be secured is that the difference of potential between the paternal and maternal chromosomes was half a unit-charge, or twice as much as between the daughter chromosomes in the previous somatic mitoses. Such a large difference of potential is out of the question, for it would be impossible for such a charge to lie dormant through the various somatic divisions which occurred previously to the maturation divisions. We must conclude, therefore, that whatever may be the real value of the potential difference between paternal and maternal chromosomes, a residual charge is left in the daughter cells of the first maturation division, and at the same time point out that the smaller we assess the potential difference between paternal and maternal chromosomes in relation to the normal somatic charge, the greater will be the residual charge.

The next division is of the ordinary somatic type, but with this difference—that there are now only half the somatic number of chromosomes, and therefore only half the number of chromatin granules in each cell. It is quite evident, therefore, that in this somatic division the respective charges cannot be neutralised, for we have the whole mechanism of mitosis but only half the proper number of chromatin granules. Following out the case above, the reduced number of chromosomes is two, and each will give two daughter chromosomes, carrying one-quarter positive and negative charges respectively, which are the normal somatic charges for the individual in question. At the end of this mitosis there will be again a balance of charge left over, for in one daughter cell there is one unit positive charge and two one-quarter unit negative charges, leaving a balance of a half-unit positive charge; similarly, in the other daughter cell there is a balance of a half-unit negative charge.

A second case, which frequently occurs, is the formation of the tetrads, and in this case, as in the previous, the result is the same—a balance of charge must be left in the daughter cells. The formation of the tetrads is due, no doubt, to the somatic division of the chromosomes taking place before the first division has proceeded very far. Assuming, as before, the existence of one-eighth unit-charge upon paternal and maternal chromosomes respectively, the first stage will be the formation

of the bi-polar gemini. These gemini will again arrange themselves across the equatorial plate of the mitotic figure and then will begin to undergo the somatic resolution in readiness for the second division. Owing to the bi-polarity being most pronounced at each end of the twin chromosomes this resolution, under normal circumstances, should begin in the centre of each twin, which thus forms a ring, the procedure being of the true hetero-typical kind. This resolution, however, will be accompanied by the establishment of a positive and negative charge respectively on each side of the ring; and, in our case of four somatic chromosomes, this charge will in each case amount to one-quarter unit-charge. This ring formation is followed by the completion of the somatic splitting and the resolution of the gemini back again along the lines of the preliminary fusion. Each ring thereby breaks into four portions, which form the tetrads, and the two cell divisions rapidly take place in succession. The distribution and balance of charges follow exactly the same lines as before, with the establishment of three-quarter unit positive and negative charges in the two first daughter cells and the further establishment of a residual half positive and negative charges alternately in the grand-daughter cells. The only proviso that we must make as regards maturation by tetrads is that the two divisions follow one another in rapid succession with no intervening resting stage. This, however, seems quite a reasonable position to take up, viz., that when the somatic division of chromosomes takes place with the formation of tetrads during the first maturation division, the second maturation division must follow the first at once. If the somatic resolution does not take place, or only takes place incompletely, then the charges will be the same whether there is a resting period between the two or not.

Before discussing the result of the establishment of the residual electric charges in maturation, it may be pointed out that the hetero-typical resolution of the meiotic gemini with the formation of rings will only take place when all the chromatin granules in each twin are perfectly uniform. We might readily imagine that the chromatin granules in one paternal chromosome, for example, are weaker in character than those in the maternal chromosome with which it fuses to form a twin. In this special case the ring would not necessarily be formed when the somatic split took place, but rather, a body of the form:

or

Moore and Arnold have described various forms of these gemini in the meiotic phases of many germ cells, and it would seem that if their existence be confirmed they can be explained by certain distributions of activity in the chromatin granules in the twins. They are, therefore, only of secondary importance as far as regards the phenomena under consideration.

It may be argued that the formation of residual charges might be prevented by the cytoplasm providing in each division centrosomes of just sufficient charge to meet the needs of such division. This, however, seems impossible of belief, for it would mean a variation in the power of the cytoplasm between very large limits in a very short space of time. Against this view, we would point out that the cytoplasmic activity of the germ cells at the time of maturation is exceedingly great, and, therefore, it seems in the highest degree unlikely that the resolving power should become half the normal value or even less, and, further, that it should vary. Although it may be said that we have arbitrarily assumed a difference of potential between paternal and maternal chromosomes and fixed it at one-eighth of a unit-charge, it must be remembered that whatever be the view taken of it, the establishment of residual charges is necessary, for only one somatic division of the chromatin granules occurs and twice the somatic number of centrosomes are brought into play. On these grounds alone, without making any assumption whatsoever as regards the existence of the potential difference between paternal and maternal chromatin being necessary to cause the preliminary fusion in pairs to form the meiotic gemini, it appears absolutely impossible for the residual charges not to be established in the maturation divisions. At the same time, as we have already shown, it is necessary to assume some type of difference of potential between paternal and maternal chromatin, and the existence of one of electrical type, as we shall presently show, is quite easy of acceptance, although its value cannot be directly estimated in the present state of our knowledge. If we, therefore, put this at half the somatic charge on the daughter chromosomes, that is to say, in our example of four somatic chromosomes, one-eighth of a unit-charge of positive and negative electricity on paternal and maternal chromosomes respectively, and follow out the mounting up of the residual charges in the maturation divisions, we arrive at the following values:—

In the first, or meiotic, division, the residual charges will be three-quarters of a unit positive and negative charge respectively, for the centrosomes each carry one unit-charge, and there are two chromosomes

with one-eighth charge on each. In one daughter cell we have, therefore:—

$$+1 + (-\frac{1}{8} - \frac{1}{8}) = +\frac{3}{4}$$

and in the other we have:—

$$-1 + (\frac{1}{8} + \frac{1}{8}) = -\frac{3}{4}$$

The second, or post-meiotic, division proceeds naturally quite independently of these charges, and as we have before shown, owing to there being only half the number of somatic granules, a further charge is established in each grand-daughter cell of half-unit positive or half-unit negative charge. To determine the total residual charges in the grand-daughter cells it is necessary to add the pre-existing residual charges in the daughter cells to those formed in the grand-daughter cells. To one pair of the latter, which carry a half-positive and negative charge respectively, we must add the three-quarter positive charge. To the other pair we must add the three-quarter negative charge, so that the total residual charges in each set of four grand-daughter cells are one-and-a-quarter positive, one-quarter positive, one-quarter negative, and one-and-a-quarter negative respectively. This is perhaps shown more clearly in fig. 3.

FIG. 3.

It may be pointed out here that the amount of the residual charges is entirely independent of the somatic number of chromosomes. We have, purely for purposes of argument, considered the special case of four somatic chromosomes. Exactly the same results and the same quantities of residual charges are obtained, as may readily be seen, whatever be the number of somatic chromosomes.

Now, in the case of the maturation of the ovum, only one of the

grand-daughter cells is utilised, the other three being rejected as the polar bodies; but in spermatogenesis each of the four grand-daughter cells produces a functional spermatozoon, so that we arrive at the interesting result that one of the spermatozoa is of the same type as the ovum and one of the exactly opposite type; while the other two are of an intermediary type.

Herein, in all probability, lies the secret of sex production and the explanation of Mendelism, for it would seem perfectly natural that if the ovum be fertilised with the spermatozoon of the same type, a female embryo will be produced; if with spermatozoa of opposite type, male; and if with either of the two intermediary spermatozoa, a heterozygote will be formed. We use the word heterozygote in the Mendelian sense, and would mean either a male embryo, which is not entirely male, but one with male characteristics predominating over the female; or female embryo in which female predominates over male. On the above lines, it is evident that the essential of sex is primarily established in the meiotic division, for it is here that the first residual charges are established. The post-meiotic, or somatic division, merely alters the proportion in which the male and female characters predominate.

These results afford a simple explanation of Wilson's¹ experiments upon the insect *Protenor belfragi*, without any assumption of selective fertilisation. The male *Protenor* possesses five chromosomes in its somatic cells, while the female has six, and as there occurs an irregular distribution of chromosomes in the spermatogenesis of the male, it is possible to follow the results of fertilisation with greater accuracy than in an ordinary case. Wilson finds that in the spermatogenesis the odd, or hetero-tropic, chromosome does not fuse with any of the other chromosomes, but passes bodily over into one of the daughter cells of the meiotic division. In the post-meiotic division this hetero-tropic chromosome divides as usual, so that of the four grand-daughter cells two give spermatozoa with three chromosomes and two give spermatozoa with two chromosomes. In the case of the oogenesis of the female, there is no irregularity, and the ovum possesses naturally three chromosomes. When the ovum is fertilised by a spermatozoon containing the hetero-tropic chromosomes a female is always produced, while if the fertilisation take place by one of the spermatozoa containing two chromosomes a male is always produced. Now, on the theory which we put forward, the male embryo receives two chromosomes from the spermatozoa and three from

1. *Science*, N.S., XXIII, p. 500 (1905).

the ovum, and when, therefore, the spermatogenesis of this individual takes place, the two paternal chromosomes fuse with two of the maternal chromosomes, giving meiotic gemini, leaving the third maternal chromosome over as the hetero-tropic one. When the splitting of the meiotic gemini takes place the two maternal portions go to one daughter cell and the two paternal portions to the other. The hetero-tropic chromosome being of maternal origin will go along with the two maternal halves of the gemini into the same daughter cell. It is this cell which, by virtue of its residual charge, has established in the female predominance, so that when one of its daughter cells fertilises the ovum the female will always be produced. Similarly, the other daughter cell of the meiotic division has male characteristics formed on it by its residual charge, so that its daughter cells always give male insects in fertilisation. Wilson attempted to explain these facts by means of attributing a female determinancy to the hetero-tropic chromosome, but owing to the thereby necessary existence of the male determinant, it became necessary to assume a selective fertilisation; this assumption, which, from first principles, seems improbable, is therefore rendered entirely unnecessary.

It is only right to point out that McLung¹ was the first to suggest from the investigations upon the accessory chromosome that the sex determinancy lies in the spermatozoa. To quote McLung's own words:— 'I must here also point out a fact that does not seem to have the recognition it deserves, viz., that if there is a cross division of the chromosomes in the maturation mitosis, there must be two kinds of spermatozoa regardless of the presence of the accessory chromosome. It is thus possible that even in the absence of any specialised element a preponderant maleness would attach to one-half of the spermatozoa, due to the qualitative division of the tetrads.'

The differentiation between the cells produced in the maturation division appears to give also the key to the problems of parthenogenesis. In the first type of parthenogenesis, as in *Aphis*, when only one polar body is formed the female only is produced. As we have already shown, the meiotic division establishes the sex of the cell, so that in *Aphis* the cell with the male character, established in it by virtue of its residual charge, is rejected as the polar body; the nucleus remaining contains the female character established in it, so that when this egg develops parthenogenetically a female insect must be produced.

1. C. E. McLung, 'The Accessory Chromosome: Sex Determinant?' *Biological Bulletin*, III, p. 43, 1902.

The second type of parthenogenesis, as occurs for example in the honey-bee, where fertilisation takes place by means of the second polar body, the egg always produces a male, while the eggs fertilised by these males always produce workers, which are, of course, female, but do not develop into queens unless specially fed during their early stages of development. On the theory of the differentiation between the four grand-daughter cells of the maturation division, the fertilisation of the ovum by the second polar body becomes at once comprehensible, for this polar body bears exactly the same relation, as regards its residual charge to the ovum, as does one of the spermatozoa; indeed, the polar body must be of male character towards the ovum, so that inasmuch as the fertilisation takes place within the one individual a male embryo is produced. This means that the female characteristic established by the first or meiotic division does not alter the actual relations between the polar body and the ovum, a view which is supported by the fact that the cleavage centrosomes arise from the cytoplasm of the ovum. Furthermore, inasmuch as the fertilisation is carried out under the aegis, so to speak, of the female dominance, the male produced will undoubtedly be heterozygote, moreover, heterozygote with an unusually large presence of female character. The spermatozoa eventually produced by a male of this type will clearly be of different character from those of the hypothetically true homozygote male. So far is the female character present that he cannot beget any but female offspring—a fact not at all incomprehensible if it be remembered that the queen bee is an unusually highly developed female. It is not surprising, therefore, that the females normally produced from the fertilised egg are undeveloped, and it at once raises the question whether they are all exactly the same. As a result of this explanation, it would be expected that the worker bees possess among themselves differences in their potential powers of development into queens. Indeed, it might be expected that the special feeding might fail in developing queens from a small percentage of the worker larvae. The important point, however, for the present purpose is the fact that the present theory gives a reasonable explanation of the fertilisation by the second polar body.

The point was raised above as regards the sex characters of the spermatozoa of the heterozygote male, and it was stated that the relations between the charges of the spermatids in each quartette would be altered. This deduction follows reasonably from the general theory, and if, for example, a male was heterozygote to the extent of three parts male and

two parts female, it is probable that the intermediary spermatozoa would be altered. It is quite conceivable, for example, that the spermatozoon, which in a normal case would give a heterozygote male, might be so far altered by being itself produced from a heterozygote as to become potentially female in character, so that, on fertilisation, a heterozygote female would be produced. On the average, a homozygote male and female would produce equal numbers of male and female offspring, but a heterozygote male would beget a greater proportion of female offspring.

Amongst the human race this may possibly account for the large predominance of male or female children which frequently occurs in certain families. Again, it is not impossible that the condition of health that the parent may be in at the time of maturation may influence the value of the residual charges in the grand-daughter cells. If the vitality were low, it might readily follow that the residual charges be reduced so far that the relative dominance be affected. This would account for the results of the experiments upon the feeding of one parent and starving the other in the case of certain amphibia, etc., when it was found that the sex of the stronger parent predominated in the offspring.

We have taken for granted in the case of the oogenesis of the female that the ovum is the one grand-daughter cell of the mother cell, which is the true homozygote female. Our reason for this is simply that it seems the most likely condition to occur, though there seems no valid reason why the other conditions should not obtain. Even if one of the other conditions were to take place, it would not materially alter any of the conclusions drawn above.

It must be remembered that the post-meiotic division tends to increase the residual charges in the resulting cells, and therefore it would follow that the fact of there being no further divisions after the post-meiotic one is due to the residual charges having already reached the limiting value. There naturally must be a limit to the power of the cytoplasm and chromatin in building up these residual charges, and, no doubt, this limit is reached in the post-meiotic division.

While it is by no means necessary, therefore, that the charges are of the actual value we have arrived at, yet the establishment of some type of residual charges seems an essential consequence of an electrical theory of mitosis, and moreover these charges can, in a satisfactory manner, give an explanation of the phenomenon of sex production.

Although it is probable in the main that the maternal chromosomes pass during the meiotic division into the female daughter cell, yet there

is no doubt that during the existence of the meiotic gemini, some re-distribution of the chromatin granules takes place. In order to account for the Mendelian distribution of hereditary characteristics, it is essential that the chromosomes formed by the splitting of the meiotic gemini be not necessarily the same individuals as originally fused together; there must be an interchange of the granules during the time of fusion, according to Dr. Vries's theory. This, however, does not concern the present purpose very much, for whether this takes place or not, no fundamental change in the relative charges will occur. It must be remembered, however, that any re-arrangement of the granules in the meiotic gemini will tend to decrease the potential difference between the maternal and paternal portions, and, therefore, the potential difference between the two chromosomes obtained when the gemini are split. From a consideration of the residual charges obtained in the first maturation or meiotic division, it is evident that the smaller the potential difference between the split chromosomes of the gemini, the greater the residual charge or sex determinance in the resulting daughter cell. This affords a reasonable explanation of the De Vries re-arrangement of the chromatin granules, viz., the decrease in the potential difference between the two halves of the gemini. For there is no doubt that the re-arrangement will take place, since such re-arrangement tends to decrease the potential difference. We may say, therefore, that the De Vries' re-arrangement of the granules is not a matter of chance; it is a direct consequence of the potential gradient existing within the bi-polar twin, and the number of individual granules which interchange will be determined by the steepness of this potential gradient. In other words, the greater the potential difference between the paternal and maternal chromatin, the greater the number of interchanges among the granules, and hence, also, the more pronounced become the sex characteristics of the grand-daughter cells.

Now there remain certain other facts in connection with fertilisation which are brought into co-ordination by this theory. In the first place we have the very profound changes which are induced in the cytoplasm of the ovum at the time of fertilisation. Space will not permit of our dealing with these in detail, but they can, in general, be explained by chemical and physical reactions taking place when the charge on the spermatozoon enters the ovum. It must be remembered that the density of the electric charge on the spermatozoon is very much higher than that on the ovum, owing to its being so excessively minute compared with the ovum, and the fact of its sudden introduction will be to cause a wave of energy to travel

through the cytoplasm. Again, the difference in polarity between the ovum and the spermatozoa nuclei will account for the different staining reactions which have at times been observed between the two, for a charge of positive electricity on a mass of protein material will increase its basicity, while its acidity will be increased by a negative charge. After fertilisation, as the charges become equally distributed, the staining reactions of the two nuclei will approach more and more nearly together.

Perhaps one of the most important results of this theory is that it leads to the view that the ovum and spermatozoon are both cells with residual charges established in them, and which cannot reproduce themselves of their own power, owing to these charges. The ovum, moreover, does not possess any material wherewith to form centrosomes and so start mitosis, while the spermatozoon, although it possesses a centrosome in the middle piece, has no cytoplasm to start the mitotic machine; when the two are brought together, the machinery is completed and mitosis can start, provided, of course, that the temperature is sufficient. We are, therefore brought to the conclusion that the chromosomes are individual entities, preserving their individuality all through each cycle, and that the centrosomes are of paternal origin. What the latter consist of, it is idle to speculate, beyond saying that they are, in all probability, discrete granules of protein, considerably simpler in character than the cytoplasm, which can be resolved by the cytoplasm into two parts of basic and acid type with a positive and negative charge respectively.

It follows that the fertilisation of the enucleated ovum will give rise to an embryo (with, of course, only half the normal number of chromosomes), this being the natural result of the theory. There is no essential need for both nuclei to be present, since the machinery is complete for mitosis when the spermatozoon enters the cytoplasm of the ovum. The converse of this, or the artificial fertilisation of an ovum, also follows, and is equally easy of explanation. The most striking case is that of Loeb, who succeeded in causing sea-urchin eggs to develop parthenogenetically by placing them in a solution of magnesium chloride. If a colloid mass be placed in a solution of an ionised salt, the osmotic pressure of the ions will be exerted upon the surface of the colloid. In time, as the water penetrates a little into the colloid, the ions, owing to their diffusion velocities, will tend to penetrate the surface. The velocities of the two ions, however, are different, so that one will always be very slightly ahead of the other, with the result that the surface of the colloid will tend to become electrified. Thus, when the eggs are put into

magnesium chloride solution the outer layers become electrified, and even though this effect be produced at only one small portion of the surface, yet, with the previously existing charge of the egg, it is enough to cause parthenogenetic development. The first result will be much the same as when the spermatozoon normally enters, viz., the same modification of the cytoplasm, which is doubtless due to the re-distribution of the charges. The production of the centrosomes would appear to arise from some portion of the cytoplasm which is coagulated, and, possibly, hydrolysed to a certain extent by the electrical and chemical stimulus given by the ions. The parthenogenetic development of the eggs of the silk worm noticed by Tichomiroff¹ on gently rubbing them with a brush is capable of the same explanation, namely, the electrification of the surface layers of the cytoplasm.

The question may be raised here as regards the continuity of the centrosomes through the life of any individual, and it may be pointed out that from the point of view of the electrical theory, there is no *prima facie* evidence why they should possess any continuity. The disappearance of the old centrosomes and the appearance *de novo* of another set is perfectly possible. They may arise from the old spermatid centrosome in the middle piece of the spermatozoon, or from one of the vesicles of the archoplasm. The same centrosome may go on dividing itself up continuously all through life, or at any period a new set may arise as far as the theory is concerned. It is not probable that any change in the centrosomes will arise after several generations of cell division have taken place, for the number of available particles introduced by the spermatozoon get fewer owing to their absorption or distribution. In the first few generations a new set of centrosomes might easily arise and, indeed, have been seen to do so.²

There is another point which may be mentioned, and which gives some support to this theory, namely, that the second polar body is sometimes not formed in the ovum until after the entrance of the spermatozoon, and, indeed, in *Chaetopterus*³ the first polar mitosis stops at the anaphase until the sperm has entered, when the mitosis is resumed and both polar bodies are formed. The explanation of these facts on the electrical theory is that the cytoplasmic power is not sufficient to carry out the maturation divisions and establish the residual charges. When the tension is relieved

1. Loeb, *loc. cit.*, p. 165.

2. *Morgan Rept. of the Amer. Morph. Soc. Science*, III (1896).

3. *Med. Journ. Micros.*, X, p. 1 (1895).

by the entrance of the spermatozoon then the division proceeds normally. This is a strong support of the view that polarity or stress is established by the maturation division and that it is relieved on the entrance of the spermatozoon.¹ Mead has noticed that the eggs of *Chaetopterus* throw out their polar bodies if a little iodide of potassium be added to the sea-water. This is quite analogous to the artificial parthenogenesis discussed above, for the influence of the potassium ions relieves the tension set up by the maturation divisions in the same way as does the spermatozoon, and the two divisions can complete themselves in the normal way.

Strong support for the electrical theory is also to be found in the fact that both males and females are rendered completely sterile by X-rays. The action of X-rays in breaking down the di-electric is well known, and in these cases of sterilisation by X-rays the cell material becomes a conductor and the residual charges are dissipated, with the result that both spermatozoa and ova are defunctionated. These facts offer the most striking support to the theory.

There remains now only to be considered the assumption made in the section dealing with maturation that a definite potential difference exists in the germ cells between paternal and maternal chromatin. As a matter of fact, there is no doubt that there is a considerable difference between the paternal and maternal chromatin, which may very possibly be established by the residual charges in the ovum and spermatozoon, for whatever may be the actual value of the residual charges produced in maturation, the greater density of charge on the spermatozoon relatively to that on the ovum must be borne in mind—a result which is due to the relatively minute size of the spermatozoon. It is possible that this difference may be the origin of the potential difference between the paternal and maternal chromatin in the germ cells, for though there is an equal distribution of the electricity tending towards neutrality at fertilisation, yet it is quite reasonable to suppose that perfect neutrality is not at once established, or, in other words, that paternal and maternal chromatin do not at once become identical. That it becomes so eventually in the somatic cells must indeed be the case, while it is not a great assumption to make that the potential difference is preserved in those cells destined to become germ cells. If this were the case, it is evident that there should be some differentiation between the somatic cell ancestors and the germ cell ancestors from the very beginning of the cleavage

1. *Lectures at Wood's Hole, Boston, 1898.*

nucleus. Indeed, Boveri¹ has found such a differentiation in *Ascaris* at the two-cell stage, for in the cell destined to give rise to the somatic cells there is evidenced a definite rejection at each division of some of the chromatin, while in those cells destined to form the germ cells this does not occur. It would appear from this that the casting out of some of the chromatin in the early somatic cells is the means adopted to establish the necessary complete neutrality between paternal and maternal chromosomes, while in the germ cells this neutrality is not established and the potential difference remains, but of too small an amount to make itself felt. As the individual grows, and the sex becomes established, the originally existing difference of potential would tend to become emphasised until it becomes sufficiently large to interfere with normal mitosis; the cells then enter their long resting stage only to emerge with the formation of the meiotic gemini.

An interesting point arises in connection with the fact that in the animal kingdom only one somatic division occurs after the reducing division. It is evident from the theory put forward of the electric residual charges that the establishment of these charges means a certain condition of stress, and it therefore follows that the work done by the organism in carrying out a maturation division must be greater than that in a somatic division. If we consider for a moment the driving force which works the somatic machine, we can clearly equate this to the integration or sum of all the small amounts of work done in each cell division. The energy used and the work done are undoubtedly commensurable and capable of expression in terms of some simple unit. There is no doubt, therefore, that the force available for any one cell division is limited, and it would appear that the limit is reached at the end of the post-meiotic division. The available force is not sufficient to carry out any further divisions resulting as they would in still further enhanced values of the residual charges.

It is no essential part of the theory here put forward that there should be one, and only one, division of the somatic type after the meiotic or reducing division. As we pointed out above, when this state of things occurs it would mean that the available energy is not sufficient to carry out another division—the limit has been reached. If, however, the stresses set up by the two maturation divisions were smaller in proportion to the driving force then the limit would not necessarily be reached at

1. Boveri, 'Befruchtung,' *Merkel und Bonnet's Ergebnisse*, 1891.

the end of the post-meiotic division, and thus further divisions would ensue until the limit is reached. The number of divisions following the reducing division should be proportional to the ratio of the driving power to the stresses set up in the reducing division.

In advancing our theory of the electrical forces of mitosis we have discussed the phenomena as present themselves in the higher animals wherein the sex characteristics are as marked and as differentiated as possible. Clearly we should find a completely graduated scale down from the animals with complete sex differentiation to the lowest organism where no sex differentiation exists at all. Following on the lines laid down in this paper we would say that the complete establishment of sex differentiation means the establishment of certain definite electric charges in the germ cells during maturation, and that the magnitude of these charges is such that only one post-meiotic division can occur. If the sex characteristics are not so strongly developed then the charges established in maturation will not be so great in relation to the driving force, with the result that more divisions will occur before the limit is reached.

We may form some idea of the evolution of sexual differences from the standpoint of the electrical theory without any assumption beyond those already made. The essential point is, of course, the first inception of the reducing division, why it first occurred and why the fusion of two cells carrying the reduced number of chromosomes takes place. If we consider a single living cell such as that of a unicellular organism with no very well defined characteristics (using the word in the hereditary sense), it is natural to imagine that this organism can reproduce itself by ordinary mitosis without any of the sexual phases. When, however, in the process of evolution more characteristics are acquired we at once expect a break in the continuity of reproduction. *When an organism possesses characteristics of opposite polarity it is an absolute necessity that a reducing division shall sooner or later take place.*

As long as the acquired characteristics are of the same type an organism can reproduce itself mitotically without difficulty, but when the chromatin granules or chromosomes carrying the characteristics show opposite polarity, a reducing division must occur, because sooner or later the difference of polarity between the chromosomes will reach a value sufficiently large to cause the fusion of them together to form the bi-polar twin. This will be followed by the so-called reducing division. Now

respectively.¹ If the distribution of charges be followed out for the ensuing divisions, it will be found that two of the cells formed always carry equal maxima of positive and negative electricity respectively, and there will continually be produced a constant ratio of neutral cells and cells with intermediate values of charge. Sooner or later the magnitude of the charges produced will cause the maximum charged cells to fuse together with the formation of new cells carrying $2n$ chromosomes, when, of course, the cycle begins again. The organism, therefore, will present the appearance of having two types of cell, one carrying $2n$ and the other n chromosomes. Some of the latter will from time to time fuse together to form new cells with $2n$ chromosomes, and so the cycle is complete. This state of affairs will be the natural result of the sex differentiation being very incomplete, or, in other words, when the hereditary characteristics have not developed the maximum possible difference in polarity. When this occurs we find the condition that, owing to the magnitude of the charges involved, only one post-meiotic division takes place, the cell being at once sufficiently charged for fusion or fertilisation by one of opposite type. *The whole difference between the various types of reproduction may therefore be summed up in the conception of sex differentiation, or of opposite polarity in the hereditary characteristics.*

It is also of some importance to note that as sex differentiation is increased the relative size of egg to sperm is increased. When the sex differentiation is small, or as we might say merely embryonic, there will be no difference in size or visible character of male and female cells. When the male and female chromatin begin to differ materially then we find a difference in the development of the two, the male becoming smaller than the female, until finally we arrive at the spermatozoon and ovum, where the ratio of size is very marked indeed.

In the development of the above argument we have attributed the variation in the number of post-meiotic divisions, i.e., divisions between the reduction and the ensuing fusion, to the ratio between the driving force and residual charges established; the greater this is, the greater the number of post-meiotic divisions. We have introduced the conception of driving force merely to illustrate our point, and would now deal with this conception in more detail and consider the relation of the chromatin to the surrounding nucleic acid. There is no doubt that during the resting period between two successive divisions the chromatin must be growing

1. Exactly the same relative values are obtained, whatever be the size of the residual charges.

by means of chemical reactions between itself and the surrounding nucleic acid. Indeed, we may go so far as to say that unless this growth occurs any somatic division is not possible, for such division would result in a decrease in the active mass of chromatin in the daughter cells, a consequence impossible to accept. Now from a physico-chemical point of view it is evident that any reaction between chromatin and nucleic acid must be based upon some essential points of similarity in structure between the two, and it would seem a natural deduction to make from this standpoint that any influence tending to decrease the similarity between the two would retard the growth of the chromatin at the expense of the nucleic acid. Hence it is quite a natural sequence that a decrease in the similarity would tend to act as a deterrent to mitosis. The establishment of the residual charges in the maturation divisions, of course, means a considerable modification in the chromatin of the daughter cells, i.e., a considerable decrease in similarity between the chromatin and nucleic acid, so that we finally arrive at the conclusion that the establishment of the residual charges is a direct deterrent to mitosis. Hence the failure in the animal kingdom of the daughter cells of the post-meiotic division to undergo further divisions may be explained at once by the fact that the residual charges prevent the growth of the resulting chromatin, so that no reason or scope for division exists.

We arrive, therefore, in this way at a very definite foundation for the assumption made previously that the number of post-meiotic divisions depends upon the ratio of driving force to amount of residual charges established, for we find that the driving force is essentially determined by the growth of the chromatin during the so-called resting period. The influence of the amount of differentiation between male and female characteristics upon the number of post-meiotic divisions follows very clearly from this view, for, as several times pointed out, the amount of residual charge in the meiotic division depends directly upon this differentiation, or, as we would now state the law: *The greater the number of different hereditary characteristics of opposite type the greater is the dissimilarity between the chromatin and nucleic acid in the grand-daughter cells of the reducing divisions, and hence the fewer the number of post-meiotic divisions.*

It may be stated here, parenthetically, that whatever view be taken of the method by which the chromatin grows or the period at which the growth occurs, the same conclusion is arrived at: that if the growth be stopped then mitosis cannot occur.

It is impossible to enter fully into the various types of reproduction which are known to occur, especially in the vegetable kingdom, but there seems no doubt that they all are capable of explanation on the theory here put forward. We have dealt with the case of the unicellular organism with no sex characteristics, those cases in the vegetable kingdom where incomplete sex differentiation exists, and the zoological cases where the sex differentiation is complete with the two sexes as distinct as possible. All other cases seem only to be intermediate between the first and last.

A very important corollary must be added to what has been said above upon the reducing divisions. At the completion of this division there is established a definite amount of residual charge in the daughter cells. In other words, a certain amount of energy is stored in the cells, and this must result in the vitality of the cell being increased. This fact is very important, for it would seem that the reducing division forms a means by which the vitality or activity of the cells is renewed, for there is no doubt that a considerable amount of energy is absorbed at the time.

Hitherto we have made the tacit assumption that the phenomena described are those occurring in the mitosis of normal healthy cells. The question now arises as to what would happen if the electric charges in the somatic cells were disturbed by some means, and the equilibrium between them upset. It is very evident that important changes in the phenomena might take place, and it has occurred to us that the various types of malignant growth might very readily be explicable by their being due to the derangement of the electrical forces present during mitosis. On studying the experimental results obtained in this field we were very forcibly struck by the support given to our idea, and we feel more than justified in offering this as a reasonable explanation of malignant growths, viz., that they are due to abnormal cell reproduction arising from a disturbance of the electrical equilibrium of mitosis.

One of the simplest methods of causing a disturbance of the electrical equilibrium in the cell is by the external application of an electrical stimulus. If, for example, a somatic cell was given an added charge, i.e., if the cell wall by some means were electrified, a natural sequence would be an artificially produced multi-polar mitosis as already described in the fertilisation experiments of Boveri and Loeb above. Furthermore, the daughter cells produced as a result of such mitosis will naturally have a balance of positive or negative electricity left in them, owing to the result of the asymmetric distribution of the chromosomes. Since there is no means of dissipating these residual charges, the effect of a

single initial external stimulus will be handed on from generation to generation of daughter cells. There is no doubt that the periodic activity of the cytoplasm resulting in its mass division would not be interfered with by the small external stimuli referred to. The mechanism of the cell mitosis would be the same in the main, but owing to the excess of electrical energy multi-polar and asymmetric mitoses must result.

Now, multi-polar and asymmetric mitoses are frequently observed in malignant growths, and, indeed, Galeotti has artificially produced asymmetric mitoses in Salamander cells by treating them with certain chemical substances.¹ These substances undoubtedly acted as a stimulant to the cell either by electrification of the cell walls by virtue of the different velocities of the ions, as already shown in the case of Loeb's experiments, or by more purely chemical means. That the action of an external stimulus is capable of producing these two pathological mitoses in cancer, by which term we understand all malignant neoplasms, is thus evident. Waller² and others have shown that electrostatic differences of potential are a normal result of any external stimulus being applied to healthy tissue, and whether we accept Loeb's³ explanation or not that the effect is due to the migration of hydrogen ions, still the fact of sufficient potential difference being set up to deflect a galvanometer is completely established. It is possible, therefore, that an external stimulus, as for an example a bruise or blow, could induce sufficient electricity to derange all the neighbouring cells, that is to say, a sufficient electric stimulus could be established to start pathological mitoses. It would thus appear that, provided the necessary conditions were existent, a blow or bruise could give rise to a malignant growth. It stands to reason that the more healthy is a cell and the stronger its vitality, the greater will be its resisting power against the effect of an external stimulus. Conversely, the lower the vitality of the cell the more liable it becomes to derangement. There is no doubt that, speaking generally, the vitality of cells must decrease with their age, so we would expect the tendency to malignant growths to increase with age; in other words, we have herein a direct explanation of the age incidence of cancer. The actual change which takes place, and which we have spoken of as a decrease in vitality, would be due partly to a decrease in the active growth of the cytoplasm and partly to a decrease in the active growth of the vital units or chromatin

1. Beib. 3, *Path. Anat.*, XIV, 2 (1893).
2. Waller, *Signs of Life*, p. 143.
3. Loeb, *loc. cit.*, p. 68.

granules. Whereas in a healthy cell the mitotic phenomena are due to forces which are periodically brought into play, so a decrease in these forces will tend to weaken the vitality of the cell. We have shown, also, that the possibility of mitosis is dependent upon the growth of the chromatin, and as this certainly will decrease with the age and differentiation of the cell, so the vitality of the cell will decrease with age. We therefore have two causes for the decrease in the vitality of a cell.

It is not possible in the present state of our knowledge to advance any definite chemical theory for the change which is developed with age, but it is fairly certain from cytological investigations that a stage is reached when the cytoplasmic power is not sufficient to resolve the centrosomes and chromosomes with the formation of the mitotic figures, and then amitotic division may and does frequently occur. It may, however, be concluded that the occurrence of amitosis is due to the fact that the active growth of the chromatin has fallen to a value below the limiting value for mitotic resolution of the chromatin granules while the cytoplasmic activity is sufficiently great to cause the mass division to take place. We have already directly connected the decrease in vitality of the cell with the occurrence of cancer, so the occurrence of the amitotic divisions of cancer cells is easy to understand. As already pointed out, the age incidence of malignant growths is the natural sequence of the fact that the somatic cells must reach a certain critical minimum of vitality before they can be disturbed by any external stimulus. We may for the present purpose give the name of the n th generation to that generation at which the cells reach the critical minimum, i.e., when their vitality has fallen low enough to be susceptible of disturbance by the external stimulus. It is of some importance at this point to notice that when any tissue is subject to continually repeated abrasion or irritation, the resulting continuous renewal of tissue will cause the n th generation to be arrived at somewhat earlier than would otherwise be the case. From Waller's experiments it is a natural sequence that any irritation or stress should tend to produce an electrical difference of potential. This would seem at once to account for the occurrence of malignant growths in those parts of the body which are subject to such stresses.

Hitherto we have been considering the derangement of a cell by external stimulus, but it is also possible that derangement may occur internally.

If we consider the case of a cell which is highly differentiated, and, moreover, one the vitality of which has sunk very low, it is evident on

first principles that the potential difference, actually set up when the vital units are resolved, has fallen to a very small value. This decrease in activity, sooner or later, as we have before pointed out, results in amitotic division. This occurrence of amitosis, however, demands that all the chromatin granules must be at a low ebb of vitality. The formation of the loose compounds between the nucleic acid and the chromatin granules must, to all intents and purposes, have ceased, or, in other words, the growth of the vital units has become very slow. It is not essentially necessary, however, that every single chromatin granule of the cell decrease in vitality at the same rate, and the question arises as to what would happen if the vitality of the various granules differ considerably within a single cell. If we consider for a moment the effect of inbreeding and hybridisation, it is perfectly evident that by far the most probable condition is the one specified, namely, a considerable variation in vitality among the granules of chromatin within each cell. Clearly this gradation of vitality among the chromatin granules can give rise to a derangement of the electrical equilibrium in mitosis, as can be seen from the following. Whereas in the normal mitosis of a healthy somatic cell the chromosomes give daughter chromosomes of equal and opposite charge, and as in true amitosis the chromosomes are not resolved at all, in the present case a condition may arise when some of the chromosomes are resolved while the remainder are not so resolved, owing to the vitality of the granules of the latter being very much lower than that of the granules of the former. These latter chromosomes would only be polarised, and therefore would not migrate to either centrosome; a fusion of the electrified daughter chromosomes with the polarised chromosomes would naturally ensue, and an asymmetrical mitosis would take place, with a reduction in the number of chromosomes. This would again cause a balance of residual electric charge in each daughter cell, exactly in the same way as occurred in the case of the external stimulus described above.

Further, it must be pointed out that the age incidence would apply to this condition just as much as to an ordinary cell, for the derangement is caused by the vitality of the weakest granules falling below the minimum value and also by a general decrease in the activity, both being the normal results of the age of the cell. To assume for the moment that this condition of chromatin granules is possible, we may now re-state our case as it stands. An electrical theory of mitosis at once renders possible abnormal mitosis by reason of the electrical charges becoming disturbed. The electrical theory of mitosis in itself receives very considerable support

from experiments upon artificial fertilisation, from parthenogenesis, from sterilisation of the ova and spermatozoa by X-rays, etc. The disturbance of the balance of electrical quantities in the cell may arise from the application of an external electrical stimulus arising from a blow or from considerable and repeated irritation or stress. It may also arise internally in the cell from a certain number of the chromatin granules being of such a character that they do not give daughter granules with sufficiently different charges. In both cases the result is the same. The normal equilibrium between the charges is disturbed and asymmetric and multipolar mitoses occur, producing daughter cells with a reduced number of chromosomes and a residual positive and negative electrical charge. The tendency to both these disturbances is increased with the age of the cell.

The main point we have arrived at is that when derangement of the charges occurs, the daughter cells are produced with a balance of positive or negative electricity and that this is accompanied by a reduction in the number of chromosomes. It is, therefore, extremely interesting that Farmer, Moore and Walker¹ claim to have discovered that a true reducing division occurs in malignant growths; that is to say, a division of the same type as the first maturation division of the germ cells. Although these results are still *sub judice*, yet the existence of cells with fewer chromosomes than the normal somatic number seems fairly well established. The condition of chromatin granules such as we have postulated would give rise to cells containing any number of chromosomes between the somatic number and half that number, and would not necessitate a true reducing division. For this reason we would give the name of *pseudo-reduction* to this process.

As was pointed out before, in dealing with the reducing division in the vegetable kingdom (that is to say, the cases where the sex differentiation is incomplete) the operation leads to an increase in the vitality of the daughter cells. When, owing to the decrease in the activity of a cell, the pseudo-reducing division occurs, the resulting daughter cells carry a certain amount of residual charges, that is to say, a definite amount of fresh energy has been absorbed by the chromatin. This clearly will enhance the activity or vitality of the cells considered as a whole, and therefore we are met with the condition of a new growth of cells of greatly increased vitality in a tissue of cells of low vitality. It stands to reason that the new cells will multiply with great rapidity and will be out of co-ordination with the soma. Their growth will depend entirely

1. *Proc. Roy. Soc.*, Vol. LXXII (1903).

upon the new lease of vitality which they have received from the reducing division, that is to say, it will be inversely proportional to the age of the cells before the derangement.

The course followed by these new cells should be very much on the same lines as that given in detail upon page 214 for the cells obtained by the true reducing division in the case of an organism with small sex differentiation. The descendants of the pseudo-reducing division of cancer will produce a certain number of neutral cells, a few maximally charged cells both with positive and negative electricity, and the remainder with intermediate charges. It is impossible to assess the relative number of the three types, since the original reducing division was not a true reducing one, but only a pseudo one with an indefinite reduction. The maximum charged cells will soon reach the limit, which cannot be passed owing to the magnitude of the charges involved, while the remainder sub-divide indefinitely. When the maximum charged cells have reached the limit the question at once arises as to their future behaviour. The normal course would be for them to fuse together in pairs of opposite charges, with production of new cells with an increased number of chromosomes. A new generation of highly active cells would thus be formed, and thus the cycle would be complete, just as in the botanical case detailed before. It must also be remembered that under the peculiar circumstances owing to the reaction of the soma there is a supply of leucocytes continuously made. These leucocytes being neutral and active cells would be expected to conjugate with the maximum charged 'reduced' cancer cells, since the electric potential would in this way be reduced. Now Farmer, Moore and Walker¹ have observed such conjugation between leucocytes and cancer cells—an observation which strikingly confirms the theory. No doubt conjugation also occurs with the cells of the surrounding tissue, to which may partly be due the infiltration of the malignant growths.

This seems to us to account fully for the cyclical form of growth of cancer in mice as demonstrated by the Imperial Cancer Research (No. 2, Pt. 2, 1905), but the space at our disposal prevents us from producing further proofs for our contention.

An important point arises here in relation to the age and differentiation of the cell. It would be readily understood that the greater the vitality of any cell, the greater will be its activity in proliferation when the malignant diathesis has once been established. If we suppose, for

1. *Proc. Roy. Soc.*, Vol. LXXII, 1903.

example, that either owing to the abnormal condition of the chromatin granules or the presence of an external electrical stimulus, the electrical equilibrium is disturbed when the cytoplasmic activity is still very considerable, it will be evident that the rate of proliferation will be greater than would be the case had the cytoplasmic activity been less. In other words, the greater the amount of the activity the more rapid the growth of the tumour, the more highly differentiated the cell and the older it is before the taint is established, the less rapid will be the growth of the neoplasm. As the age of the host is increased, therefore, the less potent becomes the taint. If the development and differentiation of the cell has proceeded sufficiently far before the cancerous diathesis is established, the smaller will be the potential differences established by the reduction in the number of chromosomes. The tumour then loses its malignancy to a certain extent, and a cancer of slow growth, such as an atrophic scirrhous, is established. There can be no doubt that the growth of the tumour by reduction in the number of chromosomes produces, as before stated, daughter cells which are out of somatic co-ordination with the host, and the tumour grows parasitically, feeding upon its host. Resulting from this condition of parasitic growth of cells out of somatic co-ordination, the wandering of some of the active cells from the seat of the tumour may occur. When one of these charged cells comes to rest, it possesses potential probability of reproducing itself, resulting in the growth of a secondary tumour of the same type as the primary one. The tendency to the formation of secondary growths must, therefore, depend directly upon the activity of the cells when the taint is first established, because, as before said, the greater the activity the greater the activity of the daughter cells of the pseudo-reducing division.

With reference to this subject we are at once struck with the remarkable facts which have accumulated during recent years with regard to the transplantation of cancerous tissue. As the Imperial Cancer Research have indicated, it is much easier to transmit any malignant growth from a mouse of one locality to a mouse of the same locality than to a mouse of another locality; moreover, there is a general concensus of opinion that cancer can in no way be transmitted from an animal of one species to an animal of another. This is the natural outcome of our view on the cytoplasmic activity.

For the more different the species of the animals in question, the more dissimilar would be their respective cytoplasms; and at a certain limit of difference, conjugation either with leucocytes or normal tissue

cells would be impossible, and the engrafted tumour would not be able to survive the reaction of the connective tissue stroma.

In order that conjugation may take place between a charged nucleus and a neutral nucleus or between two oppositely charged nuclei, it is essential that the limiting surfaces of the two masses of cytoplasm be eliminated at any rate during the process. This elimination of the surface layer can only occur if the two cytoplasmic masses be of specifically the same chemical nature. If, however, as a result of the two individuals having lived in different localities or having been fed with different food, their cytoplasmic material be of different chemical character, conjugation between the nuclei will be impossible owing to the difficulty of eliminating the limiting layers of the cytoplasm of the adjacent cells.

The malignancy of new growths varies generally indirectly with the age of the host. As a corollary to this it may be added that the condition of the chromatin granules may be such that the electrical disturbance occur at a very early age, e.g., in the embryo. The occurrence of sarcoma in utero is doubtless due to this condition, and such cases should be, as they undoubtedly are, exceptionally malignant.

We have hitherto confined ourselves to the mere statement that the existence of chromatin granules of such a type that the daughter particles produced in mitosis have a very small difference of charge will tend to cause electrical disturbances, such as seem to occur in cancer. We may now turn our attention to the investigation of this possible condition, for if this possibility be established it will afford an explanation of the true origin of cancer. In any healthy race with no close inter-marriages, it would appear from first principles that the chromatin granules would be perfectly normal, if healthy female ova are fertilised with spermatozoa of a different type; that is to say, as long as father and mother are sufficiently differentiated and both healthy, the chromosomes of their children and the chromatin granules of their descendants will be normal. If, on the other hand, close inbreeding takes place through several generations, then the chromatin granules will tend to become more and more uniform, so that they give in mitosis daughter particles of smaller and smaller potential difference. The tendency to abnormal mitosis is thereby progressively increased until a stage is reached when the incidence of the malignant growth is markedly intensified.

Up to the present we have not taken into consideration the chemical side of the problem, and although the action of certain chemical

substances has been instanced, as, for example, the production of asymmetric mitoses by antipyrine as observed by Galeotti, the influence of the metabolic products of the cells has not been discussed. We have dealt with the possibility of electrical stimulus and the disorganisation of cells by means of a bruise or blow, and it is a natural sequence of the electrical theory that disorganisation could be produced by a purely chemical stimulus apart from that arising electrically by the different velocities of two ions. Owing to the peculiar configuration of the protein molecule it must be sensitive to both bases and acids, and the influence of these two reactions seems of considerable importance.

As far as is known at the present time the normal cells seem to be strongly influenced by both bases and acids, and the influence of the former seems to be one of stimulation, while acids seem to produce the opposite effect.¹ For example the well-known case of a nerve fibre may be quoted: if two needles be inserted into the fibre and one be connected with the copper of a Daniel cell and the other to the zinc, the nerve cells are stimulated around the latter needle and depressed near the former. It is evident that around the latter there is an excess of alkalinity and an excess of acidity around the former. While several experiments giving similar results might be quoted, the above shows clearly that cells are stimulated by alkali. From a physico-chemical point of view this action of alkali is explicable if the tautomerism or dynamic isomerism of the protein molecule be considered. Recent work has shown that there is a distinct and definite tendency on the part of a - NH - CO - grouping not to exist in either of the two possible desmotropic forms - NH - C(=O) - and - N=C(OH) -

but rather as a mixture of the two in dynamic equilibrium with one another. Moreover, the chemical activity of this group as concerns either the nitrogen atom or CO group is determined entirely by this dynamic condition, for in a great number of cases it has been proved that a molecule in a static quiescence is singularly inactive to all chemical reagents. In order that a molecule should be reactive it is necessary that a certain amount of dynamic oscillation between the residual affinities be present, and the reactivity is proportional to the amount of dynamic isomerism which exists. In the case of the - NH - CO - grouping in question the phenomenon seems to be connected with the

1. Moore, Roaf, and Whitley, *Proc. Roy. Soc.*, B. 77, p. 102, etc., 1905. Moore and Wilson, *Bio-Chemical Journal*, Vol. I, p. 297, 1906. Moore, Roaf, and Knowles, *ibid.*, Vol. III, p. 279, 1908.

wandering of the hydrogen atom from the nitrogen to the oxygen. Now in all such cases the dynamic isomerism is increased by the addition of alkali and decreased by the addition of acid. Since the chemical reactivity of a substance depends upon the amount of dynamic isomerism present, so the reactivity of protein must be enhanced by the addition of alkali and depressed by the addition of acid. The activity of a cell must essentially be determined by the chemical reactivity of its components, so it is a natural sequence that alkali will stimulate and acid depress the normal functions of a cell. If we apply this argument to the special case already considered of a somatic cell whose chromatin granules vary very much in activity, it leads to an interesting conclusion. It was previously shown that owing to the potential gradient arising from the variation in the activity of the chromatin, a pseudo-reducing division can occur with production of cells possessing enhanced activity, or, in other words, a new growth is started. The application of alkali to a cell of the above type will stimulate the activity of all the granules present, and will consequently increase the potential gradient in the chromatin. The application of alkali would tend, therefore, to increase the probability of the pseudo-reducing division, that is to say alkali would tend to act as a direct cancer irritant when the necessary conditions are present, the necessary conditions being the existence of a gradation in the vitality or activity of the chromatin granules.

The term alkali has been used in the broad sense of any basic substance, and there seems no reason to doubt the direct connection between cancerous growth and irritation by basic substance. Two of the best known examples need only be quoted, namely, chimney-sweep's cancer, where the soot is the irritant, and, further, the undoubted connection between tobacco smoke and cancer of the lip and tongue. Both soot and the distillation products of tobacco are strongly alkaline substances, since they contain nitrogenous bases.

When once the new growth has started, the metabolism of the new cells comes into action, and it is not improbable that a chemical stimulus may arise from the hydrolytic and degradation products therefrom. It is conceivable that these products may themselves act upon the surrounding tissue cells and cause them to undergo the pseudo-reducing division. For this reason we do not wish to restrict ourselves to the statement that infiltration is due entirely to conjugation of the maximum charged cells with neutral tissue cells. The chemical stimulus arising from the hydrolytic and degradation products of the cancer cell metabolism can,

and doubtless does, disorganise the surrounding tissue cells, causing them to undergo the pseudo-reducing division, thus infecting them with the cancer taint.

The variations in the type of initial stimulus account readily enough for the various types of cancer which are known to arise in the same type of tissue. While it should not be possible from a given stimulus to develop more than one type of cancer cell, yet the possibility is by no means precluded of producing a new type of cancer in experimental transplantation. If a tumour be ingrafted on to a new host and if the new host were closely similar in every way to the first host, the new tumour would grow and infiltrate without great difficulty. A slight difference between the two hosts would tend to increase the resistance of the second to the ingrafted tumour, with the result it would become encapsuled. On the other hand, it should be possible to produce a new cancer infection by virtue of the chemical stimulus arising from the degradation products of the cell metabolism of the ingrafted tumour. This new infection might give rise to a cancer of the same type as the original tumour, but it might also, if slightly differently differentiated cells were affected by the chemical stimulus, give rise to a different type of new growth altogether.

Although the connection between cancer incidence, inbreeding, and hybridisation follows quite naturally from the theory of cytological processes advanced above, yet we feel the importance of entering more fully into the detail of a subject which, taken as a whole, would seem to open up a new field of research, namely Mendelism and environment as explained by electro-cytology. To turn to the major factor of the equation, in Mendelism we see the synthetical links which bind together the variations in chromatin distribution with racial index of cancer incidence. We have already pointed out that one of the fertile sources of cancer lies in the existence in the chromosomes of an individual of a certain number of chromatin granules of a poor or weakly type which tend to cause fusion of the chromosomes in mitosis with the production of daughter cells with a reduced number of chromosomes. The effect of this will be most marked when the segregation of these chromatin granules into one or other of the paternal or maternal sets of chromosomes occurs. However the Mendelian segregation of these granules takes place in the maturation division of the germ cells of the mothers, their ova will on the average contain chromosomes possessing a definite number of these granules. These ova, when fertilised by spermatozoa from men of

lower cancer incidence, will give rise to individuals having the same cancer incidence as the mothers, because the cancer incidence depends upon the presence of the weak granules in the one set (maternal) of chromosomes. A further reason for the maintenance of a mother's cancer incidence in her children is the fact that the cytoplasm of their cells is entirely derived from the maternal side. The first generation resulting from hybridisation, therefore, must preserve the cancer incidence of the mothers, although the fathers have a smaller incidence. The second generation of hybridisation will, however, decrease the cancer incidence, as can readily be seen. The cells of the first generation possess two sets of chromosomes: the maternal with their weakly granules and the paternal without them. When the meiotic gemini are formed and the De Vries re-arrangement occurs the weakly granules distribute themselves, and on the average the chromosomes formed by the splitting of the gemini will have fewer of the weakly granules. The children produced from these gametes with gametes of the new stock will of necessity have a lower cancer incidence. We have, therefore, a direct connection between the Mendelian segregation of the weaker chromatin granules and cancer incidence, a fact which explains the different incidence in the children of one family, and also the frequently observed skipping of a generation by the disease.

It would appear from what has already been said that cancer as a disease cannot be inherited—it is only the predisposition to the disease which is inherited, and we have shown that this predisposition must be influenced by inbreeding and hybridisation. We have emphasised the fact that for inbreeding to have any evil effects, it must occur throughout more than one generation; it is the inbreeding of a stock already inbred that will lead to deterioration.

Again, it is obvious that hybridisation in one generation cannot prevent the diathesis being handed down to the descendants, if the offspring of the first hybridisation be again inbred, for whether the predisposition in the inbred race is dominant or recessive to the hybrid, on again inbreeding there must be produced some pure dominants or recessives, as the case may be; on the other hand, every successive generation of hybridisation increases the immunity to the disease.

After consideration for some years past of the prevailing views concerning the aetiology of cancer, we are forced to conclude that the explanation is to be found in a study of cytology and cytopathology. We put forward in this paper the view that all malignant growths are due

to a derangement of the electrostatic forces normally present in somatic mitosis, which is initiated in the first place by a definite stimulus, internal or external, physical or chemical.

We have shown that the susceptibility of the cell to this derangement will be increased with decreasing vitality, such as occurs with age and as the result of inbreeding. Though fully cognizant of the fallacies inherent in statistics, we venture to refer to the results of a study made by us of the geographical distribution of cancer—results which confirm the important rôle played by inbreeding, hybridisation, and racial immunity. We propose to publish these statistics in detail elsewhere, and will at this time only very briefly deal with the more important facts which have come to light.

Inasmuch as the highest cancer incidence known is to be found in Switzerland, we have paid special attention to this country, and have made an exhaustive investigation. The data have been corrected for age and sex constitution of the population, and the results obtained demonstrate clearly that it is in the isolated communities, which have been created by their geographical positions and the influence of religious antagonism, we meet with the highest cancer incidence, while in the passes that have served since the time of the Romans as the highways of invasion and commerce from Northern and Central Europe into Italy, we meet with the lowest.

Thus the cancer incidence (54·77 per 10,000 persons living, aged 30 and over) is highest in the canton of Appenzell in Rhoden, a Catholic canton, wherein until 1848 no Protestant or even Catholic aliens were allowed to settle. It falls to 27·70 in the neighbouring district of Ober-Rheintal, which lies in the valley of the Rhine, in the pass which leads directly to Chur, and from thence by the Splügen to Italy.

In the canton of Graubunden the lowest cancer incidences are in the passes, viz.:—Bernina (23·56), Munstherthal (24·01), and Maloja (22·87).

The cantons of Ticino and Valais have a remarkably low cancer incidence, 19·34 and 11·61 respectively. In Ticino those districts bordering on the St. Gothard Pass (Bellinzona 12·28 and Blenio 12·60) have the lowest incidence, which gradually rises to its maximum in districts most remote from the St. Gothard. The same occurs in Valais, and it is the district of Entremont (4·11) traversed by the Great St. Bernard Pass, which has the lowest cancer incidence for the whole of Switzerland.

The immunity produced by hybridisation is fully borne out by the low cancer incidence amongst the Eurasians, as reported by Dr.

Sutherland, of the Mayo Hospital, in the Third Report of the Cancer Research Laboratories of Middlesex Hospital (p. 87), wherein he says:—

‘A striking fact is the small number of cases amongst Eurasians, who make up a large proportion of the in-patients in the Albert Victor wing of the Mayo Hospital. Only one case of carcinoma and one abdominal growth occurred out of 790 admissions for malignant disease.’

We have also made investigations as to the local origin of cancer, and we find, in comparing the cancer incidence in the various organs between the sexes and different races, that wherever any organ is specially liable to stress or excessive irritation, there is an increase in the number of malignant growths of that organ in the sex or race under consideration.

Although exception may be taken to any conclusions which are drawn from purely statistical data, yet it would appear that the evidence so arrived at is overwhelmingly in support of the fact that one of the major predisposing causes of cancer is to be found in close inbreeding. Moreover, it would also appear from a detailed comparison of the organs attacked, that those organs which are subjected to stresses and irritation are most liable to develop malignant growth. Both of these conclusions are in close agreement with the theory of electrocytology put forward in this paper.

CONCLUSIONS

The following conclusions are arrived at in this paper:—

1. The phenomena of somatic mitosis are readily susceptible of explanation by a simple theory of electrostatically charged colloids.
2. The simplest possible case is that when there are present in the cell hereditary characteristics of only one type, as exists in unicellular organisms.
3. When hereditary characteristics of two types occur, a reducing division is bound to occur at some period owing to the fusion of the chromosomes of opposite type. This reducing division is the forerunner of the maturation divisions of the more highly developed species.
4. The reducing division establishes residual charges of electricity in the daughter cells, the amount of charge depending upon the amount of differentiation between the opposite types of the characteristics.
5. In the animal kingdom where the sex differentiation is complete, the reducing division only occurs normally in the germ cells, and this

division is followed by one somatic division. After this second division no further divisions can take place owing to the magnitude of the residual charges developed.

6. In the lower types, such as occur in the vegetable kingdom where the sex differentiation is incomplete, the reducing division is not confined to the germ cells, but all the cells undergo it at some period of their development. The daughter cells of the reducing division give rise to an indefinite number of cells with the reduced number of chromosomes. Of these cells, in any one generation two have maximum residual charges of positive and negative electricity respectively, a fixed number are neutral and the remainder carry intermediate charges. The highest charged cells fuse together with restoration of the original number of chromosomes, thus completing the cycle. The occurrence of the reducing division endows the daughter cells with renewed vitality.

7. In the animal kingdom the four spermatozoa all carry different charges, one a charge equal to that of the ovum, one an equal and opposite charge, while the other two have intermediate charges.

8. The phenomenon of sex production may be attributed to these residual charges; all the phenomena of parthenogenesis, artificial fertilization and sterilization by X-rays are explained by the same theory.

9. The distribution of chromatin granules, required by the De Vries theory, is established as a necessary consequence of the maturation division.

10. The occurrence of pathological mitoses, as the result of external stimulus or internal stress, is established provided that the inherent precancerous condition be already present.

11. The possibility of a pseudo-reducing division of somatic cells is accounted for.

12. These pathological mitoses result in the establishment of residual charges in the daughter cells similar to those of the maturation division.

13. The daughter cells of the pseudo-reducing division possess renewed activity. They possess potential probability of conjugation with leucocytes and normal tissue cells.

14. The direct stimulation by alkali and bases generally is found to be a normal action, and it would seem that in certain cases alkali can act as a direct cancer irritant.

15. The stimulation of the surrounding tissue cells by the degradation products of the cancer cell metabolism is possible, and to this and the

facts mentioned in 13 is attributed the formation of a neoplasm with power of continuous growth.

16 The susceptibility of the cell to these derangements is increased with decreasing vitality, such as occurs with age, and as the result of in-breeding.

17. In close in-breeding through several generations the chromatin granules become more and more uniform so that they give in mitosis daughter particles of smaller and smaller potential difference, which markedly increases the tendency to abnormal mitosis; conversely hybridisation produces a maximum of cell stability and an individual with all its Mendelian allelomorphs as differentiated as possible.

18. The rate of proliferation depends upon the activity of the cytoplasm; the greater the activity the more rapid the growth, while the more highly differentiated the cell and the older it is the less rapid the rate of proliferation.

19. Age incidence, local origin, infiltration, metastases, transmission with all its limitations, and power of continuous growth are the natural outcome of abnormal cell proliferation induced by a disturbance of the electrostatic forces present in normal mitosis.