AN ADDRESS ON THEORIES OF INHERITANCE, WITH SPECIAL REFERENCE TO THE INHERITANCE OF ACQUIRED CONDITIONS IN MAN.

Delivered before the Brooklyn Medical Club, May 17th, 1901.

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[AFTER pointing out the curious position occupied by questions of inheritance in the minds of medical men at the present time, all being willing to admit that inheritance does play a part in the development of morbid conditions, but being unwilling to discuss or write about the exact part played by it, the lecturer pointed out that the reasons for this silence were apparently, in the first place, man himself not being for most purposes a good subject for investigation, both from the fact that generations follow each other at relatively long intervals and to the fact that he is a mammal, and that influences acting upon the susceptible foetus in utero introduce complications. He continued:—]

We have had to depend upon the biologists for our views upon heredity, and the theories elaborated by biologists, having started from morphological rather than physiological conceptions, have assumed shapes which would not disgrace the schoolmen of the Middle Ages. Add to this that the trend of these theories has been apparently in strong opposition to medical experience.

Of all the workers of late years Weismann has had the most influence upon biological thought, and his theory, if not accepted by all in its entirety—and if, indeed, now found unacceptable—has nevertheless profoundly affected the general consideration of this subject of heredity. That theory is very complicated, and with Weismann's successive publications, has not by any means become easier to follow or to epitomise in language devoid of technicalities. Still, if not every schoolboy, at least every educated man, is supposed to comprehend the general tenour thereof and its main thesis or conclusion that acquired characters—characters acquired by the individual—are not and cannot be transmitted to the offspring. Or, to use Weismann's own expression, "We maintain that somatogenic characters (characters originating in the cells and tissues of the body) are not transmitted, or rather, that those who assert that they can be transmitted must furnish the requisite proofs. The somatogenic characters not only include the effects of mutilation, but the changes which follow from increased or diminished performance of function, and those which are directly due to nutrition and any of the external influences which act upon the body. Among the blastogenic characters (characters originating in connection with the germ cell), we include not only all the changes produced by natural selection operating upon variations in the germ, but all other characters which result from this latter cause."¹ In natural selection is to be found the key of the phenomena of inheritance.

Now, up to a certain point, we as medical men are prepared to accept this teaching. We know from experience that acquired mutilations are not transmitted, we acknowledge that no clear and satisfactory examples of the transmission of mutilations have been brought forward. But there is another class of phenomena specially interesting our profession which appears to give a direct lie to Weismann's thesis. And it is, I think, this failure of this ruling theory to explain satisfactorily the phenomena in question which has been the main factor in making us as a profession not enthusiastic of late years to debate the subject.

For, accepting the theory, we must be prepared to deny wholesale the transmission of acquired defects of every order, and give ourselves over to a most serious form of fatalism.

If an individual be from the first feeble minded, that is not his parents' fault; it is either due to an unfortunate commingling of the ids or ancestral plasms composing the promiscuous ovum and spermatozoon from which he is derived, or

is due to characters which have come down to him from previous generations. If he, being diseased, begets feeble-minded children he is in no wise to blame—acquired characters are not transmitted. Either those feeble-minded children are an accident—a spontaneous variation—or more probably they represent the summation of characters inherited from long generations. If a man or a woman becomes an alcoholic, it is not his or her fault, it is the result of inherited tendencies; and if the children of the same be of weak constitution or idiotic, again the parents are blameless—characters acquired by the parents are not transmitted, the characters of the parents must have descended to them. If a man is a criminal, again he is not to blame—criminality is atavism, is a reversion to an earlier state, is an inheritance of characters or features peculiar to primæval man. We are, so the popular translation of Weismann's theory goes, the descendants of criminals, or at least, at a certain stage our ancestors were of an imperfect and criminal type. And if criminality appears in the family, with imperfect formation of head and brain and low mental state, that is due to the fact that by the fortuitous extrusion of certain ids from ovum or spermatozoon, the ids of the criminal ancestors have preponderated in the fertilised cell, and the result has been that the individual has developed possessing criminal features. However much a man abuses his soma, or body, is of little moment, the effect upon the offspring is minimal.

I put this in strong language and baldly, and it may be urged that I exaggerate the state of affairs. I do not think that I do. I believe that in making this statement I but give expression to the general, if confused, ideas of the majority; nay, more, that I state the received conception of what Weismann's theory means when applied to man and to abnormal inheritance in man.

Now if there is one conclusion to which we think experience surely leads us medical men it is that the sins of the father do tend to be visited upon the children even unto the third and fourth generation. We think we see this demonstrated day after day. But Weismann does not support the view. It is true that if we study Weismann we find that he does not state this so in so many words: he admits² that the germ plasm is not absolutely unchangeable, that the nutrition and growth of the individual must exercise some influence upon its germ cells, "but in the first place this influence must be extremely slight, and in the second place it cannot act in the manner in which it is usually assumed to take place." Certainly he does not make it clear that he believes in distinct transmission of acquired characters.

WEISMANN'S THEORY.

[The lecturer then rapidly outlined Weismann's theory, pointing out that the continuance of life and so of inheritance was through the substance or germ plasm of the germinal cells; that the ovum in the process of fertilisation comes to contain portions of the germ plasm of both father and mother, and that the germ plasm of the father and mother must, according to Weismann, contain portions of the germ plasms of the grandfathers and grandmothers, and so representatives or ids of the germ plasm of a long series of progenitors are contained in the nuclear material of each ovum and spermatozoon. At each act of fertilisation a certain number of these ids are held to be discharged so that the number in each fertilised ovum is kept constant, and as the series discharged varies in each ovum, the ids in two fertilised ova are not identical. Thus the individuals developed from these ova tend to vary. So also, according to Weismann, a certain definite series of these hypothetical ids pass into each cell of the segmenting ovum, and, according to the series entering, so are determined the eventual characters of the tissues to which those daughter cells eventually give rise.]

To explain atavism or reproduction of characters which have been present in an earlier generation but absent in more recent generations, the theory demands that some at least of these ids should have remained unchanged through a long period. In other words, the theory demands that the ids must be singularly stable in constitution. But Weismann has to admit that they become modified in their structure. He, however, fails to define the limits of alteration.

[Criticising the theory, the lecturer pointed out that practi-

cally this theory regarded the nucleus of the germ cell as containing a colony of what are to all intents and purposes separate and independent individuals, or otherwise, that the germ cell contains a colony of individual living beings. He then pointed out that so far as regards the ids, the brilliant observations of Driesch, abundantly confirmed by others, show that the conception is untenable.]

If in a segmenting ovum we find that normally each of the blastomeres or primitive segmentation cells gives rise to one special series of organs or tissues, but if nevertheless the ovum of sundry animals can have its cells shaken apart at the 2, 4, 8, and even 16-cell stage, and each separated cell can be found capable of developing into an entire if dwarfed individual, then obviously each time the nucleus segments there is no passage into the daughter nuclei of particular series of ids destined to lead to the development of one particular region of the body. Rather, the variation in structure of the different tissues must be, to employ Driesch's words, "a function of their relative positions" (*ihre prospective Bedeutung ist eine Function des Ortes*). The existence of these hypothetical ids is absolutely disproved. I dwell upon this theory because to-night I want more especially to discuss, on account of its importance from a medical point of view, this matter of the inheritance or non-inheritance of acquired characters. I hope that I have proved to you that the groundwork upon which the negative view is based is of proved unsoundness. The fact that a theory by which a position is supported falls through does not, it is true, afford proof that the position is wrong, but when we find that the dictum of non-transmission of acquired characters does not wholly accord with medical experience, we may well ask, Can we gain a conception of the intimate nature of inheritance which is in accord with that experience?

My only regret is that in striving to gain that conception I shall have to inflict upon you yet another theory; my only apology that that theory does appear to satisfy the conditions met with in man.

It is to the germ plasma, the active matter in the germinal cells, and to the properties of that germ plasma, that we must turn in order to gain our basis for any sound theory of inheritance. Weismann has done yeoman's service in emphasising this fact. This germ plasma it is which conveys living matter from generation to generation.

GROWTH—ITS ESSENTIAL NATURE.

Now, whatever life be, the fundamental phenomenon or possession of living matter is the performance of work coupled with growth—is the capacity manifested by that living matter to assimilate non-living matter of certain orders, to absorb it, to endow it with like properties, to convert it into matter like unto itself, into additional living matter, in doing which work is performed. In other words, difficult as it is to conceive or picture to oneself the details of the process, growth is essentially a process of conversion—a chemical process. And any adequate theory bearing on the phenomena of growth must primarily be along chemical lines. We are ignorant of what it is in the structure of living matter which gives it those properties; we are, if possible, more ignorant of the physics of the process of growth, of the nature of the force which, acting upon or inherent in the constitution of living matter, leads to this continuous process of assimilation and conversion; and in our ignorance we are unable to separate the chemistry and the physics of the process; we must, that is, regard growth as a property of living matter. We must also for present purposes speak of the matter which is essential to, and directly concerned in, the activity of any one species or individual as a single substance, which, following Nägeli, we can refer to as "idioplasm;" and our conception of the individual or of the separate cell units forming that individual must be that in each we have to deal with two constituents: the idioplasm, or essential and directive living matter; and the cytoplasm, which is in the strictest sense non-living, or, certainly, unable to exhibit the whole series of vital properties apart from the idioplasm, and which consists of various formed elements developed and influenced by the controlling idioplasm, intimately connected therewith, it is true, but at the same time not an essential part of the same, the cytoplasm varying in its composition and nature under varying conditions, which affect the idioplasm, the idioplasm

under all conditions retaining certain cardinal properties.

That the constitution of the idioplasm is not absolutely but only relatively constant has also to be assumed. We are bound to recognise that it is capable of undergoing modifications within certain limits without loss of its cardinal properties. And this from the following reasons. Admitting, as we must, that the highest forms of animal and vegetable life have been evolved from the very simplest, that there has been an unbroken line of development of living forms from the simplest unicellular to the most complex multicellular; admitting, also, that in every act of reproduction, however simple or however complicated, the direct conveyance of the living matter of the parent into the offspring is to be demonstrated—that, in other words, the idioplasm of the primal living being has been continued on to successive and progressive generations—then we must admit that the idioplasm of the highest forms, judging from its powers of controlling and directing the development of highly complicated organs, is something very much more complex than the idioplasm of the unicellular organisms; that in the course of evolution this has undergone successive accretions of properties, and this accretion of properties is the manifestation and accompaniment of increasing complexity of constitution of that idioplasm.

This idioplasm must be capable of modification either by its environment or under the action of some law of progressive modification. The fact that there exist to-day forms of life practically identical in the main details of structure with those of remote geological ages is against the latter view; we must hold that environment determines changes in the constitution of the idioplasm.

CHEMICAL THEORIES OF INHERITANCE—THE ISOMERIC THEORY.

It must now be asked, Can we imagine a chemical substance so constituted as to be capable of modification in its molecular constitution—and so in sundry of its properties—without undergoing complete change, without other properties being lost? We can. If, as Professor Walker, of McGill, points out to me, such relatively simple bodies as lactic and malic acids are capable of existing in more than one form—as levogyrous, dextrogyrous, and optically inactive modifications—and this with no obvious alterations in their chemical properties (though physically they show different actions upon polarised light, and physiologically we find that certain bacteria can act upon one and not the other form), then surely the much more complex proteid material which would seem to be the basis of the idioplasm may present a very great number of molecular arrangements, and each of these may be accompanied by slight differences in certain physical and physiological properties.

Certain recent observations have rendered this additionally probable. By our present method of conceiving and visualising the structure of chemical substances we regard the carbon atom in the molecule as being situated at the centre of the tetrahedron, and as capable of linking four other atoms or groups, one to each of the corners or apices of the tetrahedron. A substance like malic acid, having a single central carbon atom, may therefore be built up in three ways—with the linked groups arranged in one relationship to each other, or in the reversed relationship, or the substance may be a combination of the two atomic forms. These are all the forms we can picture as existing according to this system. But now a fourth form of malic acid has been found which is more dextrogyrous in the polariscope than is ordinary dextrogyrous malic acid. And the salts of this new form of malic acid show slight but distinct variations, in solubility, etc., from the ordinary malates. If this be so, there may be yet further molecular modifications of such a relatively simple substance as malic acid, and *a fortiori* idioplasm may be capable of an enormous number of modifications.

THE SIDE-CHAIN THEORY OF INHERITANCE.

The mode of the atomic arrangement in the idioplasmic molecule may therefore in part explain the variation in the properties of that idioplasm seen throughout the animal and vegetable kingdoms. I say in part, for if we assume that the

structure of the individual is primarily the outcome of the structure—and properties—of the idioplasm, then for each different form of living being—nay, for each individual being—we have to assume a different atomic structure of the idioplasm, or otherwise we have to assume that the modifications of this dioplasm are infinite in number. This, it seems to me, asks too much. The matter cannot be quite so simple. Each molecular modification may play some part, it is true, but our conception of the structure and modifications undergone by the idioplasm must be more elaborate. We must, I think, formulate a theory of structure somewhat akin to that laid down by Ehrlich in his now well-known theory of the nature of immunity. We can picture to ourselves the primitive idioplasm as composed of a mass of material, each molecule of which is formed of a central ring, to which there can be attached side chains, from which sundry side chains can be detached without the central ring being destroyed.

Fig. 1.—Schema of ring with side chains.

This conception, which upon first encounter appears revolutionary and opposed to our ordinary chemical ideas, is after a little deliberation recognised as being but a statement, in chemical terminology, of what has been for long years the accepted physiological conception of the nature of protoplasm. It is, if I may so express it, the fundamental—the essential—conception of the constitution of living matter; it follows logically and inevitably the postulate of assimilation and growth. Whether we agree, with the majority, to distinguish between the idioplasm and the cytoplasm of the cell, or prefer to speak simply of protoplasm, it must, I think, be recognised by all that we are bound to assume—for the process of assimilation and again in order to explain the variation in structure and properties of the various cells of the organism—that there is a central basal substance to which become linked, more or less permanently or more or less temporarily, those other secondary substances which, not in themselves protoplasm, modify the constitution of the protoplasm as a whole. And these secondary substances, we see, are necessary for the full manifestation of the properties of that protoplasm. This conception is, I acknowledge, difficult to harmonise with the prevalent elementary conceptions of chemical action and chemical constitution, but it is, nevertheless, essential for the physiologist and unavoidable. What is more (for I do not pretend to be a chemist), I learn that it is not opposed to the more recent deductions of the chemists concerning the nature and properties of the more complex carbon derivatives. In other words, it is by no means heterodox from an advanced chemical standpoint.

Accepting this view, it is not necessary to regard the molecules of idioplasm as at all times presenting their completed structure, with every side chain attached. On the contrary we are free to conceive the molecules being laid down and being transmitted in a relatively simple form, some of the side chains only becoming attached when the molecules are brought into certain particular relationships with their surroundings. It is not necessary, for example, to hold that already in the ovum there is idioplasm identical in structure with that eventually present in the muscle fibres or nerve cells developed from that ovum. Rather we must hold that in the ovum there is one common idioplasm of simple type, to which when distributed in the various cells derived from that ovum, different side chains become attached, according to the relationships assumed by those cells, so that the cells of different orders are controlled and formed around protoplasmic or idioplasmic molecules composed of these central rings plus varying series of side chains. Indeed I am prepared to go further, and to state that the idioplasm possessing its full complement of side chains must be regarded as *ipso facto* incapable of initiating cell multiplication. I base this statement upon the fact, to which I have more than once called attention during the last few months, that it is only cells which are undifferentiated or which have reverted to a simpler less differentiated form, that are found to undergo division. Highly differentiated cells never multiply as such.

INHERITANCE IN UNICELLULAR FORMS.

If the primitive unicellular individual formed by this con-

trolling idioplasm divide into two to form two individuals, each half will contain a portion of the idioplasm, and if the circumstances affecting the molecules of the new generation are the same as those affecting the parent forms, then this idioplasm will continue to assimilate to itself non-living matter and to endow it with its constitution and properties, and the individuals controlled by this idioplasm will correspond to the parent form and to each other.

But if the circumstances affecting the filial idioplasm vary from those affecting the parental then these more loosely connected side chains will be the first to be influenced. The very act of assimilation (the surrounding medium varying in its composition), may lead to the substitution of other side chains, to slight variation in the composition of the idioplasm. And the cell or individual developed or controlled by the idioplasm will therefore vary from the parent form, while the products of division of this second generation, containing as they do this modified idioplasm, will exhibit like structural modifications.

Here we have the simplest example of the inheritance of acquired characters.

There is, however, yet another property which we have to assume. It may be laid down as one of the great laws of biology that characters which are of the most recent acquirement are those which are most unstable, and are first lost, these which are oldest are the last to disappear. In man, for example, the first signs of generalised systemic weakness and imperfect development show themselves in connection with those properties which differentiate man from the animals most nearly allied, namely, in weakness and arrest of the higher functions of the nervous system, or again in susceptibility to certain specific diseases which are peculiarly liable to affect man, relative immunity towards which on the part of the healthy individual must be regarded as a comparatively recent acquirement. And as my old teacher, James Ross, of Manchester, was the first, I believe, to point out, when there is progressive atrophy of the cells in the cortex of the brain, the first motor cells to show signs of that atrophy are those governing those muscles which differentiate man from other animals, namely, the opponens muscles of the hand.

Hence it has to be laid down that the attachment of these side chains which are recently acquired is relatively unstable, that such recent side chains are most easily detached, so that the idioplasm, and the organism developed around that idioplasm, are liable to return to their former condition, or lose characters gained by recent progenitors.

The more side chains become attached, the more complicated the structure, the more unstable the equilibrium; hence the greater the liability to revert. As Professor Walker points out to me, parallel conditions are to be recognised in organic chemistry. The old-established view of the existence of "radicles" to a large extent admits this principle; certain central atomic groups in a compound are seen to be more fixed, and not to undergo change when the attached groups are removed and replaced. Still more closely allied is what has been observed in connection, for example, with aniline. The composition of this is $C_6H_5NH_2$. Here the H atoms of the NH_2 group can be replaced by other groups, by methyl (CH_3) and ethyl (C_2H_5) groups, etc.; and it is found under certain conditions that, in carrying out a series of these replacements, the last group attached is the first to be split off and replaced.

We see this principle in action in the lowest forms of life. Contrary to what Weismann has laid down regarding parthenogenesis and asexual reproduction, it is comparatively easy to impress new characters upon the bacteria. By subjecting a growth of pigment-producing bacteria to the action of a temperature just below that which will cause their death, we can bring about a loss of pigment production, so that the rapidly-succeeding generations are perfectly colourless, but gradually, in the course of time, the cultures made from the original (heated) tube regain the power of pigment production. This may be in two or three days, or again only after several transplantations at the end of two or three weeks, and when we remember that a bacillus divides and so forms a new generation in, on the average, something considerably less than an hour, it is seen that the acquired character may be impressed upon the race for some hundreds of generations. The more intense the alteration to

which the bacillus is subjected, the longer and the more frequently the race is subjected to the altered temperature conditions, the longer it is before there is a sign of return to the normal. Translated into the terms of this theory, heat leads the idioplasm either to have certain side chains modified or lost, and this modification or loss is inherited; but return to the normal environment leads the modified idioplasm in the process of growth and metabolism eventually to assume side chains of the same composition—the conditions of growth being similar to those under which the species originally acquired the side chain. Yet another solution, though it is one which I do not favour, is that not all of the molecules of the idioplasm undergo modification, a minority retain their original constitution, and under favourable conditions gradually come to preponderate.

SEXUAL CONJUGATION AND INHERITANCE

How next does this theory bear upon sexual conjugation and its effects—for this also is met with in many unicellular organisms? I shall not take up the explanation of the development of male and female characteristics; that is too large a subject, but I would discuss how fusion of the idioplasm of two individuals affects inheritance. In that fusion we have a mixture of the two idioplasms, and, as already pointed out, these idioplasms, as a result of the varying influences which have acted upon them, tend to vary in certain particulars in their constitution. This fusion must be either a mere admixture, so many molecules of one idioplasm become admixed with so many molecules of the other, or a true chemical combination. If we presuppose a mere mixture we are led along the lines of Weismann's theory, and have to regard the idioplasm of the individuals of one generation as being composed of idioplasmic molecules or ids which have been passed down from the long line of previous generations. I have already pointed out the difficulties in which we find ourselves if we accept this view. The other view largely, if not entirely, removes these difficulties, nor does it introduce any fresh crop of serious difficulties.

We may regard, then, the idioplasms from the two parent forms as undergoing a true chemical combination,* the resultant idioplasm of the new generation being in truth a new idioplasm not possessing the identical properties of that of either parent, but being intermediate, tending in its characters and constitution towards the constitution of either one or the other, according, it may be, to the number or chemical activity of the molecules of one or other parent entering into combination. Weismann supports his view by pointing out that for a certain period the maternal and paternal material in the chromosomes of the daughter nuclei remain distinct, and reaches the bold and utterly unsupported conclusion that when the chromosomes fuse to form the irregular network prevailing the nucleus, their constituents nevertheless remain distinct and sharply separable from those of the other chromosomes. But we have no evidence, in the first place, that the chromosomes alone contain the idioplasm, that chromatin and idioplasm are identical. Everything points to the fact that the idioplasm is contained in the nucleus, but we cannot with certainty advance further. It may be that the chromatin is but the cytoplasmic framework, the mechanism, as it were, by which the idioplasm is distributed.

If the germ cells of both parents possess certain loosely attached or unstable side chains of more recent acquirement, which are of like nature, there is no sufficient reason why the protoplasm of the offspring should not also possess them. We can thus realise how it is that abnormal features present in both parents may be equally or more prominent in the offspring. But in general we must recognise that the parents varying in different directions the tendency of conjugation is to preserve the mean, to bring about an approach to uniformity in the constitution of the idioplasm of successive generations of one species exposed to like influences.

I need scarce say that in these higher unicellular organisms which present conjugation the cell already presents a nucleus, and that everything indicates that this nucleus is the con-

*It may be asked, How can identical or almost identical substances undergo true chemical combination? Physicists nowadays freely recognise this possibility. Thus everything points to the molecule of water being, not H_2O , but $\text{3H}_2\text{O}$; numerous other examples might be brought forward.

trolling and directive body in the cell—that it is the nuclei which undergo conjugation—and that in short we have to recognise that the idioplasm of the individual is contained in the nucleus. It is by no means necessary to conceive that the whole of the nuclear material is idioplasm, or that the whole of the idioplasm enters into chemical combination with the molecules derived from the conjugating germ cell, molecule for molecule. I mention this in passing to indicate that it is not necessary to assume that when polar bodies are extruded the material forming them is identical with the idioplasm of the remaining nuclear material. The difficulties in explaining polar bodies and the reduction of the remaining substance are no greater by this than by Weismann's theory. The exigencies of time demand that I should not enter into detail into the consideration of these subjects. Rather I must give the broad outlines of the theory and pass on to consider inheritance in multicellular organisms.

INHERITANCE IN MULTICELLULAR FORMS.

Every multicellular organism arises from a single cell, the fertilised ovum, itself in all sexually-produced forms, the result of fusion of a male and female cell, of the ovum and spermatozoon. Studying the method whereby this one cell gives rise to the adult multicellular organism, we see that by successive acts of division this one cell gives rise to all the cells of the body. In the course of this process its nucleus divides and redivides, and that in such a way that at each division like portions of the nuclear material pass into each daughter cell. This regular distribution of nuclear material affords a sound ground for believing that there is an equally regular and uniform distribution of idioplasm into each cell. Now, I have already pointed out the value of Driesch's observations in overthrowing Weismann's contention that there must be a qualitative difference in the idioplasm distributed to the daughter cells. We have absolutely no ground for believing in any such qualitative difference. On the other hand, it is a legitimate inference that the idioplasm is modified by its environment. To take the simplest example—a multicellular organism composed of a spherical mass of cells. Those cells which come to form the peripheral layer of the individual

Fig. 2.—Schema of multicellular organism to indicate diverse relationships of peripheral and centrally situated cells.

are subjected to a series of reactions quite different from the series telling upon the centrally-situated cells—and it requires no stretch of imagination to predict that in the process of assimilation and growth on the part of the idioplasm of these outer cells that idioplasm tends to be altered in its constitution as compared with the idioplasm of the centrally-situated cells. So that the results of division of the peripheral cells if retained in the same environment will tend to produce the characters impressed upon the parent cells; and so that, if this subjection to the special set of conditions be continued and impressed upon this order of cells for a sufficiently long period or with sufficient intensity; even when pressed or passing into other environment, the cell generations will retain these modified conditions, so that, for example, cells of mesoblastic origin will tend to maintain characters different from those derived from epiblast, and this whatever the ultimate position of the cells in question.

In fact, as a first law, we may lay down with Driesch that the structure of the cells in a multicellular organism is a function of their position, and this because the position of the cell determines the modification undergone by its idioplasm. As a second law we may lay down that the greater the change impressed upon the idioplasm of these cells and the longer that idioplasm is subjected to the conditions inducing this change, the more permanently will the daughter cells exhibit the peculiar alteration in the idioplasm, with consequent modified structure wherever they find themselves in the economy. We have, in short, to recognise that two orders of forces determine the structure of every cell in the body: (1) The previous influences acting upon its idioplasm and causing it to be of a particular constitution, and (2) the position in which the cell finds itself and the forces acting momentarily and immediately upon its idioplasm. Or, briefly, these two series of forces are inheritance and environment, and inheritance and environment determine the constitution of the idioplasm and the structure of the cells.*

Following this line of thought we can understand how it comes to pass that the body cells and the germ cells in the higher and more complex organisms become so sharply divided, how is it that the body cells are no longer able to reproduce the whole organism. Their idioplasm has become altered in certain directions to such an extent that it is able under favourable conditions to divide and reproduce cells like Nature, but the very extent of the modification it has undergone has taken from it that constitution or structure which is necessary to allow it to reproduce each and every order of cells which together form the individual. The germ cells, on the contrary, undergo no such extensive changes in constitution—as a function of their position in the organism their idioplasm as it grows and is distributed into the successive germ cells retains its fundamental constitution with but little alteration, and when these germ cells are discharged they and their idioplasm brought into like relationships to those affecting the parent germ cells, undergo the like series of developmental changes, and reproduce the whole series of cells, tissues and organs characteristic of the species to which they belong.

In the terms of this theory, therefore, inheritance essentially depends upon the chemical constitution of the idioplasm or the life-bearing or biophoric protoplasm of the germ cells, not upon the number of the separate ids or biophores or ancestral plasmids or pangenes contained in the idioplasm; and variation whether slight and individual or extensive, and leading to the production of species, is ultimately the expression of modification in the constitution of that idioplasm brought about by environment. Whereas Weismann's theory lays stress upon relative fixity in the constitution of the idioplasm, this theory admits freely the capacity for change in structure of the same. So long as the surrounding conditions are unaltered the idioplasm is unchanged; alter these conditions and the idioplasm is liable to variation in constitution.

*ATAVISM.

Lastly, in regard to atavism and reversionary degeneration of the cells of the individual, this conception of the idioplasm with attached side chains, which are more firmly or more loosely attached, affords a perfectly adequate explanation. The more advanced the organism the greater the

number of these attached side chains, the more recent the attachment of a side chain, the more unstable that attachment. As a consequence, any profound disturbance will, according to its intensity, tend to cause the loosening and removal of the more unstable of these side chains in general in the order of their stability of attachment. And as the structure of the individual and of the individual cells is the expression of the constitution of the idioplasm, of the germinal idioplasm, and of the idioplasm of the individual cells, so according to the intensity of the disturbance will there be greater or less reversion to an earlier stage in the developmental history.

Let us now apply this theory to those special problems which I have referred to as being of peculiar interest to us as medical men—Can acquired defects be transmitted?

In seeking to answer this question, at least three orders of phenomena have to be recognised and distinguished. These are:

1. THE NON-INHERITANCE OF ACQUIRED MUTILATIONS.

To these I have already referred. We cannot conceive the direct transmission of identical lesions of this order from parent to offspring. At most we can conceive the possibility of indirect effect where the mutilation is extensive or affects organs playing an important part in general nutrition.

2. THE INDIRECT INHERITANCE OF ACQUIRED DIATHESIS.

With reference to diathesis, this also may be laid down that acquired disease and the effects caused by disease cannot in general be transmitted in such a way that the offspring presents lesions identical with those produced in the parent, though it has to be recognised that there is the possibility of modification in that offspring due to the parental disease. There is the possibility of a certain amount of transmission not of the identical local lesion caused by the disease in the parent, but of a modified or impaired condition of the germ plasm. We must recognise that constitutional disease, by leading to disturbance in the activity of important organs, tells not only directly upon these organs, but secondarily upon other organs—that it leads, for example, to altered condition of the blood, and so to altered nutrition of all the cells of the body. Among other cells, the germ cells may be directly affected, their idioplasm modified, and the offspring directly influenced. Conditions affecting the parents are capable of influencing and modifying the descendants. It is this which is forcibly brought home to us in our medical work. It is changes of this order which are almost inevitably neglected by the biologists—for they are not within their ken. The changes brought about in the tissues by what is essentially chronic intoxication may be so slight as to be inappreciable; microscopical examination may reveal nothing, even by their physiological effects can their existence be recognised. It is in the study of these conditions and their effects that medicine can afford the most valuable aid in the matter of inheritance.

All infectious diseases are intoxications. If a parent be the victim of syphilis, it is obvious, from febrile and other phenomena, that not merely are there local toxic phenomena at the foci of growth and multiplication of the germs of the disease, but that the toxins pass into the general circulation. They may produce no immediate structural changes in the cells and tissues, but we have evidence that the protoplasm of various tissues is affected, although the results of the disturbance may only show themselves after long years. Indeed, the only explanation we can give of many remote effects of syphilis is this: that during the active period of the disease there has been a change wrought in the constitution of the cells of sundry tissues, slight and subtle it may be, but sufficient to lead to premature exhaustion of the idioplasm of those cells. It would be absurd to argue that the immature germ cells lie absolutely dormant in the organism; they need nourishment, they assimilate, they are thus also liable to absorb circulating toxins and their idioplasm must be affected in this act. Hence, while syphilis as such is not inherited, the toxins of the disease must be regarded as liable to set up molecular disturbances in the germinal idioplasm, and the offspring may show, not syphilitic lesions but parasymphilitic lesions—various forms of arrested and imperfect development of different tissues, due to the intoxication and therefore modification of

*To the worker in bacteriology the hesitancy on the part of biologists in general to accept environment as a most important factor in originating variation is almost incomprehensible. Nothing is more remarkable in the study of the lowest unicellular forms of life than this effect of environment in bringing about changes in character—changes which tell not only upon a limited series of generations (as I have already pointed out), but permanent in their nature. By no means, save altered environment, could Hansen, taking isolated yeast cells or "spores" (100 per cent. of which, when cultivated under ordinary conditions, gave rise to spore-bearing forms), and subjecting these to the highest temperature at which growth could still occur, obtain a race or variety of yeast which now, after twelve years, has continued to grow under ordinary conditions without once developing spores. By no means save altered environment is it possible to explain Vincent's conversion of the absolutely harmless potato bacillus, or again, the bacillus megatherium (by long-continued sojourn within closed collodion capsules in the peritoneal cavity of animals) into a form profoundly pathogenic and fatal to rabbits, mice, and guinea-pigs in the course of a few hours. The argument that phenomena observed in unicellular organisms cannot be applied to multicellular organisms is, to say the least, severely strained. The extent to which environment acts as a factor may, it is true, be diminished in these, but surely it cannot be regarded as being eliminated and rendered negligible.

the germ plasm while still a portion of the parental organism.

Parental intoxication, therefore, is seen to be capable of directly affecting the germ cells, and if there be no direct transmission of the effects of such intoxication, certainly there are indirect effects. In demonstrating the truth of this statement, it must be freely admitted that conjugation and intrauterine existence introduce grave complications. In fertilisation, it is obvious that the idioplasm of the sound parent may largely neutralise the defective constitution of that of the diseased parent; while we have constantly to guard against ascribing to defects in the germ plasm conditions acquired during intrauterine life. If the mother is the subject of any toxic state (to use the broadest possible phrase), not merely may the ovum be directly affected prior to fertilisation, but in the course of foetal existence the organism of the offspring, deriving its nutrition as it does from the maternal blood, is liable to be affected and disturbed by circulating toxic substances, and the development of the different tissues to be correspondingly influenced. The only conditions we can safely study are those in which the father is the subject of disease or intoxication, the mother exempt. Nor is it easy in cases of infectious disease, nor, even in frank intoxications such as the alcoholic, to be perfectly sure regarding maternal exemptions.

Paul's observations, however, upon the effects of lead poisoning afford a most convincing demonstration along the required lines. Plumbism is peculiarly a trade disease. It particularly affects those following certain occupations; thus often the male wage-earning member of the family is alone exposed. Studying the history of 32 pregnancies in which the father was the victim of saturnine poisoning, the mother free from the condition, Paul obtained the following remarkable statistics:

Twelve resulted in death of the foetus before term (11 abortions, 1 child born dead); 20 children were born alive, of which:

- 8 died during the first year.
- 4 died during the second year.
- 5 died during the third year.
- 1 died later.

2 alone were found to be living, 1 aged 20 years, the other only 21 months.*

In connection with the effects of paternal syphilis, Fournier has contributed strong evidence along the same lines, pointing to the great frequency of arrested development of various orders, from intrauterine death to infantilism. To his statistics objection may be made that certain of the infants recorded by him probably suffered from the actual disease acquired *in utero*, secondary to local infection either of the placenta or the membranes. Discounting this possibility in a certain proportion of cases his figures still remain very remarkable. But what is needed is a more searching study of these cases of defective children, the offspring of a healthy mother and an infected father, to make sure that we are dealing with parazyotic as distinct from zymotic lesions. In connection with the subject, Gheorghiu, studying malformations, has pointed out that the remarkable frequency with which there is on inquiry obtained a history of not merely of the mother, but of father or mother having been a sufferer from acute or chronic infectious disease at the time of conception.

3. THE DIRECT INHERITANCE OF ACQUIRED CONSTITUTIONAL STATES.

In the above series of phenomena we have dealt, as I say, not with the direct transmission of acquired conditions, but with the deleterious influence leading to general defects of development and due to the action of toxic agents upon the germ cells prior to conception. Can we advance further and see evidences of direct transmission of acquired constitutional states? I think we can.

If, for example, an animal acquires immunity to a disease, we are convinced that the process of acquirement is a chemical process, that the action of the toxin of the disease has been to set up certain molecular changes, certain alterations in the composition of the cell substance, so that that cell sub-

stance now responds in a different manner when brought into contact with the toxin; and once this modification in the cell substance is produced the descendants of this cell retain the same properties. So that immunity to one special disease is not merely a momentary but is a more or less lasting state of the system. It is true that it tends not to be permanent; we see that where it is attainable, the more prolonged and the more severe the changes set up in the process of immunisation, the longer it lasts. We recognise further the action of the law that properties of most recent acquirement are soonest lost, and that there is a distinct tendency for the condition, or acquired state, of the cells to pass away. Nevertheless, we admit that inheritance of the acquired condition has to be granted in the case of the body cells in this connection. Here again, if these processes obtain in connection with the body cells we must logically admit their action in the case of the germ cells. The idioplasm of body and germ cells is of like origin, and must be susceptible to like influences.

The toxins circulating in the blood of the individual undergoing immunisation must also affect the germ cells; they must acquire immunity—and the individuals developed from them must, subject to the law of loss already noted, have the same properties. Now, as a matter of fact, this transmission of acquired immunity has been occasionally noted, where, for example, both parents (rabbits) have been rendered immune to the *B. pyocyaneus*, the offspring have been found more refractory to pyocaneus infection, but in general the observations have been negative. This, as I have hinted, is only to be expected, on account of the easy detachment of, if I may so express it, newly acquired side chains. It is, however, legitimate to suppose that successive immunisation through several generations will cause the new side chains to become more and more fixed, and that racial immunity is brought about by these means—a view more probable than the alternative of mere "survival of the fittest."*

Conversely, in those cases where immunity is not developed, in the case of chronic conditions like tuberculosis, we can along these lines comprehend how the toxins weaken the germ cells along the same lines as they weaken the general tissues of the body, and as the resistance of the body in general to a special microbe and its products becomes less and less, so also the idioplasm of the germ cells becomes less and less resistant, and so from parental disease the offspring gains a peculiar susceptibility to one special disease. So that, in short, from disease acquired by the parents a particular diathesis is developed, a special susceptibility to the particular form of disease.

Here Weismann would make the somewhat subtle distinction that we are not dealing with the direct transmission of acquired parental defects; that the toxins produce these results not by acting on the body cells but by direct action on the germ cells; that the inheritance is blastogenic, not somatogenic.³ This is a sorry and almost Jesuitic play upon words. Let us grant that they are of blastogenic origin; they are nevertheless of individual acquirement. The individual consists of body plasm and germ plasm, and whether the defect tells primarily or secondarily upon the germ plasm of the individual we have here examples of conditions acquired by the individual being transmitted to the offspring. But we can go further.

Exogenous and bacterial intoxications are not the only intoxications. We recognise yearly more and more the existence of states of truly endogenous intoxication, autointoxications—of disturbed states of the constitution due to disturbances in glandular activity—to excess of certain internal secretions, or of the substances ordinarily neutralised by the same. Such disturbances acting on the germ cells would be truly somatogenic.

If gout and the gouty diathesis are, as many hold them to be, of the nature of true autointoxications; if in a given percentage of cases (in France 12 per cent., according to Bouchard) the gouty state shows itself in those giving an absolutely negative history of gout in their progenitors, then we are at liberty, I think, to regard the gouty diathesis as an

* Legendre, in his essay in Bouchard's *Traité de Pathologie*, vol. i (which the first place directed me to Constantin Paul's admirable article) gives a table of 141 pregnancies which I cannot find in the paper referred to. Possibly this is from a later article by the same author, but the proportion of abortions as given by him is so much larger that I doubt if this can be the case.

* It goes without saying that where both father and mother are immunised through successive generations and the foetus—and its germ cells—acted upon by the maternal blood and milk, the development of acquired inherited immunity should become yet more assured.

example of truly somatogenic acquirement of an inherited and inheritable constitutional state.

Defect in bodily metabolism has led to intoxication of the germ cells, and the offspring show a peculiar liability to be the subjects of intoxications of the same order. Here what is transmitted is a constitutional state, and that constitutional state may manifest itself in more than one way, but no one will deny that this is truly inheritance of an acquired condition. We must therefore, I hold, be prepared to admit the transmission of inheritance of certain orders of acquired constitutional conditions. We must see that it is not necessary with Weismann to deny strenuously the inheritance of each and every order of acquired defect, and that along the lines of some such theory as that outlined this evening, we gain a fuller harmony between theoretical considerations regarding the nature of inheritance and the facts as they present themselves to us day after day.

REFERENCES.

¹ Weismann, *On Heredity*, authorised translation by Poulton, Schönland, and Shipley, Oxford, 1889, p. 413. ² *Loc. cit.*, p. 170. ³ Weismann, *On Heredity*, p. 410.

THE PATHOGENESIS OF TABES AND ALLIED CONDITIONS IN THE CORD.

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If the etiology of tabes were accurately determined, a large and important chapter in neurology could be written. Two sets of views prevail. The view generally held regards the degeneration of the neuron as primary, and the affections of the connective tissue, vessels, and neuroglia as secondary, in importance. A few writers hold another view, directly negative of the first. According to them, the primary affection is to be found in the vascular connective tissue in which the nerve fibres lie. This constitutes what is known as the vascular theory of the disease, and the various considerations in its favour and against it have from time to time been keenly discussed. In 1880 Adamkiewicz proposed to explain all cases of tabes in this way; a few years later he concluded definitely that some cases were parenchymatous in origin. Records of isolated cases have been published, notably of cases in their early stages, in which the vascular origin of the disease has been clearly established. But while the accuracy of these observations has not been questioned, the cases recorded have been regarded as accidental, and they have not shaken the commonly-received opinion. Some living authorities entertain the vascular theory in a modified form—namely, with regard to the nutrition of the posterior nerve roots (Redlich and Obersteiner). But, on the whole, it receives little support, as may be seen by a perusal of recent discussions and important writings on the subject.

At a discussion on tabes by the London Pathological Society in 1899, reference to the vascular theory was confined to one or two speakers, who hinted that perhaps too much was taken for granted with regard to the secondary importance of the vessels. The same thing occurred two years ago at a discussion in the New York Neurological Society, and no greater deference is shown to the theory in a recent critical summary of views upon the subject of tabes by Soury,¹ who, however, gives clear expression to an opinion which is pretty universally held, when he states that the old view which regarded tabes as a disease of the posterior columns, or even as a disease of the cord itself, must be abandoned. It is to be regarded, he says, as a disease of the central nervous system. This marks a distinct advance upon earlier conceptions. Put shortly, then, tabes is now almost universally regarded as a primary disease of the nervous system. The general position is thus defined by Gowers:

The great fact of the pathology of tabes is that it is a neural degeneration in the sensory nervous system, peripheral and central. . . . The degeneration commences in the nerve elements themselves, the overgrowth of connective tissue which gives to the lesion its characteristic features is secondary.

The views advanced in this paper bring me into line with those who support the vascular origin of the disease, as opposed to those who hold that the nervous elements are primarily affected. I do not propose to discuss the condition

of the cells in the posterior root ganglia, nor the condition of the membranes over the posterior columns and nerve roots, as the inconstancy of these changes is admittedly so great as to indicate that they cannot reasonably be considered to have primary significance. Moreover, the experimental work of Lugaro, corroborated by that of Marinesco, van Gehuchten, and others, has shown that section of the posterior nerve roots, and even of the columns themselves, does not morphologically affect the posterior root ganglion cells. It will probably conduce to clearness if I preface my detailed argument by a brief outline of the position I occupy. I hold that tabes is not a "nervous" disease in the sense usually apprehended, and that the lesions in and around the vessels are of primary importance, the lesions of the neurons being determined by local interference with the blood supply. (This does not exclude the consideration of a varying vitality of neurons as an important factor in the disease.) Further, there is, I think, good ground for the belief that the condition is dependent on a chronic autointoxication, the vascular lesions being to some extent general, but tending to be more advanced locally, and that the more advanced local changes determine a failure of nutrition in the adjacent nerve elements. If these views are correct, it appears to me that the condition ought to be curable in the early stages, and further, that the present tendency to differentiate tabes sharply from many other diseases in which there is a well-marked lesion of the cord of an allied character is to be deprecated. We should rather investigate the nature of different toxins and the conditions which have brought about variations in the results of their action.

COMPARATIVE PATHOLOGY.

The importance of the study of comparative pathology for the elucidation of problems in the etiology of nervous affections in the human subject is hardly sufficiently realised. It is more than probable that a close study of nervous disorders in lower animals would contribute largely to our knowledge of the causation of allied diseases in man. Until recently no attempt has been made to give a systematic account of any disease of the nervous system in domestic animals. While the existence of such diseases has been inferred from observation of symptoms during life, complete pathological records are wanting, and even the clinical descriptions of these supposed nervous disorders, given in standard veterinary works, are extremely vague and unsatisfactory.

Some time ago I had an opportunity of observing a horse affected with ataxia, paraplegia, and a bilateral affection of the knee-joints of a nature not described in veterinary literature. The combination of clinical features led me to diagnose a lesion of the cord, most marked in the posterior columns, with associated neurotrophic joint lesions, of a nature akin to tabes in the human subject. The lesions found at the *post-mortem* examination were of a grosser and more widespread nature than had been anticipated, but the diagnosis was found to be substantially correct.² Special emphasis is laid on the greater proclivity of the vessels in the posterior part of the cord to be affected with an extreme degree of hyaline and fibroid thickening, and it is suggested that the process is due to some toxic action. I am aware that, even if this suggestion were established as correct, its value as a contribution to the etiology of tabes depends upon the existence of a real relationship between tabes and the pathological condition described. I believe that such a relation exists, and that, if due regard is paid to the different life-histories and habits of the two subjects, the nervous disorder in the horse throws a direct and important light on its analogue in the human subject. This opinion may be corroborated by the striking fact that the clinical appearances arising from the disturbance of the muscular sense in the lower animal correspond in the main to those encountered in man. The features presented in the early stages of such a disturbance are well represented by Fig. A. The animal shows an unnatural position of the hind limbs, which are more spread out than is natural, and an undue prominence of the knee-joint with slight eversion of the limb is apparent. The fore legs also are unduly wide apart. The condition of the joint referred to is due to loss of muscle tone, and probably also to direct relaxation of the joint structures. Although this