SOME REMARKS ON THE INHERITANCE OF ACQUIRED IMMUNITY.

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IF our notions regarding the process of generation have become somewhat more distinct by recent investigations into the minute structure of the cell and the mode of its propagation, yet this advancement of our knowledge is so infinitesimal compared with the mystery in which the whole matter is enshrouded that it throws little or no light on the many problems of importance with which physiology and clinical medicine confront us concerning the laws of inheritance. Even with regard to that fundamental and much-disputed question of the transmissibility of acquired characters we have not come to anything like a general and complete understanding. Weismann's theoretical objection to the possibility of such transmission is derived from our inability to conceive how an alteration in the cells of the body could react upon the germ cells in such a manner as to induce in the latter a reproduction of the acquired character. It has to be admitted that the hypothetical and often fantastical constructions which have been devised to explain such a relation between body cells and germ cells are altogether unsatisfactory, and never rise above the level of more or less acceptable hypotheses. But in a subject so involved in obscurity the present incomprehensibility of certain relations can hardly serve as an argument against their existence. The development of the apparently uniform germ plasma into the infinite differentiation of a complex cell state is, although no longer a matter of doubt, perhaps not less inconceivable.

Of more convincing power is the critical part of Weismann's argument. It is his incontestable merit not only to have given a more precise shape and formulation to many questions relating to the subject of hereditary transmission, but also to have done away with many prejudices by showing the frailty of the basis upon which they were founded. Frequently the hereditary transmission of some pathological condition, for instance, had been accepted, for no better reason than that it was found in two or more subsequent generations. If the weakness of such a conclusion is obvious it is nevertheless frequently to be met with in medical literature, and it is in this sense that only lately the complaint has been made, not without justification, that in discussing the hereditary transmission of pathological conditions, the question itself was frequently but incompletely understood. If Weismann has not succeeded in disproving the possibility of the hereditary transmission of acquired characters, his opponents are equally at a loss to furnish exact proof of its existence.¹

This fact is well illustrated by O. Hertwig's² excellent work on the cells and tissues, in which the whole theory of biogenesis and the problem of inheritance form the subject of a thorough and most exhaustive investigation. With many of the most distinguished biologists of our days, he believes that acquired characters are transferable to the germ. He endeavours to render this process intelligible by pointing to the analogy between it and certain properties of the brain substance, at the same time admitting that "this analogy is far from being an identity." But the proofs which he adduces in support of the existence of the supposed relation between body cells and germ cells are scanty and unconvincing. Two of them are taken from one-celled animals. The first is derived from the phototaxis of certain algae, the second from certain "physiological varieties" of some bacteria, which under certain artificial conditions lose their toxic qualities, and transmit this "acquired character" of lost virulence to the next generation.

With regard to the irritability of the algae to light, we are told that it can be modified by exposure to strong light and to high temperature, and that "nobody would be surprised" if their progeny also showed "some similar property." This supposition may be psychologically correct, but it does not furnish an example of the hereditary transmission of an acquired character. In the case of the bacteria the loss of their toxic properties can hardly be described as the acquisition of a new character. But, quite apart from the

inadequacy of the testimonies thus adduced, it is obvious that observations taken from unicellular organisms are unsuitable to explain the mechanism by which the different cells of a complex body act and react upon each other.

As regards the more complex organisms Hertwig gives only one instance. This is taken from the domain of pathology—namely, the hereditary transmission of acquired immunity, which, as he says, has been demonstrated by the experiments of Tizzoni and Ehrlich. But while the experiments of Tizzoni are inconclusive, those of Ehrlich point just in the opposite direction. Ehrlich's ingenious experiments—made on mice with the vegetable toxins of ricin, abrin, and robin—have led him to the conclusion that no trace of immunity is ever conferred by parent upon offspring through the germinal cells, either by the sperm or by the ovum. This has been confirmed for the toxin of tetanus by experiments made by Hübener and Vaillard on mice, rabbits, and guinea-pigs, and for the toxin of diphtheria by experiments made by Wernicke on guinea-pigs. I am therefore unable to understand how Ehrlich's experiments could have been adduced in proof of the germinal transmission of immunity. Tizzoni, on the other hand, believed he had demonstrated the paternal—that is, germinal—transmission of immunity by experiments made on rabbits with the toxin of rabies.

These experiments exhibit a marked source of error, because the female animals were not in a normal condition, but had been previously rendered highly immune to the tetanus toxin. Roux and Calmette have shown that the artificial immunity to certain toxins is not strictly specific, that in the same way specific antitoxins may be protective against more than one toxin; thus, for instance, the tetanus antitoxin is also protective against snake poison, and the same property belongs to the serum of animals which have been rendered immune to rabies. The possibility is therefore not excluded that the serum of animals rendered highly immune to tetanus may have a certain influence upon the poison of rabies—in fact, that the immunity observed in the offspring of Tizzoni's experiments may not have been due to paternal transmission, but to the conveyance of the tetanus antitoxin from mother to child by the placental circulation. Moreover, Tizzoni's experiments have never been corroborated by any other observer. The germinal transmission of immunity, therefore, so far from being a fact established by experimental research, is negated by all the reliable experimental evidence we possess. It is also negated by all clinical experience. It is certainly a noteworthy fact that it is the only instance which a biologist of greatest learning is able to adduce in favour of the hereditary transmission of acquired characters.

The above-mentioned investigations by Ehrlich have also led to a positive result of considerable importance—namely, that the offspring may derive immunity from its mother in a twofold manner, by either the blood or the milk—that is, by the placental circulation or by suckling. It goes without saying that in these cases it is not the immunity which passes from the maternal organism to that of the child, but the antitoxin, and that the passive immunity of the offspring thus produced cannot be considered as an acquired character transmitted by true inheritance.

Ehrlich's results were obtained by experiments made on mice with vegetable poisons. Subsequent investigations have shown that these two forms of passive immunisation of the offspring do not necessarily go together. According to Vaillard, neither in guinea-pigs nor in rabbits does any degree of immunity to tetanus pass from mother to child by suckling; and Wernicke found that the suckling immunity to diphtheria in guinea-pigs, if it exists at all, is much less pronounced than, for instance, the suckling immunity to tetanus in mice. Yet in rabbits and in guinea-pigs as well as in mice a certain degree of blood or placental immunity is conferred by the mother on the child with regard to both the tetanus and the diphtheria toxin. These facts, interesting in themselves from a biological point of view, impart at the same time a wholesome warning against rash and premature generalisations. In particular they seem to dissuade us from the unhesitating application of results gained by experiments on lower animals to human pathology. Ehrlich's experiments have of late been made use of to explain all sorts of real or imaginary phenomena of clinical medicine. In truth, how-

ever, up to the present day no clinical observations exist pointing to the existence of a similar transmission of immunity in the human race. If there is nothing to prove that immunity as an acquired character—that is, active or histogenic immunity—is ever transmitted to the next generation by true inheritance—that is, by the germinal cells, the placental and the suckling immunity also have, as far as we know, no exact parallel in human pathology.

Only a short time ago a question closely connected with this subject was again raised in one of our leading journals, and led to some controversial correspondence—the question of intrauterine vaccination. It seems to have escaped the attention of those who originated and took part in this discussion that exactly the same question had been raised for the first time some twenty-five years ago in the same journal, and that it has since been the object of much careful clinical research. All the most reliable evidence we have got on this point leads to a negative result. It will be found that the few apparently positive results which have been reported are more or less open to doubt, because the methods employed and the precautions taken afford no sufficient guarantee for their conclusiveness. Even if these exceptionable and more or less contestable cases are granted, the fact remains that, as a general rule, intrauterine vaccination does not take place. If vaccination is only a form of bacterial infection, it is an open question whether the few alleged exceptions, are cases of intrauterine infection in its proper sense or of intrauterine intoxication, that is, of conveyance of the toxic agent of vaccination from mother to child through the placental circulation. Of the milk, as the vehicle for the conveyance of vaccinia, nothing is known.

It has long been remarked by clinical observers that the newborn enjoy a certain degree of immunity from certain acute infectious diseases, which childhood is particularly liable to, such as measles, scarlet fever, etc., and that this relative immunity extends over the first six months, and to a lesser degree even over the first year of life. This has been explained in different ways. While some are inclined to attribute it solely to the relative want of the opportunity for infection, which it is said is not given to its full extent in infancy, others have ascribed it to a certain state of congenital immunity to a peculiar condition of the infantile tissues.³ At the same time it has been observed that mothers suffering from such infectious diseases (also from small-pox) may on the whole suckle their healthy-born children without infecting them. This fact also has found different explanations. On the one hand it has been attributed to the natural immunity of the newborn in general to certain infections, and on the other hand to a particular immunity acquired either *in utero* or during lactation, and consequent upon the mother's disease. Here, again, Ehrlich's experiments have been referred to as a parallel. But it is evident that these experiments have been totally misunderstood. In Ehrlich's experiments the mother is in a high state of immunity, while in the case we are discussing the mother is suffering from the actual disease.

Exactly the same mistake has been made as I have pointed out before,⁴ with regard to the explanation of the so-called "law of Profeta." Whatever the right interpretation of the infantile immunity may be in these different cases, there is no doubt that Ehrlich's experiments give no clue to it, nor that it can ever be regarded as due to hereditary transmission.

In fact, everything that is acquired by the child during its intrauterine life cannot be considered as the outcome of heredity in its proper sense, even if due to a similar or the same condition in the mother. In this stricter sense, those characters only are inherited which lie "preformed" in the germinal cells at the time of impregnation. By some writers on hereditary syphilis a difference has been made between hereditary and congenital syphilis, in so far as the latter term has been applied to the disease if present at the time of birth, while the former is restricted to those forms of the disease which do not lead to obvious symptoms until some time after birth. This distinction is unsatisfactory, and has generally been abandoned, because the syphilitic infection, whether germinal or placental, does not as a rule manifest itself until some time after birth, and because congenital syphilis in this restricted sense may follow either mode of infection. But a

distinction has always, and rightly, been made between germinal infection on the one hand, and post-conceptional or placental transmission of syphilis on the other. Although we do not know by any difference in the outward symptoms whether the infantile syphilis is derived in one way or the other, yet from a pathological point of view this distinction is of considerable importance. Of course all paternal infection can only be germinal.⁵ That such a thing as germinal transmission exists in maternal infection we can only presume from analogy, because, as said before, germinal and placental syphilitic infection do not differ in the nature or succession of the clinical symptoms they produce.

It seems that in the case of small-pox congenital immunity to vaccination in the child is occasionally produced where the mother is suffering from the disease during gestation. A number of observations exist in which children born under such circumstances have been vaccinated without result. Statements of this kind are always open to the objection that the inefficiency of the vaccination was due to some imperfection of the method employed, or that vaccination was not tried repeatedly. Yet there are cases on record which seem to hold out against all reasonable criticism. But we do not know of any case in which the parent's disease or vaccination previous to impregnation has produced the same effect. It has been alleged that such an influence of the vaccination of previous generations could be traced in the fact that in countries in which compulsory vaccination is practised occasional small epidemics of variola are of a milder character than formerly. But this fact admits of a different and more natural interpretation. This mitigation is certainly partly due to the bulwark which general vaccination has erected against the spread of the disease, partly to the advancement in the treatment of infectious diseases in general, partly and not least to the more hygienic methods—such as prompt and complete isolation, etc. On the other hand, cases of a very severe, destructive, fatal character are not altogether uncommon even under these circumstances. As far as our present experience goes, no influence of the parent's vaccination previous to impregnation is traceable in the offspring, either by insusceptibility or by a diminished susceptibility to vaccination—that is to say, that nothing is known about a germinal transmission of immunity from parents who, previous to impregnation, had been subject to vaccination or to an attack of small-pox.

Ricord believed that a person who by a first attack of syphilis has acquired immunity to subsequent infection confers this immunity upon his offspring. But his frequently quoted saying, "*C'est un heritage comme un autre*," is only one of his many *bons mots* which in course of time, and through the prestige of his great authority, have gained the credit of scientific truths. In my paper on Congenital Immunity to Syphilis I endeavoured to show that the facts which might be, and have been, adduced in its support are insufficient in number as well as in demonstrative power, and that, on the other hand, the general experience of every-day practice points in the opposite direction. What is true for these two infections holds good for all of them. It seems that in some infections, as for instance tuberculosis, parental disease creates in the germinal cells a certain predisposition which renders the offspring more liable to acquisition of the same disease, but we know of no infectious disease which in the same manner exercises a protective influence upon the product of generation. With regard to that congenital immunity which in some infectious diseases is occasionally conferred upon the offspring by a mother suffering from the disease during gestation, I have only to add that this immunity is always only temporary and of short duration, and that for this reason alone it could not be regarded as an acquired character.

If no clinical proof exists to show that parental immunity is ever transmitted by the germinal cells to the next generation, there still remains the possibility that such transmission takes place all the same, only to such a minute extent that it escapes detection by the rough and somewhat clumsy methods of clinical observations. In his lectures on the Pedigree of Disease, Mr. Hutchinson expresses views which are on the whole adverse to the hereditary transmission of acquired immunity, yet he cautiously adds that if it exists at all it can only be in an "infinitesimal" degree. If I understand

him rightly, he means to leave open the possibility that during the succession of generations each succeeding generation may acquire an additional degree of immunity, and that this originally infinitesimal amount may accumulate to a finite appreciable amount, or even to total immunity, in the same way that Darwin, to account for the hereditary transmission of acquired characters, presupposes the accumulative effect of a long series of generations during which the influence which first led to the acquisition of the new character was constantly at work. In this form the theory of the hereditary transmission of immunity has indeed frequently been advanced in order to explain the immunity which certain human races—negroes and mulattos—enjoy with regard to certain tropical diseases. While originally liable to the deleterious influence of these infections in the same way and to the same extent as the white races, they are said to have become proof against them by living in regions in which every following generation is exposed to and attacked by the same poison, and in which every generation leaves to the next the “infinitesimal” amount of immunity inherited from the preceding *plus* the equal amount acquired by itself. With regard to this theory I have in the first place to remark that it is by no means identical with that first advanced by Dr. W. C. Wells as far back as 1813, and adopted by Darwin, which explains this racial immunity by natural selection, by the “survival of the fittest.” According to Wells, among the different varieties of men which populated the middle regions of Africa some were better able to resist the endemic maladies than others, they consequently survived and spread, while the others perished. It therefore is not an acquired character that was transmitted, but a natural immunity inherent in a dark-coloured race. This theory is unsatisfactory, because, while it may explain the extermination of the light-coloured races and the survival of the others, it does not account for the immunity of the latter. Not long ago the same hypothesis has been extended to the microcosm of the animal cell state, and has been made use of to explain acquired immunity in general (Grawitz). The “fittest” of the cells, those best able to resist the toxic influences of bacterial poisons, survive and multiply, while those of inferior powers of resistance succumb. But in this extension the theory is less satisfactory still, because there is no imaginable reason why of an aggregate of uniform cells, without any “racial” differences whatever, some should be endowed with defensive properties which the others want. Any theory which explains the immunity of certain races by some natural process of evolution will be more acceptable than this “first case of recognition of the principle of general selection,” which leaves the racial immunity altogether unexplained as a mysterious appendix of a pigmented skin surface. But this accumulation hypothesis, which implies the co-operation of inherited and acquired immunity, if at first sight plausible and captivating, is also not free from objections.

In the first place a more thorough study of tropical diseases in our colonies has somewhat shaken the unconditional belief in many a statement which by textbooks has been stamped with an almost axiomatic and catholic character. The immunity enjoyed by coloured races seems by no means so absolute as has been generally taught. In not a few cases on close inquiry—and a reliable previous history is, under the circumstances, not always an easy matter—the immunity of the adult natives seems to have been the result of an attack in early life. On the other hand, it is the newcomer, the inexperienced settler, who is most exposed to infection, while those who become accustomed to the climate and a suitable mode of living are much less in danger. But there is one circumstance in particular which more than any other detracts from the plausibility of this theory, that is, that no similar gradual immunisation has ever been observed in the white races with regard to any of the infectious diseases which they have suffered from.

With regard to vaccination it may be objected that a long enough time has not yet elapsed to produce such a result. The same objection, however, could hardly be raised in the case of syphilis, or indeed that of small-pox, unless one assumes that the struggle between the black races and certain tropical diseases dates back to prehistoric times. Until we have at least some clinical or experimental proof that infectious diseases lead by themselves to a gradually

increasing immunity in the offspring, the accumulation theory as an explanation of racial immunity, will remain an unsubstantial hypothesis.

NOTES AND REFERENCES.

¹ It goes without saying that I am not speaking here of the hereditary transmission of infectious diseases. Wherever this has been adduced to support the doctrine of the inheritance of acquired characters, it has been done in utter misconception of its meaning and scope. It has also to be remarked that bacillary infection of the germ plasma as the cause of congenital infectious disease, although perhaps a clinical postulate, has not yet been demonstrated pathologically. The experiments made by Baumgarten and Maffucci to prove germinal infection, by injecting tubercle bacilli into fowls' eggs, and thus producing chickens affected with tuberculosis, are based upon the same fallacy of which Sir John Falstaff was guilty when he objected to “pullet-sperm in his brewage.” The hen's egg (ovum) is not the female germ (ovum), but an intermediate stage between the latter and, as Cressida has it, the “chicken 1 the shell.” The argument which underlies those experiments reads like a kind of pathological quibble on the double entente of the term “ovum.” ² Hertwig, Oscar, *Die Zelle und die Gewebe*, Jena, 1898. ³ The remarkable experience which J. Schreiber (*Deut. med. Woch.*, 1891, No. 8) has had with tuberculin in newborn children of non-tuberculous extraction—he injected 40 healthy infants with large doses of tuberculin (up to 5 c.cm.) without any febrile or other effect—either seems to prove that the infantile tissues possess a degree of irritability to certain bacterial products which totally differs from that of the adult, or that the power of excretion is much higher. In the same way the tolerance which infants show to comparatively large doses of mercury may be explained. ⁴ *British Journal of Dermatology*, vol. ix, 1897, p. 436. ⁵ Indeed, the absolute proof of the possibility of the inheritance of acquired immunity should primarily be sought for on the paternal side. In this way all questions of mere evanescent immunity acquired from the mother *in utero*, or during suckling, and which is to be regarded as nothing more or less than an accidental poisoning of the fetus or child, would be entirely eliminated. No believer in the doctrine either of “acquired characters” or of “acquired immunity” would be likely to assert that the dominant factor was the ovum rather than the sperm. If we assume that the sperm equally well with the ovum can “pass on” an “acquired character” or an “acquired immunity” to the offspring, the convincing proof of the hypothesis were best sought for through the father, because, unlike the mother, his part in the production of life ceases with the act of coitus. ⁶ *Virchow's Archiv*, Bd. cxlii, 1888.

NOTE ON THE RESULTS OBTAINED BY ANTITYPHOID INOCULATIONS IN EGYPT AND CYPRUS DURING THE YEAR 1900.

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I AM indebted to the kindness of Colonel W. J. Fawcett, R.A.M.C., Principal Medical Officer in Egypt, for the following statistics dealing with the incidence of enteric fever and the mortality from the disease for the year 1900 in the inoculated and uninoculated among the British troops in Egypt and Cyprus.

	Average Annual Strength.	Number of Cases of Enteric.	Number of Deaths from Enteric.	Percentage of Cases Calculated on Average Annual Strength.	Percentage of Deaths Calculated on same Basis.
Uninoculated ...	2,669	68	10	2.50	0.40
Inoculated ...	720	1	1	0.14	0.14

These figures testify to a nineteenfold reduction in the number of attacks of enteric fever, and to a threefold reduction in the number of deaths from that disease among the inoculated.

In a note appended to the statistical table printed above, Colonel Fawcett observes that the measure of protection resulting from the inoculation is not fully disclosed by a comparison of the figures given in the table. Owing to the circumstance that soldiers inoculated in previous years are in the statistics included among the uninoculated, the number of the uninoculated was in reality smaller, and the number of the inoculated was in reality greater, than the figures set down for these groups in column 1 of the table above. The figures in