of the perchloride of mercury and iodide of potassium, has perhaps a theoretical basis of justification, but practically little good can be ascribed to it. The latter-mentioned solution may have a higher claim, as in several cases in which it has been administered temperature falls and the patient seems easier. It may be, however, that the mere pricking of the tense capsule of the gland, even by needle punctures, may serve to relieve tension and thereby pain. This leads one to the belief that subcutaneous incision of the gland may be attended with beneficial results, and it is a method of surgical procedure not without precedent. Early free incision of the gland is not to be recommended, nor can excision be in any way justified. The disease is a polyadenitis, and of so extensive a nature that eradication of infected glands is an impossibility. A gland when swollen, red, and painful may be smeared with glycerine and belladonna, or poulticed to relieve pain, and when fluctuation is perceptible it should be opened, but further procedure is useless. When pus is evacuated, dusting the wound with iodoform and ensuring thorough drainage are the means by which the best results are obtainable.

Retention of Urine, a frequent concomitant during the delirium of plague, renders the use of the catheter imperative.

OBSERVATIONS ON A CONDITION NECESSARY TO THE TRANSFORMATION OF THE MALARIA CRESCENT.

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BIGNAMI, in the *Policlinico*, July 15th, 1896, gives a lengthy critique of Dr. Patrick Manson's views, expressed in the Goulstonian Lectures for 1896, as to the mosquito being the alternative host of the malaria parasite. Beginning by opposing Manson's leading postulate, that the so-called flagella are in reality flagellated spores intended for the continuance of the life of the parasite within some suctorial animal, on the grounds that the crescents are "deviate and sterile forms," and that the flagellate bodies are products of degeneration, Bignami proceeds to advance a mosquito theory of his own on certain epidemiological considerations. This he reaches by a process of exclusion. Refusing to admit either water or air as the medium of malarial infection, he arrives at the conclusion that that infection must be produced by inoculation—namely, by the mosquito; and assumes for these reasons that the mosquito is the alternative host of the parasite.

With respect to this latter part of Dr. Bignami's paper, it may be remarked that in it he does but repeat the almost obvious reasoning which must have led Laveran and others, besides Manson, to connect the disease with the mosquito, so that it appears scarcely necessary to consider this part at length here. We may perhaps object to some of his citations. Thus not everyone will be willing to discredit the possibility of malaria being carried from a shore to a neighbouring vessel, nor will everyone deny that drinking water may convey the disease. Bignami cites the general opinion of Italian peasants in favour of the view that water is not the medium; in India, however, an opposite opinion is frequently expressed, not only by natives, but by forest and survey officers, and sportsmen who are intelligent men, and who are continually in contact with malaria. On the whole, however, one may agree with the general trend of Bignami's remarks in this direction, but I cannot exactly perceive the grounds on which he assumes, as he seems to assume, that these views are distinct from Manson's, and hence worthy of such detailed examination. Manson has already suggested many of them in the Goulstonian Lectures and in the BRITISH MEDICAL JOURNAL, December 8th, 1894, and would doubtless have discussed them in greater detail if he had not thought them to be rather self-evident. Given the broad epidemiological facts of malaria, and granted that the mosquito is the carrying agent, we are easily led to conjecture that it may also be the alternative host, and that it may cause infection by means of its bite or otherwise. The latter idea has probably occurred to scores of people. I remember talking it over with Dr. Manson two years ago, have thought much about it since, and in August last, before seeing Dr. Bignami's paper, performed several negative experiments with a view to producing infection by mosquito inoculation.

But what should be emphasised here is that such epidemiological data are so uncertain that it is really quite impossible to base upon them alone any substantial theory. Dr. Bignami accuses Manson of expounding a theory of his own, and attempting to back it up with proofs, which are, however, matters of speculation more than of observation; and then proceeds to expound just the same theory, except that the most convincing argument is omitted.

Fortunately the theory as developed by Manson is founded on something far more solid than such merely plausible conjectures as Bignami has to advance. It is founded on his induction (for which we are indebted to him and to no one else) that the process of exflagellation is a developmental one intended by Nature to continue the life of the species within some suctorial animal. The epidemiological considerations serve only to fortify the presumption that the suctorial animal is the mosquito. And it is here, just at the climax of the induction, that Bignami falls away. He returns to the involution (degeneration) theory of Antolisei, Grassi, and Feletti, and of himself and Bastianelli.

Of course, if this involution theory be the true one, the evolution theory of Manson falls to the ground. On the other hand, if the evolution theory holds, the consequences must be far-reaching, because the parasites must evolve somewhere, and in all probability must evolve within the mosquito. Hence I should like to reopen the discussion here, especially as I think that I have some new facts to offer in respect to the transformation of crescents—facts which I believe to be subversive of Bignami's views.

Before considering such facts, however, we must remember that the crescents (which may be taken as typical of the flagella-bearing forms) are much larger, more permanent, and perhaps altogether as numerous in their allotted period as the æstivo-autumnal fever forms are in theirs. Hence any theory which ventures to stigmatise them as being sterile, degenerative, or useless, and the flagellate bodies as being mere agony forms, must face the question as to how it is that Nature, usually so purposeful, has in this respect proceeded so aimlessly. Is it likely that after producing bodies so carefully adapted in every detail to their habitat as the fever forms, she should proceed to fill the blood with as many sterile bodies which have no function to fulfil in favour of their species? On the contrary, the position appears to be directly opposed to the first teachings of the Darwinian system, which lay down that useless forms are excluded by the evolution of the species. If the crescents serve no purpose, how comes it that they exist? Either the case must be an extraordinary exception to a great general law, or, what is far more likely and what so often happens with those who argue the inutility of phenomena, the degenerationists have failed to detect the purpose served by the bodies referred to, and, in failing to detect it, have fallen back rather rashly on the supposition that there is no object. Hence we are, I think, justified in demanding at the onset very conclusive facts before accepting a theory so much at variance with accredited views as to the usual intentionality of Nature.[1]

The facts really given, however, are far from conclusive. Bignami, in the critique referred to, does not even reply to Manson's cogent reasoning against the degeneration theory; and he has not repeated my experiments with the mosquito. He returns simply to the old arguments which have already been traversed, partly at least, by Laveran, Danilewsky, Mannaberg, Manson, and others. They are:

ARGUMENTS FOR THE INVOLUTION THEORY.

1. That the nuclei of crescents do not participate in the development of the flagella, and that the latter contain no chromatin. Manson admits that this will be fatal to his theory, but cites Sacharoff (also a degenerationist) as giving an opposite opinion. Mannaberg also appears to be in opposition; so that in view of such disagreement among those who have specially studied the subject, as well as of the delicacy of the necessary investigation, we can hardly venture to accept the statement as being final; while, on the other hand, convictions forced upon us by other observations lead us to

doubt whether some mistake has not been made, and whether a revised inquiry will not demonstrate the facts now denied by Bignami.

2. The fact that flagellate bodies are found only after the blood has been drawn is looked upon as suggesting that they are dying or "agony" forms. But the same fact can be also explained by Manson's theory on the ground that exflagellation is the first step of the parasite outside the human body (in the stomach of some suctorial animal), and therefore necessarily occurs only after the blood is drawn.

3. The frequent vacuolisation met with in crescents and crescent-derived spheres is supposed to support the same view as 2, but similarly can also be shown to be consistent with Manson's theory. By this the flagellate body is taken to be an act of birth of the flagellated spores accompanied by the death of the residual mass of the parent body—a parturient dissolution, in short. Hence, in these residual masses, as well as in those crescents and spheres which have failed to give birth to their contained flagellated spores and which must evidently die sooner or later, we must certainly expect to find vacuoles as we find them in dying fever forms. The flagellate body is a degenerative body to the extent that all of it except the flagellated spores is dying; but this, while explaining the vacuolisation, does not admit that the flagella necessarily participate in that death.

4. Similar cases of degeneration are quoted, and Dr. Bignami does not hesitate to repeat the old comparison of the flagella with "the bacilliform filaments which in special conditions, as, for instance, under the action of an elevated temperature, originate from the red corpuscles." Even if there were any real similarity, we must seriously object that such similarity cannot prove identity. As a matter of fact, as Laveran and Mannaberg have already shown so vigorously that one is surprised at seeing this argument crop up again, there is no real similarity. For example, even Thayer and Hewetson, who reserve their opinion on the general question, say of the flagella, "Their appearance, their activity, the regularity of outline, the shape of the flagella are very much against their being compared to the sarcodic prolongations of degenerating red corpuscles, which are certainly very dissimilar in appearance." For my own part, I feel compelled to say that when we carefully observe the movements of free flagella, which are as vivacious as trypanosomes, and more vivacious than spirochætes, we must refuse to admit such a comparison for a moment.

ARGUMENTS FOR THE EVOLUTION THEORY.

Such are the arguments in favour of the degeneration theory: in my humble opinion the first only is of any value. Keeping this argument in mind, however, we may now consider the reasons against this hypothesis:

1. Both crescents and crescent-derived spheres undergo another process of degeneration after death—a process unlike flagellation, but similar to the degeneration of fever forms, and seen best in sealed liquid specimens. Crescents tend either to shrivel at the ends, leaving after a day or two nothing but the central mass of pigment (and this without true spherulisation or the escape of flagella); or become vacuolated, the pigment often being somewhat distributed and frequently taking on after twelve or more hours a rapid Brownian (?) movement, sometimes within the vacuoles (*sic*). The crescent-derived spheres tend to swell up after several hours like dead leucocytes, the pigment at first collecting eccentrically and then often assuming a lively Brownian movement. These, I submit, are the true degeneration forms of these parasites.

2. The flagella cannot be extruded sarcodic processes of dying bioplasm, not only for the reasons given by Laveran and Mannaberg, but because they may sometimes be seen within the parent parasites. I observed lately a sphere in a situation specially favourable to examination, within which three active flagella could with ease be detected, coiling and uncoiling themselves and tossing about individual pigment granules, their movements persisting after those of two other flagella, which had partially escaped, had ceased. The flagella referred to were clearly within the parasite and not above or below it; and were of the same size and shape as flagella seen in the usual positions. I have seen the same thing on several previous occasions.

3. If exflagellation be a process of death, why, we may ask, does it not occur among the fever forms? As it does not do so we must assume, on this hypothesis, that the bioplasm of these must be very different from that of the flagella-bearing bodies, which undergoes such extraordinary degenerative changes. Are we justified in believing that such a marked difference in the bioplasm of various individuals of the same species can exist?

4. But, perhaps, the strongest argument which may be adduced against the involution hypothesis is that the process of transformation of the crescents behaves under experimental conditions like a process of evolution, and not like one of degeneration. If (*a*) it be one of death and degeneration we may reasonably expect that it is due to some inherent quality in the bioplasm of the crescents—a quality which will produce the transformation referred to, either independently of surroundings, or, if anything, to a greater degree under conditions which hasten the death of the parasites. On the other hand, (*b*) if the process be one of life and evolution, it is likely to be encouraged by condition which exactly suit that life and evolution. In other words, (*a*) to support the involution theory we have to show that the transformation always occurs in, at least, a certain percentage of dying crescents, whatever the surrounding conditions, short of actual chemical alteration of the blood, may be; and that it is hastened by conditions which tend to kill the parasites. But (*b*) to support the evolution theory we should show that, unless a certain condition propitious to that evolution be present it will not proceed at all, and that, on the other hand, if we supply the required condition we may encourage it as much as we please. I venture to maintain that we can entirely check, or produce as much as we please, the transformation of crescents, and this simply by withholding or supplying the condition necessary to it.

Experiments suited to this inquiry are somewhat difficult to devise, because, if we use reagents to kill the crescents, and if thereupon it be found that they do not become transformed, it is sure to be said by the involutionists that the phenomenon has been checked by some subtle alteration in the bioplasm of the parasities induced by the reagent used; on the other hand, if the reagent hastens the transformation, it will be said that it has killed the parasites without altering the bioplasm, so that the result is only what was to be expected by the involution theory; and it will be very difficult to controvert these statements. It will be seen presently, however, that reagents are unnecessary; and that we have but to discover the condition necessary to the transformation in order to control it as we wish.

EXPERIMENT I.—The following experiment entirely checks the full transformation of crescents, and appears to me to be equally damnatory of the degeneration hypothesis. A lump of vaseline free from air bubbles is placed on the finger, and the skin is pricked through it (Plehn's method). A balloon of blood rises in the vaseline, which is then removed, blood and all, to a glass slide, care being taken not to expose the blood for one instant to the air. A cover-glass is now laid on the vaseline, which is so flattened out by pressure (either at once or later) as to produce sufficiently thin fields of vaseline-surrounded blood. If the experiment be properly done, it will be found that hardly any of the crescents have become spheres, even after twenty-four hours, and that none of them have become flagellate.

I have lately had the opportunity of repeating this experiment frequently with a case containing swarms of crescents. In one specimen alone I counted no fewer than 400 crescents, kept for four hours in vaseline, without chancing upon a single crescent-derived sphere; after this number was counted it appeared unnecessary to count further. Occlusion in vaseline clearly checks the transformation practically altogether. How explain the fact on the degeneration hypothesis? It cannot be argued that the vaseline exerts an inhibitory chemical effect upon the phenomenon, because if the blood be exposed to the air even for half a minute before occlusion in vaseline, the transformation does proceed even in crescents lying close to the grease; and again considering that the blood is merely surrounded by the vaseline and not mixed with it, it is otherwise extremely unlikely that this inert substance should have such a remarkable and immediate effect on crescents lying in the centre of the drop of blood. Nor can it be argued that the absence of transformation is due to the crescents remaining alive in the vaseline, because a specimen may be kept for any length of time without showing true spherulisation of the crescents, which, it is presumed, must die sooner or later. Moreover after twelve hours or so they exhibit the obvious signs of death referred to above. They die, but they are not transformed. Hence we may justly ask, How is it, if the transformation be a process of death, that it does not occur here, even though the parasites die? We say that a certain phenomenon is due to the death of an animal; the animals die in hundreds and do not exhibit it; what are we to conclude? (See also Experiment IV.)

It is evident, on the contrary, that the transformation is rather one of life and evolution, but that in the vaseline experiment we have excluded some condition which is necessary to its occurrence. It remains to discover that condition. The following experiments will, I think, show what it is.

EXPERIMENT II.—The finger is pricked and the drop of blood allowed to stand on the skin exposed to the air for five seconds to four minutes, and is then taken up on a coverglass and laid on the slide in the ordinary way. It will be found that the longer the blood has been exposed to the air the greater, roughly, is the number of crescents which proceed to spherulisation. The experiments should, if possible, be done with blood containing numerous crescents, say one or two in every field. Examination of the specimen should at first commence directly it is made, and an assistant should be ready to record observations as soon as taken. In a specimen made with thirty seconds' exposure (that is, an ordinary specimen) it will be found that about 20 per cent. of the crescents become spheres. Thus in an experiment which I take at haphazard from those made from the case referred to, which swarmed with parasites, I found, after thirty seconds' exposure and during five minutes' search, 158 parasites, of which 38, or 24 per cent., had become spheres in that time. In such specimens it will generally be noted that it is the parasites lying close to air bubbles which more commonly become spheres. An exposure of even half a minute long will as a rule result in the transformation of many more crescents; and with three to four minutes' exposure we shall find that about 90 per cent. of them have changed. Thus, in another unselected experiment made with three and a-half minutes' exposure and examined for five minutes I found 268 parasites, of which 242, or 90 per cent., had become spheres and 1 flagellate in that time. In another made with three minutes' exposure and examined from fifteen to twenty minutes after the finger was pricked I found 81 parasites, of which 68, or 85 per cent., had become spheres; of these 81 parasites, 20, or 26 per cent., were flagellate.

The following observations should be recorded in this connection. Making the specimen tends to check the transformation except in the proximity of air bubbles. I have not yet succeeded in converting all the crescents by any exposure. Perfect spheres may be already found within one minute after pricking the finger. The above experiments should be compared with Sacharoff's method of obtaining flagellates.

Comparing these experiments with the vaseline experiment we shall conjecture that exposure to the air is the condition necessary to the transformation of crescents. This, however, is not the case.

EXPERIMENT III.—A mosquito is allowed to suck the blood which is removed from the insect from a quarter of an hour to one or more hours after it began to suck. Even after a quarter of an hour practically all the crescents have become spheres. From fifteen to thirty minutes numerous flagellates are often found. At one hour 60 per cent. of the spheres present the appearance of a sphere after the flagella have escaped. I have examined over 20 mosquitos, and find the rule that all crescents are converted to be almost invariable. Of course if we examine the insect too soon we shall find some crescents which have only just been ingested.

EXPERIMENT IV.—Leeches are applied, removed at various intervals, and evacuated by means of salt rubbed into the mouth. The results are the same as those observed in the mosquito, except, perhaps, that the transformation is more tardy. Numerous flagellates may be found occasionally.

Now what is the condition necessary to the transformation? It cannot be a low temperature, as Sacharoff and Manson have conjectured, because I found, working at Secunderabad at a temperature nearly that of the blood, that the process went on to the same degree at that temperature as in control specimens kept on ice, and I have never noted temperature to have any effect. It cannot be exposure to air, because blood in leeches and mosquitos, where the transformation is most complete, is no more exposed to air than in the vaseline experiment, where it is entirely checked. It cannot be contact with the stomach of these animals, because the change occurs nearly as much in the exposure experiments, and because it commences very rapidly, long before the blood can be acted upon by digestive juices (if any), and, indeed, long before leucocytes and even small amœboid bodies are at all affected.

The condition must be abstraction of water from the serum. This is clearly absent in the vaseline experiment; while more and more water is abstracted by evaporation the longer blood is exposed to the air. Lastly, the mosquito and leech abstraction of water is very rapid (evidently in order to reduce the bulk of the blood). Not only does the microscope give evidence of this in the greater huddling together of corpuscles in blood taken from these animals, but the mosquito can easily be observed to void droplets of water every ten seconds or so while she is sucking, while the profuse sweating of feeding leeches is well known. Hence the view that the condition required is found in the said abstraction of water is the only one (which at least has occurred to me) that fits the facts; and it fits them very accurately indeed.

EXPERIMENT V.—We may now make a concluding crucial experiment which clearly demonstrates the effect of the necessary condition, and, at the same time, strikingly illustrates the living nature of the phenomenon. A vaseline preparation is made as in Experiment I; after one or two hours it is examined, and found to contain only crescents; it is then opened, and the blood is removed to a clean slide, where it is exposed for evaporation in the air for a minute or two, and lastly covered with a fresh cover glass. In a few minutes the transformation begins, as in Experiment II. Numbers of the crescents become spheres, and many of them become flagellate. The crescents have remained alive in the vaseline for the one or two hours, so that they are still capable of retaining their function when taken out and brought into the presence of the necessary condition. Again, a similar vaseline preparation is kept for twenty-four hours, after which it also is opened. None of the crescents now become spheres; many of them have vacuoles and oscillating pigment; in fact, they are now dead, and no longer capable of undergoing transformation. I think that the crescents begin to die after an hour or so, but am not yet in a position to state the usual time of death definitely. In all vaseline experiments a few parasites are found, which have, so to speak, attempted to become spheres, and these are readily taken up by phagocytes; but there is no true process of spherulisation. Crescents showing shrivelling vacuoles, or the slightest oscillation of pigment, are quite dead.

All these experiments should be made from a patient containing numerous crescents, who has not been taking quinine. The experiments should be repeated so frequently as to assure the observer that he has arrived at the real facts. He must, of course, be able to distinguish true spheres from crescents hanging end downward in deep blood, and from the spurious spherical degenerative change of dead and shrivelled crescents. The vaseline experiments require very careful manipulation to exclude air, the presence of air bubbles in the grease, and even (I think) the existence of too thin a film of it between the blood and the air being sufficient to allow a few crescents to become spheres. The best results are obtained, I imagine, by pressing out partially at once by means of the cover slip, which is, of course, entirely impermeable to air; and perhaps some better medium than vaseline may be found; but the number of spheres seen even in carelessly made specimens is so small as compared with that in exposed blood, that the main principle in question can scarcely be denied.

It may now be asked, How and why does abstraction of water from the serum affect the crescents? I suppose that the slight alteration of density caused thereby is instantly appreciated and taken by them as a signal that they are now in a proper position to undergo further development with advantage. As to the why, we may remark that, at first at all events, the only sudden alteration which occurs in blood ingested by the mosquito is, so far as we can see, this same alteration of density. It is so rapid and marked that in a field of mosquito-drawn blood we find two or more corpuscles or parasites to one which we shall find in a field of finger blood made quickly into a specimen. In all other qualities the ingested blood probably remains at first much the same as when it was in the capillaries; there is no exposure to air; there is a certain amount of motion; the temperature must fall very slowly at first; and there is not likely to be any digestive action during the first few minutes after deglutition, namely, those when the transformation occurs, and possibly must occur, to enable the flagellated spores to escape the approaching viscidity induced by the extravasation of hæmoglobin. Hence it seems that alteration of density can be the only alteration on which the crescents can rely in order to know, so to speak, when the time has come for them to give birth to their included spores. That it is the alteration on which they actually do rely is evident; and our knowledge of the exquisite arrangements which Nature is wont to make for emergencies of the kind suggests that this is another example to the same effect.

In view, however, of the fact that I have never been able by any exposure to the air to convert all crescents into spheres with the constancy found in the mosquito, I am inclined to believe that in the latter there is some slight subsidiary condition, perhaps some subtle coincidence of temperature, which also affects the phenomenon. Flagellation also appears to depend on some additional condition which I have not yet been able to ascertain, because it occurs very markedly to a different degree in different specimens, or even in different parts of the same specimen. Still, abstraction of water is the first condition; and I feel justified in saying that anyone who considers the above experiments with due attention must conclude that the mere fact that an extrinsic condition so necessary to the phenomenon exists at all negatives the view that the phenomenon is due to any intrinsic change, such as the degeneration theory assumes it to be. More than this, the same fact seems to me strongly to enforce Manson's theory by reasons based on direct observation. We owe to him the view that the transformation of crescents is intended for the propagation of the parasite within the mosquito; and later I was able to show that the same transformation does actually occur within the mosquito, and occurs there to a greater extent than in ordinary specimens. But the above experiments appear to demonstrate, further, not only that the transformation must be a vital phenomenon, and not one of degeneration as some say it is, but that the condition which is absolutely necessary to its occurrence is just the one which is most conspicuously found in the stomach of suctorial animals (mosquitos and leeches).

I may also mention here, as being opposed to the involution theory, the effect of quinine on the transformation of crescents. Though I am unable to speak yet with any absolute certainty on the point, the effect appears to me to be one of partial restraint both on the change of crescents into spheres and of spheres into flagellates (not one of complete repression, as Manson has through a misapprehension given me as saying). Thus in a specimen taken from a cinchonised patient fewer crescents will be transformed and fewer flagellates found than in one taken from an untreated person. I have often remarked this, but have not yet attempted a quantitative examination of the question. The fact (if it be one) will, as Mannaberg has already suggested, be strongly opposed to the degeneration hypothesis, according to which crescents killed by quinine should be the first to undergo transformation. Direct treatment of crescents with reagents, such as water, quinine, and methyl blue, always appears to check exflagellation, again contrary to the degeneration hypothesis.

EXPERIMENT VI.—The last series of arguments which may be directed against the involution theory are those based on a careful study of the appearance and movements of free flagellated spores, a subject which may be treated at such length that I am not prepared to enter upon it here. Dr. Bignami describes Manson's remarks under this head as "a mere matter of impression," and I think we shall be willing to let the matter rest at this for the present. It is our "impression" that the said movements are eminently indicative of independent life—the same sort of impression which convinces us that a flying bird or a galloping horse is a living animal and not a dead one. In favour of the degeneration theory it is impossible to feel any impression whatever. That theory appears to have arisen from an insufficient scrutiny of the minutiæ of these phenomena, and probably from the spectacle of those flagellate bodies whose spores cannot free themselves and therefore die *in situ*. Some of my own experiences in regard to these points may, however, be briefly recorded here. The movements of free spores (which may live for two hours) are very similar to those of trypanosomes. All living free spores seen by me have had a nearly uniform structure, namely, that of a central enlargement, probably the spore, with a flagellum on either side, and I opine that this central body will, with suitably staining, be demonstrated to contain chromatin. The spores are capable of attaching themselves, apparently by the extremity of the flagellum or by the body, and I have on several occasions seen them attached to red corpuscles, and pulling them along. The ordinary flagellate body is generally such a confused mass of waving flagella, that it is impossible to make out the structure of the spores until they effect their escape. Much work in this connection, however, remains to be done.

REMARKS.

It is interesting to note that Bignami has not succeeded hitherto in finding the parasite in mosquitos—an experience which, so far as it relates to the post-flagella stages, coincides with mine up to the present. His argument, delivered with much confidence, that it is impossible for the mosquito to convey the parasite out of the human blood, since in this case we should expect to find the disease communicated from an infected person to healthy individuals in his neighbourhood, appears to me to be of little value, because in the first place I doubt whether such cannot occasionally occur—witness the first appearance of malaria in the Mauritius in 1866; and, in the second place, it is possible that each species of parasite requires for its propagation a special species of mosquito, so that, if this be absent in a locality, the parasite cannot exist there at all, and therefore cannot spread there.

Bignami refuses to credit that a case of fever following upon a "mosquito water" experiment was one of malaria. Crescents were certainly not found after the fever; but this was possibly because they were not carefully enough looked for. I think that the case was one of slight malarial infection; and it may be remarked that the natives of India appear often to be comparatively immune to the effects of the parasite, as Thayer and Hewetson have remarked in the case of the negro. Thus, I have lately treated several cases in which the clinical symptoms gave no idea of the numbers of parasites found. Marked rigor is, of course, frequently absent. Since this experiment I have had similar slight reactions in 2 out of 21 experiments of the same kind; 3 more experiments were performed as follows: Mr. Appia, assistant surgeon of my hospital, volunteered to be bitten by numerous mosquitos fed on malarial blood. In August last he was bitten on three occasions by altogether 36 mosquitos, most of which had been fed on a case containing quartan, mild tertian, and æstivo-autumnal parasites. Two other volunteers underwent similar experiments. All the results were entirely negative. These 25 experiments are detailed in a paper read in October before the South Indian Branch of the British Medical Association, in which I conclude that no definite inferences can be drawn from them. For various reasons the similar experiments cited by Bignami appear to be equally inconclusive.

Dr. Bignami quotes Calandruccio's results with the mosquito as being opposed to mine. I have not had the good fortune to read Calandruccio's observations in this connection, but understand that he worked with fever forms, which, of course, die in the mosquito. My work, on the other hand, refers to the transformation of crescents, which beyond all doubt occurs in the insect, though, owing to the difficulty of the investigation, I am not in a position to state whether or not the flagellated spores undergo further development then.

NOTES BY THE AUTHOR.

I had just written and dispatched the above when my attention was called to a letter by Dr. Marshall, from Rio Tinto, Spain,[2] in which he states that the addition of a small quantity of water not only causes all crescents to become spheres, but encourages exflagellation as well. This appears to be diametrically opposed to my own conclusions; and it became necessary therefore not only to repeat my experiments once more, in order to see whether some error had not been made, but also to ascertain the exact effect of the addition of water. Being in charge of a patient whose blood was rich in crescents, I have been able to effect the necessary observations in time for the publication of this paper.

Repetition of my experiments given above yielded precisely the same results; and a further experiment was devised, which led still further to the conclusion that unless water is abstracted from the blood the crescents will not change. The finger was pricked, and then quickly held over warm, not hot, steam, and kept there for one minute. Blood will evidently not evaporate so copiously under these conditions as when it is exposed to comparatively dry air; and consequently, by hypothesis fewer crescents will change. The experiment is not so complete as the vaseline experiment and is difficult to do, not only because the hot blood escaping from high pressure in the capillaries has an immense tendency to evaporation, which is but partially resisted by the incompletely saturated air over a steaming vessel, but because the drying edge of the blood and air bubbles in the specimen cause a rapid increase of density in their vicinity, which affects the parasites there. Nevertheless, it was found that in blood exposed for a minute over steam only about half as many parasites change as in blood exposed for the same period to dry air, and that those parasites which do change are generally to be observed near air bubbles and the edge of the specimen. Further, in experiments conducted in this manner it was determined from the microscopical appearance of the blood that often a certain amount of water had been added (from absorption of globules of steam). I am therefore of opinion that if the blood density be kept at its normal amount, or even if it be slightly lowered by admixture of very small additions of water, transformation will be checked.

So far, then, the former conclusions were again justified; but it was now necessary to observe the effect of larger additions of water. Here I may say that I (for one) was already familiar with the fact that an excess of water causes all crescents to swell up into spheres. I did not deal above with the fact, because I held somewhat hastily that it was due merely to absorption of water by the parasite, and therefore looked upon it as an example of the effects of the reagents, which I was not considering. On second thoughts, however, it became evident that the change is not in this case due merely to "imbibition of water," as Dr. Marshall thinks, and, as I once thought, because the transformation is here not a mere mechanical swelling up of the parasites, but a genuine transformation which may be complete in all its stages. It is therefore necessary to admit, contradictory as it may appear, that decreased density may provoke transformation as well as increased density can; and it is equally necessary to consider this new fact.

The following are the results obtained by me: A large drop of water is placed on the finger, and the skin being pricked through it, a small quantity of blood is mixed with the water. The well-known effect follows, that the hæmoglobin is dissolved out, and the leucocytes are swelled into spheres. At the same time the crescents have become spheres, almost always without thick outline. The spheres are larger than normal (?), and the pigment remains clustered in a mass, and soon takes on a Brownian movement. Many eviscerated crescents are found (a form noticed, I think, by Canalis), in which we may observe lying together the shell of the corpuscle and the outline of the crescent, with the pigment extruded from it in a mass. At this stage transformation is checked, pigment is rarely distributed, and exflagellation does not occur. In short, excess of water accelerates the first stage of transformation, but then kills the parasites.

Again, a small drop of water is placed on the skin and is mixed with a larger quantity of blood. On examination it is found that the hæmoglobin is not dissolved out, but that the corpuscles are swelled up so much as to prevent their forming rouleaux. The crescents rapidly become spheres, and if too much water has not been added some of them proceed to exflagellation, about as many as become flagellate in blood exposed for forty seconds or so. The stages of transformation are precisely the same as usual, exflagellation occurring almost invariably at eleven, twelve, and thirteen minutes; and I think equally in parts removed from air bubbles as in those near them. If, however, sufficient water has not been added numerous crescents still remain, and spheres and flagellates are generally found only in parts in proximity to air. We must conclude, then, that the addition of a certain quantity of water (say 30 per cent.) encourages transformation just as the abstraction of a certain amount of water does. To sum up I reach the following conclusions:

1. Transformation does not proceed unless the normal density of the blood be changed to a certain extent—that is, either increased or decreased.

2. If the normal density be decreased too much, crescents become spheres, but are then killed.

The addition of water as practised by Dr. Marshall—namely, by mixing water into blood which has already been exposed to the air for a few seconds—gives rather dubious results. In some crescents transformation appears to be started by exposure to air, in some by the effect of water, in others (generally numerous) by the proximity of air bubbles; while many crescents—namely, those which happen to have come in contact with excess of water—may be first transformed and then killed. Judging from many such experiments, however, I hold that change of density has the effect merely of starting transformation, and does not much control subsequent developments, except in the case of excess of water. I think, too, that transformation once started addition of a little water helps the next stages by increasing the bulk of the blood, and so preventing undue pressure of the cover glass on the parasites.

Exposure to very hot steam kills the crescents. Normal salt solution permits some crescents to proceed in development, but a stronger solution checks transformation. Hayem's solution is quite inhibitory so far as I have examined. Many interesting experiments with reagents, such as solutions of various salts, sugar, etc., may be tried. I have not had leisure to attempt them. One interesting experiment in the same line as the vaseline experiment may be suggested—namely, to check transformation temporarily by means of a salt or Hayem's solution, and then to endeavour to resuscitate the crescents by further dilution with water.

We have now to consider how the new fact bears upon my former deductions. An argument in favour of Manson's theory was derived from the observation that increased density, which is just the condition found in the mosquito's stomach, is also the condition necessary to transformation; and it will now be said that the argument no longer holds, because decreased density is also necessary, while decreased density is not found in the mosquito's stomach. To this the answer seems to be that the argument still remains sound, because increased density is the natural condition which provokes transformation, being that condition which obtains in the mosquito; whereas the effect of decreased density is an accidental or artificial one, due to its producing some action upon the crescents similar to that produced by increased density. What is this action which is produced both by condensation and by attenuation of the medium? I think it is an alterative action on the shell of the corpuscles containing the parasite. If we carefully examine crescents becoming spheres, we shall observe that the first step of the change consists in an apparent thickening of the outline of the crescent. This thick outline persists not only while the crescent becomes an oval, but for a minute or two after it has become a complete sphere. Then, generally five minutes after the blood was drawn, the thick outline is suddenly discharged, and we find a sphere without any limiting line at all. The thick outline is connected with the shell of the corpuscle which contained the parasite, and its disappearance is due to its rupture by a slight but often distinct stretching movement of the parasite—a fact which may repeatedly be observed in exposed blood four to eight minutes after it was drawn (I hope to describe the exact steps of exflagellation hereafter). Now both increased and decreased density appear to have an alterative effect on corpuscles; either, if carried far enough, produce extravasation of hæmoglobin; and I judge, in short, that it is the beginning of this alterative effect which determines the commencement of transformation. But while condensation is the natural incentive to the change, attenuation is accidentally capable, so to speak, of producing the same effect by having or threatening a similar alterative action on the shell of corpuscle. For all we know, many reagents may be found which will give the same result; though, however numerous they may be, condensation will remain the natural condition leading up to the phenomenon.

I must here correct a misapprehension of Dr. Marshall's; he evidently thinks that transformation in the mosquito is occasioned by the addition of some fluid which has the same result as the addition of water. "What bearing these phenomena (effects of water) may have on Dr. Manson's theory," he writes, "I cannot venture to say, but only express the opinion that they are due to the imbibition of water by the crescent, and that this may take place as well in the stomach of the mosquito as in any other place where blood containing crescents is mixed with a comparatively inert fluid." In the stomach of the mosquito there is no fluid mixed with the blood, certainly not enough to cause transformation; water is abstracted.

I have forgotten to note that in making most of the above experiments a fairly large drop of blood should be examined; that two or more exposure specimens should not be made from the same drop of blood, and that the great effect of air bubbles in promoting transformation should be always remembered.

REFERENCES.

[1] It is difficult to understand Bignami's own views in respect to this theory, or what exactly he means by his "deviate and sterile forms." As, however, in this paper he opposes Manson's evolution theory, there is no option for us now but to class him among the degenerationists.
[2] *Lancet*, October 24th, 1896.

LOCAL DEATH-RATES.—At the last meeting of the Royal Statistical Society Mr. Thomas A. Welton called attention to some of the fallacies which vitiated the calculated local death-rates. In particular he pointed to the practice of charging all deaths in workhouses and lunatic asylums to the district in which the building happened to be situated, and urged that the workhouse deaths ought to be distributed, and the asylum and hospital deaths shown separately. He further showed ground for believing that in large towns, where many persons were employed at the ages 15 to 35, whose parents resided in rural districts, these persons when taken seriously ill returned to their country homes and died there. He pointed out also that the death-rate of watering places and pleasure towns were made to appear too heavy because their average population was based upon census returns taken at a period of the year when visitors to such places were fewest in number.

ANTITOXIN IN LOUISIANA.—The Louisiana State Board of Health has announced that it will supply antitoxin free of charge to poor patients suffering from diphtheria.