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The Theory of Specific Factors

By Fredr. Robertz

An Unpublished Paper

[As the following memorandum has been hurriedly drawn up amid the pressure of other work it is hoped that some allowance will be made for the form in which the subject is presented.]

The Theory of Specific Inhibitory Factors

Synopsis. Theories at present held in explanation of natural & acquired immunity 1–4. Some physiological relations of micro-organisms, 4–10. Objections to theories at present held 11–21. The theory of specific inhibitory factors — 22–28. Consideration of preliminary difficulties in way of theory 29–32. Evidence from microscopic observation, and experiments 33–46. Further points in support of theory 46–54. Mc tuberculae dentis — a theory 54–61.

It may be said that there are three distinct theories which are at present advanced to explain natural and acquired immunity. (Natural immunity = insusceptibility to the growth of non-pathogenic as well as certain pathogenic organisms in the body)

1. The theory according to which it is held that a certain micro-organism can only grow in an animal body provided that some special substance which it requires for its nutrition is present in that body. "It is quite possible that pathogenic organisms have this special character that if the soil (animal body) contains a certain chemical substance they are capable of growing & thus producing a definite ferment" (which he supposes produces the irritation characteristic of the disease) Klein, "Micro-organisms & Disease p. 236. — "Where there is no alcohol present the organisms producing acetic acid fermentation cannot grow; where there is no

sugar or similar substances present the saccharomyces cannot grow and so also a particular organism — the bacillus anthracis — cannot grow in the living tissues of the living pig dog or cat but grows well in those of rodents, ruminants and man; the bacillus of swine plague grows well in the pig the rabbit and the mouse, but not in the guinea pig". Klein. According to this theory acquired immunity is to be explained by exhaustion in the living body of the special substances necessary for the nutrition and growth of the organisms producing the disease. e.g. protection from a second attack of scarlet fever after recovery from a first attack. This is the "Exhaustion Theory" of acquired immunity.

2. The Phagocyte Theory (Metschnikoff) according to which micro-organisms entering the body are destroyed by the white blood corpuscles. By many authorities this power is also ascribed to the cells of the body in general and the theory is referred to as "The Standard Vitality Theory". "The "vitality" or "the living state of the tissues per se is the inhibitory force". This theory explains acquired immunity thus "The cells of the special part of the body affected by a specific disease, in their combat with the organised germs or excitors of disease, acquire an increased vital energy which enables them to overcome the same adversaries if attacked by them a second time" Payne

3. The theory according to which it is held that micro-organisms are prevented from growing in the animal body by the antitheric action of chemical substances produced by the living tissues. This theory is intended to explain only natural immunity. It is spoken of by Klein thus "The most feasible theory seems to me to be this that this inhibitory power is due to the presence of a chemical substance produced by the living tissues."

In explanation of acquired immunity there is the closely allied "Antidote Theory" the special antitheric substances in this case being produced not by the living tissues themselves but by the organisms which caused the disease. "The organism growing and multiplying in the body during the first attack pro-

duces directly or indirectly some substance which act as a sort of poison against a second immigration of the same organism. I am inclined to think that this theory is in harmony with the facts." Klein "Micro-organisms & Disease" p. 265.

Before attempting to show that none of these theories are capable of explaining all the phenomena to be observed I wish to enumerate a number of facts known about the physiological relations of bacteria and to refer to some results that have recently been obtained by bacteriologists.

(1) The number of specific micro-organisms belonging to the class schizomycetes now known to exist is practically without limit. Several hundreds have been described and it is certain that there exist many more which have not yet been described. According to Eisenberg there are at least 70 pathogenic bacteria. 27 of these are pathogenic in the human subject. Referring to the statement Payne says "The number of existing species is doubtless enormously greater."

(2) Each specific organism — pathogenic & non pathogenic, presents distinctive characters as regards the conditions best suited to its growth — soil, temperature, presence or absence of oxygen, its method of growth in ~~stick~~ plate cultivation, its staining reaction, the chemical substances which it produces (ptomaines) &c. Probably no two distinct species are exactly alike as regards these characters, and it is known that between some there are the widest differences eg. compare as regards these points the organisms in erysipelas, malignant anthrax and in leprosy.

The fact that the poisonous substances or ptomaines produced by each specific organism are distinct is to be specially noted.

(3) That every pathogenic organism when it grows in the body produces characteristic effects which differ widely in the case of each specific organism. In several respects a gradation may be traced in the effects produced by these different specific organisms. I wish to point out two of them.

(a) The time they remain in the body.

(b) The severity of the symptoms produced.

As regards the time they remain in the body, on the one hand there are the organisms that are supposed to cause for example scarlet fever and epidemic influenza which remain in the body only for a short time, and on the other hand the organisms in leprosy which remain in the body throughout life. ~~Secondly~~ ~~and more important~~ As regards severity of symptoms or degree of irritation produced, on the one hand there is the intense irritation resulting from the ptomaines manufactured ~~Secondly~~, by the organisms ~~which~~ causing hydrophobia, tetanus, cholera and malignant anthrax, and on the other hand the comparatively slight irritation produced by the ptomaines of the organisms in leprosy and syphilis. It is particularly to be noted how slight the irritation produced may be in the least. It may indeed be for a long time practically nil, — we are continually connecting with cases of patients who have undoubtedly had syphilis and are yet not aware of the fact. One is justified in citing syphilis in illustration of this ~~point~~ point since an authority of the standing of Payne says "The nature of the syphilitic virus is not positively known but from its power of reproduction within the body, and communicability to other persons it is clearly some living poison ... It is a perfect type of an infective disease, produced by a virus introduced from without."

(4) The very remarkable facts known about the inhibition of the growth of organisms by their own ptomaines and by those produced by other organisms. "It is an interesting fact in connection with these fermentative processes that the substances produced by the organisms immediately stop their growth and development" Dr. Russell's Lecture. e.g. Alcoholic fermentation stops at a certain point owing to the action of the alcohol upon the organism producing it. It is known that there is a struggle or competition between various species of bacteria when the soil in which they are growing contains food material suitable for each species. One specific organism can only affect the growth of another specific organism so far as we know in two ways, — by removing food material necessary to the other's growth or producing ptomaines which inhibit its growth. It is clear that under conditions in which the food material is abundant only the latter

influence can act. ~~Not only the to the~~ These ptomaines are really antitheric substances just as ~~also~~ carbolic acid is an antitheric substance. The alcohol~~s~~ produced in the process of alcoholic fermentation not only arrests the growth of the organisms producing it, but, even in the ~~strength~~ concentration in which it is produced, it is an antiseptic of considerable power in relation to other organisms. Further it is to be noted that in a complex fluid cultivation ~~mat~~ medium into which several specific forms of micro-organisms have been introduced, one set of of organisms does not hold the field by growing with a vigour out of proportion to all the rest but several different species are found to be represented, yet no one species in such large numbers as it would have been found had it been introduced alone in the cultivation medium.

(5) The remarkable difference between animals in regard to their susceptibility to the growth of specific organisms within their bodies. A large number of examples have now been collected.
e.g. (a) Koch's Bacillus of septicaemia in mice.
Susceptible — house mice and sparrows
Insusceptible — field mice; rabbits only a slight lesion conferring subsequent immunity.

(b) The Bacillus of Malignant Anthrax
Susceptible — many rodents, herbivorous animals, rats with difficulty.
Insusceptible, pigs, dogs, cats, and Algerian sheep (though ~~others~~ common sheep insusceptible).

In this connection there is to be borne in mind the liability of certain families to tubercular lesions, and the immunity enjoyed by others from such lesions.

(6) Pasteur's recent work in inoculating successfully for the prevention of hydrophobia malignant anthrax and some other diseases due to micro organisms; and his explanation of his ~~the~~ results.

In the case of hydrophobia he holds that what he really does by his method of inoculation is to gradually saturate the body with the poison or ptomaine produced by the pathogenic organism and that as a result that organism cannot afterwards grow in that body. (Practically the antidote theory)
In the case of malignant anthrax he holds that by introducing an attenuated virus he has been able in the same way ~~to~~ without serious

injury to the animal to saturate its body with the ptomaines produced by the organism of malignant anthrax, and thus to render it ~~that animal for~~ for some months to come an unsuitable ~~unsuitable~~ medium for the organism. (Antidote theory again)

(8) The attempts that have been made (it is contested by the experimenters with some degree of success) to antagonise the bacillus of tuberculosis (in phthisis) by the bacterium termo, and the supposed pathogenic organism of cancrum oris by the micrococcus of erysipelas.

In the same connection may be mentioned the occurrence of cases such as this mentioned by Professor Thiene in his lectures, — he says — "I have seen a case in which syphilis was for a time aborted by influenza. The effect of the influenza was to check the progress of the syphilitic disease. Its bases are arising and cases are being observed in which there is the effect of one disease upon another" Lectures 1888-9 He also mentions a case in which he says syphilis was aborted for two years by an attack of scarlet fever.

Objections to the theories at present held in explanation of natural and acquired immunity.

1. (vi ante)

If this theory cannot explain natural immunity from the attacks of certain pathogenic organisms, a fortiori it cannot explain why non-pathogenic organism do not grow in the living tissues. That it cannot explain the former is clear from the following. "The objections to this view are that there is no proof of the existence of any such substances though the number of them would by the theory have to be very large, since there must be one corresponding to every specific disease". Payne. — and — "The tissues and juices of a pig when obtained as an infusion or otherwise are just as good a nourishing material for the bacillus anthracis as the tissues and juices obtained from herbivorous animals." Klein, Micro-organisms & disease.

That the theory is incapable of explaining acquired immunity is also clear from the following argument. "There is absolutely no

ground for the assumption that if any infusion of the tissues of this animal (a bullock recovered from anthrax and now having immunity from another attack) were made the bacillus anthracis soon in it would not thrive luxuriantly seeing that the bacillus anthracis grows on almost anything that contains a trace of proteids" Klein. The same argument is applicible to cases of acquired immunity from any other disease in connection with which this phenomenon is seen.

2. Objection to the Phagocyte Theory.

As regards their supposed action in destroying non-pathogenic organisms (1) It is difficult to understand how leucocytes can have the discriminative power of seizing upon all living bacteria that come within their reach and allowing to pass unmolested blood plaques, micrococcus. That they seize upon dead matter is certain, but this may be explained by purely mechanical and physical laws, without the necessity of believing in what almost amounts to an act of volition on the part of the cell. That they may sometimes in a similar manner take up micro-organisms I am willing to believe, but that they as is contended "attack the invading microbes", for which we are I think not warranted in believing, to be possible.

(2) Experimental evidence will subsequently be produced to prove that there is the same inhibition of the growth of these micro-organisms under circumstances in which leucocytes and other cells are absent.

Nevertheless I know that very careful observations have been made which seem very strongly to support the theory that leucocytes play an important part in destroying putrefactive organisms and I am willing to believe that there may be some truth in it, but that these leucocytes or these leucocytes plus the cells of the body in general have any important influence in producing the phenomena of natural and acquired immunity from the growth within the body of pathogenic micro-organisms is I hold capable of being completely disproved.

(1) As Klein points out the presence of micro organisms in amœboid cells does not prove that these cells are destroying the micro-organisms because there are many diseases in which the micro organisms are present

in the cells almost exclusively, eg bovine tuberculosis & leprosy.

(2) "It would be absurd to say that in the sheep which has passed through a mild form of anthrax &c as is well known, has hereby become insusceptible to a second attack the leucocytes have altered in character so that before the first attack they have been unable to swallow up and destroy the anthrax bacilli, but by the first attack had become endowed with this new power" Klein.

(3) Similarly it would be absurd to say that the white blood corpuscles differ in two individuals the one having a marked tubercular diathesis and the other having no tubercular diathesis

4. Similarly it would be absurd to say that the white blood corpuscles of the house mouse differ from those of the field mouse so that the former is susceptible to Koch's bacillus of septicaemia in mice and the latter is not.

5. Koch gives it as his opinion that the theory is "not capable of explaining all the facts of the case"

All these objections may be applied with equal force to the "standard vitality theory" which attributes the power of inhibiting micro-organisms to the living cells of the body in general. In addition however it may be shown, I think, that this theory does not explain how death from asthenia is possible. This is a point of very great importance, and raises I think an insurmountable difficulty in the way of the theory. Surely we have as typical cases as can be found of "lowered vitality" in patients slowly dying from malignant disease, from pernicious anaemia or from lymphadenoma, and yet such patients may die by pure asthenia without any outbreak of septicaemia. If this theory were correct we should be entitled to expect that these patients would be carried off by septic infection at a very early stage of their illness. It cannot be said that this does not occur because bacteria do not gain admission to their bodies for Klein has proved that even in health bacteria are continually entering the tissues from the alimentary tract.

In connection with the standard vitality theory, which so many clinicians seem to accept

as if it explained the whole mystery of insusceptibility, it is to be pointed out that to speak of micro-organisms being destroyed "by the vitality of the tissues" is really to explain nothing. All that we know as to the nature of life is that it expresses a series of phenomena manifested by living beings. But what these phenomena are in relation to the attacks of micro-organisms is the very thing that we want to know. Failing proof that the living cells actually seize upon and digest micro-organisms — pathogenic and as well as non-pathogenic — if our knowledge of this question is to make any progress at all we must seek to explain the phenomena we discuss in the terms of chemistry. Whether or not our knowledge of this matter makes any progress is indeed no light matter when we consider that thousands of lives in this country alone are sacrificed every year simply because we really do not understand by what physiological mechanism the living body protects itself from attacks of injurious micro-organisms.

There who (for an explanation) are dissatisfied with a phrase the meaning of which they do not understand find do not help matters on.

3. Objections to the theory that the living tissues produce antitoxic chemical substances, and to "the antidote theory".

As regards natural immunity —

(1) It is difficult to understand how these antitoxic substances should be produced by all the tissues of the body indiscriminately, seeing that these tissues differ so widely from each other in structure and in function. Some one or two organs or kinds of tissue must be concerned in their elaboration. Yet there is no single organ or kind of tissue disease of which renders an individual specially liable to the attack of a specific organism or to organisms in general. Thus for example these antitoxic substances might be produced by the lymphatic glands. Yet one may often see a patient with every lymphatic gland in the body the seat of disease — lymphadenoma — and yet that patient may for days or it may be weeks lie in a condition of extreme weakness, and die at last not of septic infection but of pure asthenia. Again these antitoxic substances might be produced by the liver, or by the muscular tissues or by the red blood corpuscles. But

a patient with very extensive carcinoma of the liver, or a patient having progressive muscular atrophy, or a patient with pernicious anaemia dies as a rule from asthenia uncomplicated by any outbreak of septicaemia, though we know that even in health organisms are continually passing from the alimentary canal into the general circulation.

(2) If this theory is correct the following circumstances (many examples similar to which might be given) seem ~~inexplicable~~ anomalous. "The tissues ~~of~~ and juices of the pig (which is insusceptible to malignant anthrax) when obtained as an infusion or otherwise are just as good a nourishing material for the bacillus anthracis as the tissues and juices obtained from a herbivorous animal" (which is susceptible to malignant anthrax) Klein.

(3) If this theory was correct we should be entitled to expect that in conditions in which there is defective excretion as in chronic Bright these antitoxic substances would be retained ~~and~~ in abnormal quantity and that therefore there should be a more powerful inhibition of micro-organisms than when excretion is going on in a normal manner. Yet we know that exactly the opposite is the case, — the inhibitory power of such a patient is decreased rather.

(4) The theory does not explain any more than the ~~[illegible]~~ standard vitality theory how death from pure asthenia is possible.

Granting even that all the organs in the body are concerned in the production of these antitoxic substances it can scarcely be maintained that when a patient is in a condition of extreme asthenia these substances can be produced in the same way as in perfect health. Yet a patient with chronic phthisis may lie for weeks in a state of extreme asthenia with general waxy disease and die at last from asthenia without any outbreak of general tuberculosis or of septicaemia. A patient dying of malignant disease pursues a similar ~~[illegible]~~ anomaly if this theory is correct. In cases of malignant obstruction to the oesophagus there is added the additional weakening factor of starvation and yet such a patient will die

purely by antitoxic. A person ~~dying~~ of old age presents another anomaly of the ~~the~~ same kind which it seems to me this theory is incapable of explaining.

(5?) It is difficult to understand how the tissues of the infant in their condition of active growth should produce the same antitoxic substances as the tissues of the aged person which are undergoing a process of involution, and yet in these two types of persons there is the same kind of inhibition to micro-organisms.

(6) This theory does not explain the fact that this inhibition is just sufficiently powerful to protect the animal body from the attacks of most micro-organisms and no more. If the living ~~body~~ tissues (why do they not produce) produce these antitoxic substances in sufficient abundance to completely inhibit the growth of all injurious organisms? For example why is it that if a small dose of pus, containing micrococci, is introduced into a healthy animal these ~~micrococci~~ micrococci do not develope, while if a slightly larger dose is introduced ~~they~~ do develope? If a nutritive fluid containing 2% of carbolic acid was treated in the same way in neither case would the organisms develope, and yet according to this theory we are to believe that the living body is analogous to an artificial cultivation material protected from the growth of micro-organisms in this way.

As regards acquired immunity ——

~~Of~~ Recent experiments in pharmacology have shown that alkaloids and indeed all substances not entering into the formation of the living tissues, if not precipitated in an inert form, are excreted from the body with great rapidity. Their complete excretion is effected in a few days. It is therefore impossible that Pasteur's explanation of his results obtained by inoculation for hydrophobia and for anthrax can be correct. The true explanation, whatever it is, must be different.

When many months of ~~study~~ studying this question these objections to the theories at present held, together with many other objections which time has not allowed me to mention, seemed to me to prove that there must be some factors in the production of this inhibitory power in the living body which had not yet been recognised. After studying the question for some length of time I was led to the conclusion by a pure deduction from the ascertained facts about micro-organisms, some of which I have already enumerated, that the true relation of micro-organisms to the body of warm blooded animals must be such as stated below. I insist upon this that I did not frame the theory and then try to make phenomena square with it. The theory was suggested to me purely by a deduction from the facts which I had before me. Again & again I rejected it as utterly absurd but again and again the same train of reasoning brought me to the same conclusion. Briefly stated that train of reasoning was something like this. Considering that the number of different specific organisms is so very large, that each specific organism produces characteristic ptomaines, that each pathogenic organism by the action of the ptomaines it forms produces in the animal body characteristic symptoms which differ widely in different diseases, considering that a gradation may be traced in the severity of the symptoms produced by the different pathogenic organisms and that in some diseases, such as measles and syphilis the symptoms of irritation may be extremely slight, and considering also how the living body has the power of acquiring a degree of tolerance of alkaloids and other poisons (eg. Opium, arsenic, nicotine), considering too the thousands of years that may be allowed for evolution, and that during all these years various species of micro-organisms have been constantly battling for admission to the living body, is not one entitled to expect that the series of micro-organisms capable of existing in the living body does not end with the least irritating specific forms believed to exist but that there are others which produce ptomaines still less irritating to the living body — organisms which indeed produce no irritation at all and are not pathogenic though they resemble the pathogenic organisms in being able to exist in the living tissues ~~[illegible]~~ ?

I saw that if such were the case it

If such organisms exist, and their growth can only be limited by their own ptomaines i.e. that will be growing in the body to self-inhibition, and these ptomaines must act as antiseptic substances to other micro-organisms.

would explain many epidemic anomalies, and I thought that it was at least worth while to try to get the light of microscopic investigation and direct experiment upon the supposition in order to ascertain whether or not there was any substantial evidence to support it; and I subsequently carried out a number of investigations which it occurred to me from time to time might serve to test it. I can now honestly say that I believe that every microscopic observation I have made and every experiment I have performed in connection with this investigation has tended to confirm the theory I was led to entertain. That theory, which may be referred to as the Theory of Specific Inhibitory Factors, may be stated more fully as follows.

In the body of healthy warm blooded animals there are present various specific forms of micro-organisms belonging to the class schizomycetes the growth of which is limited by the collective ptomaines they produce, and these ptomaines while producing an imitation of the living tissues constitute the chemical substances which tend to prevent the growth of injurious microorganisms in the living body. In other words, the body of the warm blooded animal in its relation to septic and pathogenic organisms resembles the relation of a complex fluid nutrient medium in which there are growing up to self inhibition various distinct forms of micro-organisms to other organisms most of which are unable to live in that medium because of the presence of the ptomaines produced by the former; and it does not resemble the relation of a fluid nutrient medium mixed with an antiseptic such as carbolic acid to these organisms as it is practically supposed to do by the theories at present held by Klein and many others.

How such an arrangement as is supposed by this theory to exist is possible may require further explanation.

Suppose we have a sterile fluid cultivation material of very complex composition (such as to be analogous to the living sanguinis) kept at a temperature of 100° F. (abs.), and at hand pure cultivations of various species of micro-organisms. If we add only one kind of organism to this material it will multiply rapidly, but presently its growth will be checked by its own

ptomaines & it will begin to grow very slowly. If now we add a second kind of organism though the ptomaines of the first organism will be detrimental to its growth they will not likely be sufficient to altogether prevent its growth. At first it will grow slowly. It will produce ptomaines which in their turn will have a certain effect upon the organism of the first form introduced and further check their growth. As dissipation of the ptomaines is always going on slowly the second organisms introduced may go on increasing in numbers. At length a sort of balance of power will be established & so long as the nutrient medium holds out the numerical relation of the one set of organisms to the other represented by this will be maintained. If now a third species of organism is introduced it is possible that it also will be able to grow notwithstanding the influence of the ptomaines of the other two species. We might go on in this way adding additional specific forms until we had say ten or more different species growing in the nutrient medium, producing an aggregate of ptomaines which according to definite laws

limited the growth of each species. It is certain that in such nutrient media exposed to the air, after a time a large number of different species are found. But as we set up to the higher numbers and go on adding additional species to the cultivation material it will become more & more unlikely that the next organism we introduce will be one capable of growing there at all. The larger number of different species of organisms you get to grow in the cultivation material the more powerful influence will the collective ptomaines have. So no species of organism will grow in such abundance as it would do were it the only organism in the nutrient material, but according to definite laws the growth of each form will be limited and the total ptomaines produced will be in part contributed by each species of organism. It is evident that such ptomaines must be more powerful than the ptomaines of only one form of organism growing to self inhibition. Of course as you go on adding new species of organisms not only may certain forms that you introduce be unable to live under the conditions established

but certain forms that you have before introduced may find as it were that their existence is impossible in the changed conditions produced by later introductions, and be killed out.

~~[illegible]~~ It is contended that a condition of things analogous to this exists in the body of warm blooded animals and that it has been slowly evolved starting from the conditions which I think there is strong evidence to believe exists in the body of cold-blooded animals. That condition I think is an inhibition of bacteria purely by the action of ~~[illegible]~~ antiseptic chemical substances produced by the tissues of the animal ~~itself~~. [In this connection it may be pointed out how extremely irritating the blood of a newt is when applied to a cut finger] A priori there is not the slightest reason for doubting that the inhibition of bacteria by ~~the~~ warm-blooded animals could be ~~is not~~ affected in the same way, but a posteriori there is very strong reason for believing that it ~~is~~ really is not the method by which ~~the inhibitory~~ ~~[illegible]~~ it is effected, — viz that there are clinical & other phenomena which are quite inconsistent with it. The impetus which a high temperature gives to the growth of micro-organisms has probably been the great factor in starting the evolution

towards the arrangement which it is contended now exists. As the new force has evolved the old has gone down before it as superfluous and is ~~[illegible]~~ now of little or no importance, though it may still be to some extent in operation.

There are one or two objections which at the very outset may seem to render this theory quite untenable.

(1) It may be urged that it has been proved that in ~~the healthy~~ health micro-organisms are absent from the living body. [Experiments of Ballance and Shattock and others, though Horsely & others state that they are present] In answer to this objection while it is admitted that organisms having the characters by which they are commonly recognised are undoubtedly not present in any large numbers in the healthy body, evidence will presently be given to prove that micro-organisms differing in one particular which renders their recognition difficult do really exist in the living body of warm blooded animals and in numbers sufficiently large for the requirements of this theory.

(2) It may be contended that the very

rder of the existence of such a salutary precaution is unnatural & revolting." To this it may be replied that there are in nature other instances of a parasitism beneficial to the host e.g. the action of the Bacillus butyricus in the stomach and intestines of the herbivora. It is also to be pointed out that the existence of such organisms within the body does not imply that they are in the living tissues. We find that persons unacquainted with medical science are often slow to realise that man is a hollow animal and that the contents of his alimentary tract are no part of him; but even medical men are still slower to recognise what is equally true, that the fluids in the body — the lymph in the lymphatics, and the liquor sanguinis are not part of the living body at all — that they are essentially dead material outside of the part that is living, viz the protoplasm of the cells. It is not contended that these specific inhibitory factors are present in the cells of the body, but that they are in the liquor sanguinis and in the lymph in the lymphatic vessels and spaces, and are really as truly outside the living elements of the body as the bacteria in the large intestine.

(3) It may be difficult to understand how these specific inhibitory factors are handed on from the mother to the child, in other words how the passage of the placenta can be effected. I mention this as it was recently urged as an insuperable objection to my theory.

Now the fact of the matter is that there is abundant physiological and pathological evidence to show that there is no difficulty in the way of the theory from this point at all.

The following statement by another will be quite sufficient to put the matter at rest. "Various substances introduced into the blood of the mother have been found to pass into the blood of the foetus. Substances such as cinnabar and indigo blue have been found thus to travel from the maternal into the foetal blood. The mode of transmission is not certain." Prof. A. R. Simpson. Lectures.

(4) It may be contended that the existence

of such organisms in the body would render nutrition of the body impossible, — that they would remove all nutrient material from the blood. Now there is abundant analogy to show that this would not in the least be a necessary result. For example at a certain stage of syphilis every drop of blood of the patient may be proved to be teeming with the syphilitic virus [Ref. to Lang's injections] though that virus has not yet been satisfactorily demonstrated. Now in that patient (unless the theory of specific inhibitory factors is accepted) we cannot imagine any force that is limiting the growth of that virus but ptomaines, since it is able to grow so luxuriantly. Yet I never heard of the syphilitic cachexia of such a patient being attributed to the organism of syphilis abstracting from the patient's blood so much nutrient material as to interfere with his general nutrition.

I may here mention that I hold that there is strong reason for believing that the syphilitic virus is really an organism of the nature of one of the inhibitory specific factors, which owing to the nature of the ptomaines it produces is pathogenic in man.

Evidence in support of the Theory of Specific Inhibitory Factors obtained from microscopical observation and experiment.

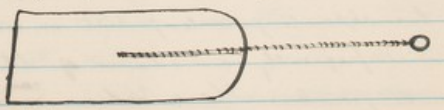
I shall produce evidence (1) That there exist in the body of warm blooded animals factors corresponding to those demanded by this theory and (2) that they produce substances which tend to prevent the growth of organisms injurious to the animal body.

(1) Evidence for the existence of inhibitory specific factors.

I admit at once that organisms which may be demonstrated like ordinary bacteria do not exist in any great numbers in the body in health — certainly they are wholly insufficient for the purposes of this theory. These ordinary bacteria consist of an albuminous material which is surrounded by a more or less dense membrane composed of cellulose and allied substances, or the latter alone. This membrane possesses great powers of resistance to acids and alkalies. It is not affected by boiling unless it is prolonged. That its character differs considerably in different species of organism is to be particularly noted. So these differences are chiefly due

the differences in the staining reactions of various organisms. The function of this membrane is to protect the organisms from external influences which would injure them, and to such influences they are as a matter of fact being from time to time exposed. Pathogenic organisms it is believed pass some stage of their existence outside the living body and hence require that this protective membrane should be highly developed. Now if there are organisms which pass the whole of their existence within the living body it is clear that they are placed in circumstances in which they are never exposed to sudden changes in the character of their surroundings, and hence to influences which will tend to injure them such as excessive cold, excessive heat, absence of moisture &c. To such organisms thick cellulose coats would be a superfluity, and by the operation of known laws of nature, and in accordance with a hundred known analogies which illustrate the operation of these laws, they would slowly change into thinner & less resisting membranes. One would then have an organism which was much less conspicuous when examined with the microscope without any staining reagent, and which when stained with the usual dyes would not retain them with any greater avidity than the nuclei of cells do since their proper substance is an albuminous material of a nature similar to that of nuclei. It is such organisms as these that it is contended do exist within the body of warm blooded animals, and the evidence in support of this contention will now be given.

1. Examination of fresh animal fluids by the looped wire method. I devised this method in order to overcome the difficulty arising out of possible contamination by slides & cover-glasses — a difficulty which I experienced for many weeks before using the method. The apparatus consists of a piece of platinum wire, which is doubled and twisted into a spiral, a small round loop (about 1/12 in in diameter) being left at the end. The other end is fixed into a flat piece of hard wood of convenient size to lay on the stage of the microscope



The end of this wire with the loop may be raised to white heat in the flame of a spirit lamp, and when withdrawn, owing to the wire being so thin, it becomes quite cool in about five seconds. The loop is then dipped in fresh blood or other fluid that it is desired to examine unstained, and a thin film is obtained stretching across. The instrument is then placed in position on the stage of the microscope & examined. By this method contamination is impossible, and blood may be examined within ten seconds of its withdrawal from the finger.

Using this method along with a 600 power microscope, with Abbé condenser and an iris diaphragm which permitted careful regulation of the light, I made the following among many other observations.

(a) In fluid from lymphatic glands of newly Killed healthy sheep there are large numbers of very minute granules showing Brownian movement. These granules sometimes assume a dumb-bell form, which however it is to be admitted is a deceptive appearance often, as it may arise from the contact of two separate granules; but in addition to this I frequently saw chains of three of these minute granules. These bodies can only be seen when the light is very carefully adjusted and are very much less distinct than ordinary micrococci in septic fluids.

Similar appearances have been seen in fluid from the lymphatic glands of newly killed rats & Kittens.

(b) In the blood of newly killed sheep, rats, mice, pigeons, and Kittens and also in blood drawn from the finger examined by the same method may be seen in addition to blood plaques, and far smaller than blood plaques, minute granules similar to those seen in lymphatic glands, and like them showing dumb-bell forms & occasional chains of three.

In the rat in addition there is a minute bacillus. (I afterwards ascertained that this had been observed before)

2. Examination of sections of Lymphatic Glands.

In sections of lymphatic glands of sheep put into absolute alcohol while still warm, there are similar minute granules which have a strong affinity for nucleus staining dyes & for other nuclear stains such as logwood, but which lose these stains again very readily when the section is treated with decolorizing agents. By the use of methods which

~~decoloration~~ remove very little ~~amount~~ of the dye these granules may be studied. If the sections are treated by the ordinary methods for demonstrating bacteria these granules are not seen. By the use of a special method (which I am not at liberty to describe as it has been used in a modified form in another research) it may be shown that these granules have a different staining reaction from the lymphoid cells, so that they cannot be granules which have been extruded by these cells as has been suggested.

All the staining reagents ~~used~~ and other fluids used in the preparation of these specimens were passed through the finest filter paper, that is made.

3. Examination of human blood

(a) Coverglass specimens ~~of~~ of human blood stained with a one per cent watery solution of vesuvin brown for 20 minutes and then washed out in filtered distilled water, dried in air & mounted, show similar stained granules especially on the red corpuscles. By this method there is ~~no~~ a minimum of decoloration. In the same specimens blood plaques are also seen. There is not the slightest ~~doubt~~ difficulty of ~~mistaking~~ distinguishing the two bodies, the latter being many times the size of the ~~nucleus~~ stained granules.

4. Examination of white of fresh and incubated eggs.

(a) Treated in the same way (& also by Loeffler's method) similar granules are to be seen in the white of fresh eggs of various birds.

(b) After a fresh egg is incubated for from 24 to 48 hours these granules are increased in number (This was the verdict of one who was opposing the theory of specific infectious factors, on being shown specimens) In stained specimens of white of eggs which have been incubated for this time there are appearances which tend very strongly to confirm the idea that these granules multiply by fission.

(c) That these granules in white of egg are not to be attributed to any peculiar coagulation of the ~~fluid~~ albumen due to the method employed is proved by the fact that after filtering ~~the~~ it through the finest filter paper and ~~[illegible]~~ then heating it in the same way it is found that these granules have practically entirely disappeared

(2) Evidence that these granules produce substances which tend to prevent the growth of organisms injurious to the anemial body.

a Details of Experiment upon ~~that~~ Incubated Hen's Eggs. (April 1890)

Eleven fresh eggs were placed below a clucking hen, and 38 hours afterwards 9 of them were innoculated with fluids containing bacteria. The method I employed was the following. I placed the egg upon cotton wool and with a clean sharp pointed pen-knife partly bored & partly chipped out a small piece of the shell. Below this was the egg membrane uninjured. This I pierced with a moderately large clean needle, about four times the thickness of the wire I used subsequently to innoculate with. On withdrawing the needle a small hole was left through which the white of the egg tended to ooze. I next dipped the point of a clean platinum wire about a shat way into the fluid with which I intended to innoculate the egg. The point of the wire carrying on it the septic fluid was then passed into the hole in the egg membrane at least one quarter of an inch in. It was then withdrawn & the opening sealed with flexile collodion. As soon as this had

dried the egg was replaced below the hen.

It appeared to me when I commenced this experiment that its result would form a crucial test of the theory which I was seeking for evidence to either to disprove or prove. The result of this experiment three weeks later was as follows.

Egg.		
1.	Innoculated with fluid from a very putrid duck's egg from a full time setting. It showed no embryo. It contained cocci of various sizes & forms.	Rotten
2		Hatched
3		Hatched
4	Innoculated with fluid from a putrid egg in which there was a two weeks (about) duckling.	Hatched
5		Rotten
6		Smashed by hen.
7	Innoculated with my own saliva	Hatched.
8		Rotten
9		Hatched.
10	Not manipulated.	Hatched
11		Hatched.

As in every setting at the place where this experiment was carried out, there are on an average two or three rotten eggs it is evident that this setting was practically unaffected by what was done to the eggs.

My contention in regard to this result of course is that the putrefactive cocci were prevented from growing by the action of the ptomaines produced by the granules already described as having been found in the white of a hens egg which recieve no incubation.

I. The phenomenon of a "clear" egg.

~~About~~ I examined a very large number of eggs which had failed to hatch after incubation for their full time.

I found that in many the chick had developed for a time & then died. For the purpose of the inference I am going to draw I shall take only those which had developed for more than two weeks & then died. I examined about a dozen such eggs & found that they were all putrid. Some that I examined microscopically contained cocci in abundance, & as those that I did not examine microscopically were exactly the same in appearance & smell I concluded that they also were septic.

Another description of egg that I found a great many of is what is termed "a clear egg." After three weeks incubation some eggs are found which are ~~almost~~ as clear as they were when laid by the hen. An embryo is usually found but it has evidently failed to resist development after incubation. Only a very slight opacity is visible in them. They are not in the least putrid, ~~but they have~~ ~~they smell~~ I examined the white of several eggs of this kind. It showed no micrococci of the ordinary form but there were in abundance the granules ~~of~~ already described as occurring in the white of fresh eggs. Immediately below the yolk membrane there was in most cases a distinct opacity & this I found was associated with the growth of a micrococcus, & widely indicated commencing putrefaction.

Now I believe there can be no doubt that the cause of the death of the chicks ~~of~~ in the former eggs was that the eggs had got from below the hen & been allowed for a time to get cold. ~~If this~~ In such eggs why do putrefactive organisms ~~rapidly~~ always rapidly developed and not they do not for long develope in an egg in which the embryo has failed to resist development? ~~[illegible]~~ That putrefactive organisms are present in practically all eggs is I think rendered certain from the above observations. Why do they not develope sooner in the "clear" eggs? Why do they ~~both~~ develope in the egg the chick in which has died ~~&~~ after two weeks growth and yet do not develope during the first week of incubation ~~of~~ of the same egg? ~~How the embryo is put to death~~ To explain these phenomena by the theories at present held about inhibition is quite impossible. That these phenomena, however, are exactly what we should expect if the theory of specific inhibitory factors is true, is I hold

capable of being shown. Putrefactive organisms do not for a long time develope as a rule in eggs in which the embryo has failed to restart because they are inhibited by the inhibitory specific factors present until the albumen begins to undergo changes which cause it to become a less suitable soil for the inhibitory specific factors, owing to their having withdrawn the materials most suited for their growth from it. For a similar reason in eggs which do develop chicks putrefactive changes do not occur during the first week of "natural" incubation, when it can scarcely be thought that the "vitality" of the embryo can have any influence in inhibiting organisms. When a two weeks embryo dies it undergoes changes analogous to those which a mammalian body undergoes after death, & even though the temperature is raised again it is no longer a suitable soil for the inhibitory specific factors. Hence the putrefactive organisms take possession.

That these observations carry with them weighty evidence in favour of the theory of Specific Inhibitory Factors can scarcely be denied. But for the weight that they have I should not be so bold as to advocate a theory which certainly prima facie seems awkward & absurd. Upon anyone who undertakes to oppose the theory must devolve the difficult task of proving that these granules — which agree with micro-organisms in every particular except the non-essential one of the thickness of their envelopes and hence in their staining reaction — are really something else than micro-organisms; and he will have to advance a new theory to explain what none of the present theories can explain, (1) the results obtained by the above experiment upon hatching eggs and (2) the phenomenon of a "clear" egg.

Regarding the occurrence of a bacillus in the healthy gut something is to be said. There is no evidence to show that this organism is producing any pathogenic effect. It is not in very large numbers. What then limits its growth? It does not appear to be in sufficiently large numbers to be inhibitory to own growth. Yet it must be producing ptomaines & these ptomaines must have a certain antitheric value. Say a thousand years hence what changes should we from known laws expect to take place in these bacilli? In the first place we should expect that its thick chitinoid membrane will have become thinner & more quite thin, & unresisting; And secondly owing to this change in its membrane we should expect that it will not have retained its distinct rod-like form but have changed into a pointed organism. In short it will have become like one of the minute granules which may be demonstrated in the blood. Explained by the light of the theory of specific inhibitory factors, we should say of the occurrence of this organism in the gut, that this bacillus has already taken its place among the specific

inhibitory factors of the patient — functionally it is one —; in much less than a thousand years it will be also morphologically one of them. Just by evolution along similar lines I contend that the other specific inhibitory factors have arisen.

Some further points in favour of the theory of Specific Inhibitory Factors.

I maintain that it offers an intelligible explanation of many phenomena which none of the other theories explain, and that of many others it offers a better explanation than they do.

(1) It explains why loaded bowels so injuriously affect inflammations which are accompanied by the growth of bacteria e.g. whitlow. When faeces are long retained in the intestines they undergo excessive putrefactive changes and at the same time they are present in abnormally large quantity. Hence there is absorption to a very unusual degree of the ptomaines the result of these putrefactive changes. Now according to laws which I have endeavoured already to indicate these ptomaines must to some extent check the growth of the specific inhibitory factors. The character of the aggregated ptomaines will be slightly modified in a direction less inimical to septic organisms. Hence the increased liability to growth within the body of the staphylococcus pyogenes & other organisms. Administer a brisk purge — you clear away the manufactory of the ptomaines that are being absorbed from the alimentary tract, their influence upon the specific inhibitory factors is soon withdrawn for those

present in the blood are soon excreted by the kidneys, and the full inhibitory power of the individual is restored re-established. A septic amputation stump instead of the intestinal tract may be the seat of the ptomaine production and in such a case a similar result will be seen. How this theory, in the same way, fits in with the phenomena of septic infection and pyaemia from a septic wound must be apparent.

(2) It explains how death from pure asthenia, uncomplicated by septic infection is possible, e.g. in cancer, lymphadenoma, pernicious anaemia [redacted]. Though in an asthenic condition all the processes that go on in the living body are very inefficiently performed & some of them probably very totally arrested, yet the fluids of the body remain a suitable soil for the specific inhibitory factors, which therefore still grow to self-inhibition. Hence there is no decrease in the inhibitory power of the patient commensurate with the diminished vigour of the patient's vital powers, and the patient may die of pure asthenia uncomplicated by septic infection. I am very anxious that I should not be misunderstood upon this point. I do not mean to contend that if one was to amputate the leg of such a patient the result would not be unusually disastrous. The stump would almost certainly go

of

septic in spite of every precaution. But this theory in favour which I am arguing is not in the least discredited by this result, on the contrary it explains it. The vitality of the whole tissues of the body (let it be understood that that merely designates a series of phenomena the details of which we little understand) is undoubtedly lowered so that the mechanical injury the result of the amputation may completely kill the neighbouring already moribund cells. There is inflammation in the tissues, their vessels become occluded, the blood containing the antiseptic substances can no longer reach them and they become a suitable nidus for putrefactive organisms. Hence the sloughs, but the essential cause of the tissues becoming a suitable soil for putrefactive organisms has been the failure of the circulation in the part, not the loss of vitality of the cells. Besides it is to be remembered that favouring this occurrence there is a weakened heart to pump the blood to the part, and, as explained in (1), in such a case the influence of excessive ptomaine absorption from the intestines, naturally following upon the consequent of their diminished functional activity, is also to be taken into account. I strongly insist upon this clinical fact that diminished vitality — diminished vigour in the performance of all the bodily functions — does not in itself involve any commensurate diminution in the inhibitory power.

(3) It explains why digestive recovery after operation results in decrease of inhibitory power instead of increase. Under such circumstances there is probably an excessive accumulation within the body of putrefactive ptomaines absorbed from the intestines and as explained above these must to some extent check the growth of the specific inhibitory factors, and these will result the production of a less powerful aggregate of ptomaines. (4) It throws a flood of light upon the curious fact already pointed out, viz, that the body of warm-blooded animals in its behaviour to micro-organisms is analogous to the behaviour towards other micro-organisms of an artificial fluid cultivation medium in which various species of organisms are growing to self-inhibition.

(5) It explains how it is possible that there is the same kind of inhibition of micro-organisms by the living body of the infant and that of the very old person.

(6) It offers, I hold, a better explanation of the peculiar instances of some (which I have already mentioned) of susceptibility and insusceptibility to the attack of certain organisms seen among warm-blooded animals, than the present theories do. In other words it gives a new explanation of natural immunity. For example it is contended that why the pig is insusceptible to anthrax [or nearly so] and the sheep is very susceptible to it is that in the two animals the specific forms of the organisms constituting the inhibitory factors are not quite identical. Hence the component parts of the ptomaine aggregate produced are in the two cases not quite the same, and therefore these two aggregates though in both cases the result of

with up to natural inhibition according to certa
, differ slightly in antitheric properties. I on
ig it happen to have a more powerful antithe
influence against the bacillus anthracis that it has in
he common sheep, and hence the difficulty of getting t
bacillus to grow in the body of the pig. For a simila
eason Algerian sheep are insusceptible to anthrax;
It is & the many other instances of similar natural
insusceptibilities that might be given are
I suggest that to be explained upon the same lines

(7) It is contended that this theory offers
a better explanation of the phenomenon of
acquired immunity than any of the theorie
at present held.

To try to make clear my meaning I shall
use again the illustration of a artificial flui
cultivation material of complex composition in which
there are various species of micro-organisms grow
ing up to inhibition by their own collective ptomain

If we have pure cultivations of various other
organisms at hand and add them from time to time we should
probably find that there were at least three
distinct types of behaviour on the part of
the various species of organisms introduced.
Firstly we should probably find that mos
specific forms we tried to introduce (always of course
inoculating with fluid from one pure cultivation
at a time) would not grow at all.
Secondly we should probably find that some when ad
introduced took their place among the other organisms
& retained it.

Thirdly, we would probably find that a few
other forms when introduced grew rapidly for
a time, but presently their growth was checked
and in a little time longer they became less
numerous until at length they were killed out.
This is of course a theoretical experiment
to illustrate my meaning but I believe
that there are on record accounts of ex-
perimental results which justify one in
stating that the illustration gives a true
idea of the physiological relations of bacteria
to each other in fluid cultivations. How
the first & the second cases are brought
about is explained from what has been
said. But with the third I confess
there is more difficulty. Did time permit
I could I think advance more than one
reasonable theory to explain how some specific
organisms might after growing for a short time
be killed out. I have little doubt in my
own mind that such a phenomenon would occur
in the case of some specific forms and that ex-
perimental evidence of the fact would not be
difficult to obtain if one had the necessary

with up to natural inhibition according to certa

apparatus. While therefore I admit that as yet experimental proof of the point is wanting I may use it merely to illustrate the explanation that the theory of specific inhibitory factors offers of acquired immunity.

The natural immunity of the frog to anthrax the field mouse to mouse septicaemia, & warm blooded animals in general to the vast majority of organisms (i.e. the non-pathogenic) is explained on the analogy of the first case. On the analogy of the second type of cases we have leprosy & the acquired immunity of the sheep to anthrax after a first attack, & of the human subject from scarlet fever after a first attack, are to be explained on the analogy of the third type. Just because the force which killed out the anthrax bacilli continues in operation for some time after they are killed out the sheep is insusceptible to another attack for some time. That force was really the antitheric substances produced by the specific inhibitory factors of the sheep. When the bacillus was first introduced there were not able to inhibit its growth. But the ptomaines of the bacillus

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after it had grown for a time reacted upon the specific inhibitory factors according to the analogy of type third, so disturbing the former numerical relation of one species to another that the component parts of the aggregate of the ptomaines produced were markedly changed and therefore the antitheric character of the aggregate was changed. This change in the case of anthrax in the sheep happens to result in the production of a more powerful antitheric force towards the anthrax bacillus, the growth of which is first checked, & then the organism is killed out altogether; and this arrangement of the inhibitory specific factors remaining for a time after the bacillus has gone the sheep is "protected." Did time permit I might attempt to show that the results of vaccination are explicable along the same lines. That the modification of the numerical relation of the different species of inhibitory factors to each other by a pathogenic organism should result in the production of an aggregate of ptomaines more powerful than before against that pathogenic organism is

with up to natural inhibition according to certa

not essential. The alteration may be in an opposite direction. In such a case the organism will not be eliminated but death will probably result more or less rapidly e.g. in Asiatic cholera. In the case of leprosy there is an intermediate result, - the organism becomes as it were one of the ~~most~~ inhibitory factors for the rest of the patient's life though it ~~still exists~~ continues to exert a pathogenic effect. The explanation of the results obtained by innoculation for hydrophobia is essentially the same only instead of introducing the organisms into the body to produce their ptomaines there, the ptomaines themselves, manufactured elsewhere, have been introduced, with effects similar to those obtained in the case of anthrax. All this is of course quite theoretical, - so is Pasteur's explanation of his results. The effects produced must depend upon the physiological relations of bacteria to each other a subject at which little work has as yet been done, & about which our knowledge is therefore very limited.

I do not wish it to be thought that I am myself satisfied that the theory of specific inhibitory factors is proved to be correct by the forgoing arguments.

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I am merely seeking for further light upon the extremely difficult problems of natural and 29
acquired immunity. The theories at present held upon these points are all possible explanations, but I say that they do not explain all the phenomena to be observed, - indeed that there are clinical facts which prove that they at least cannot be the full explanation. The theory of specific inhibitory factors I have been endeavouring to show furnishes another possible explanation. I do not say that it ~~either~~ gives a full explanation of all the phenomena to be observed either. There are phenomena which I cannot I still cannot understand, and which I might easily frame into arguments against the theory. All that I insist upon is that the theories at present held are incapable of explaining all the facts of the case, and that the theory I have suggested has sufficient evidence in its favour to render it deserving of careful consideration and to make it desirable to seek the light of further observation and experiment which will either disprove it or confirm it.

Still less do I wish it to be thought that I ~~believe~~ am satisfied that the theory which I am going ~~to~~ to suggest, in concluding, ~~about the~~ in explanation of the tubercular diathesis is proved to be true. Here too I am but

with ref to natural inhibition according to certa

seeking for light where all is not dark
ness. If, ~~upon~~ in explanation of so importa
a problem, anyone has a new theory to suggest
that is supported by experimental & other evidence
however incomplete, no harm but ~~good~~ possible good
will result from putting it forward,
whatever comes of it. The question that I
want to answer with a definite theory is this,
Supposing the theory of specific inhibitory
factors to be correct, what light does
it throw upon the tubercular diathesis,—
what explanation does it give of it?
In the first place I should like to point
out that susceptibility to tubercular lesion
is something which is different in its
nature from, for example, the sheep's sus
ceptibility to anthrax. In the latter case there
is susceptibility to growth within the body
of one particular organism, but in the former
there is unusual liability to the growth in the
body not of one organism but of several dif
ferent organisms, yet probably not of all
organisms. We hear many people speak of
the tubercular diathesis as if it implied ~~that~~
merely special liability to the growth of the tubercle
bacillus within the body. There is however abundant
evidence to prove that this view is an error, but as
time does not permit of my discussing the questions
[illegible] place among the other organisms
[illegible] retained it.

shall take it for granted that it is admitted
that the tubercular diathesis is a condition in
which there is unusual liability to the attacks
of many more specific organisms than the
tubercle bacillus. Two other points about this
peculiar condition of susceptibility are to be noted,—
it may be inherited and it may be acquired.
Now I think that, supposing the theory of specific in
hibitory factors is correct, a rational theory may be
advanced which will explain these three phenomena.
If in the artificial cultivation medium already used
in illustration there are growing a large number of
organisms it will be very difficult to find
a new species which when introduced will grow
in the medium. But if we could by some means
suddenly eliminate say one-third of the different
forms growing in the cultivation material,
while the remaining forms still grew up to
natural inhibition, it would now be much
easier than before to find a new organism
which would grow in the medium along with those
already in it. The quantity of ptomaines in the
two cases would be exactly the same—up to
natural inhibition, but those produced by
the smaller number of specific forms would
necessarily be less complex than those produced
by the larger number, hence they would be of small
er antitheric value, and therefore more new

specific forms that it might be attempted to introduce into the cultivation material would be able to grow than before. Now I suggest that the tubercular diathesis is a condition analogous to this. Here must be in individuals a continual tendency to the dying out or elimination of some specific forms of the inhibitory factors, and there are certain influences which no doubt make the tendency more pronounced such as bad hygienic conditions, chronic pneumonia, absorption from the alimentary tract, the presence of pathogenic organisms in the body as in scarlet fever, measles, diphtheria, syphilis, &c. The conditions of transmission of the inhibitory factors — supposing they exist — must be, I think we are justified in assuming, the same as in the case of the virus of syphilis. What these are is well known. It is evident then that the child cannot inherit a larger number of specific forms of inhibitory factors than its parents possessed. If they possessed fewer specific forms than normal, they would probably give evidence of having the tubercular diathesis and as they transmit the same factors to their children, they also would have the tubercular diathesis. But if, say

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the mother possessed a normal number 31
of neither she nor her children would have the
tubercular diathesis, though they might subsequently acquire it.
If this theory were correct it would imply, among
other things, that if we could put into an individual
having the tubercular diathesis some additional specific
forms of inhibitory factors his tubercular diathesis
would probably be removed. These additional specific
forms could be obtained by introducing blood from a
person without any tubercular diathesis. By means
of Neale's digest I turned up the literature of
"Transfusion" expecting that it would be found
to at once knock this theory on the head. I find
however that it very far from does so. I ascertained that there is a large amount of Journal
literature upon the transfusion of blood in cases
of haemorrhage, but only a very little upon transfusion for phthisis, — none that I could find
upon other tubercular lesions. The following is a
summary of all that I could find upon
the subject of transfusion for phthisis, —
Lancet 27. 7. 76. From Chicago Medical
Journal. — Transfusion of defibrinated
human blood. Patient in last stage of
phthisis. Night sweats ceased on third
day after transfusion, and the haemoptysis
which had been frequent disappeared. He began at once to gain appetite, strength and flesh.

In less than a month he gained 17 lbs in weight and is increasing in weight at the rate of ¾ of a pound daily. The dyspnoea is now insignificant and the destruction of lung tissue seems to have been arrested". Evidently evoked by this there appeared in the same journal a few weeks later the following:

Lancet 26.8.76.- Conclusion of Dr Howe, New York

He lately transfused in three cases with negative results, a temporary amelioration being observed in one case only.- His conclusions "(1) The operation of transfusion in phthisis is peculiarly dangerous because with a weakened heart there is obstruction to the circulation in the lungs and deficient aeration of the blood which both tend to overcome the heart's action and produce syncope. (2) The introduction of healthy blood temporarily improves the condition of the patient in much the same manner as alcohol and quinine do when taken into the system. (3) The transfusion of blood in advanced phthisis is scarcely a justifiable operation because the temporary benefit obtained does not by any means compensate for the risk of the operation."

Now it is to be noted that these experiments were not based upon any particular theory that encouraged the belief that a success would follow. The treatment was entirely an empirical one, or at least it was only adopted with a view to prolonging the patients lives by the introduction of what would temporarily improve their condition "in much the same manner as alcohol and quinine do". How is the remarkable result obtained in the first case to be explained? I suggest that the explanation is this. By a mere accident there was introduced into the patient defibrinated blood from a person who was a typical non-tubercular subject and that the patients tubercular diathesis was actually removed by the addition of new additional inhibitory factors. Hence the tubercle bacilli and their allies growing in his lung were rapidly killed out and he recovered. Doubtless the same treatment was tried again & again with other patients without success,- simply because the conditions which headed to success in the first case were not understood & therefore not fulfilled. While it would be impossible to transfuse from the same person again after he had lost so much blood, it is almost certain that the persons who were chosen as the donors of the blood for the succeeding cases would be near relatives of the phthisical patients. According to the theory I have suggested no benefit could possibly result from the transfusion of their blood. The opera-

tion would produce no benefit — probably much harm — therefore, no doubt, the method of treatment was abandoned. Howe's experiments were evidently carried out upon the same lines. Near relatives were probably chosen as the donors. It is to be noted also that the cases were all far advanced.

I think I am therefore justified in saying that there is nothing in the literature of "Transfusion" to discredit this theory but that on the contrary there is much in it to encourage the belief that it may be correct. The possibility that there might be some special communicable virtue in the blood of a non-tuberculous person seems never to have been suggested. The theory that there is may be true. I therefore urge that the effect of the introduction of blood from a very carefully selected healthy person with a typical "good family history" should be tried in cases of tuberculous disease. Transfusion of a large quantity of blood would not be necessary. A few minims are all that would be required. I do not say that if this theory is correct large cavities in lungs would be made to close, but the destructive process would be stopped & the best possible chance of cicatrisation would be given. The beneficial results in cases of other tuberculous lesions might be expected to be more complete. If the theory of specific inhibitory factors were correct I believe that the most important result that would come from it would be this. I therefore urge that this simple experiment should be tried. It is the teaching of history that the simplest things may remain undiscovered for years though they are all the while lying ready to men's hands.

Edinburgh. 13. II. 90. W. E. Robertson.

introduced took their place among the other organisms and retained it.