work in a responsible position, and able to acquit herself well. Of the other three, one, in which only a middle lobe or enlarged isthmus was removed, has improved very slowly, and only does housework at home. The other two are young ladies; one, the younger and more delicate type, is quite pleased with herself, but is evidently far from well yet; the older and stronger lady is certainly very much improved, and considers that she has regained her old health. I think this is putting matters at their best; and, although it is not quite as definite and satisfactory as one would like, it is sufficient to encourage me to continue the operation in all suitable cases. In adenoma the success is all one could wish, and I believe one might almost say the same in regard to parenchymatous goitre; but in Graves's disease the circumstances are different, and I should be sorry if, by painting the results in too glowing colours, I encouraged anything like reckless operating in so serious a condition.⁶

NOTES.

¹ These have since been doubled. ² It has not recurred. ³ Have since had reason to believe it to be very necessary. ⁴ Just seen accidentally, looking very well, and says she is very well; so there may be some mistake in regard to the unsatisfactory report. ⁵ Since writing this paper, I have had the misfortune to lose a case of parenchymatous goitre, which I will report later. The case was complicated by advanced idiopathic cirrhosis of the liver. ⁶ Since this was written the improvement has been very marked in all the cases of Graves's disease.

A LECTURE ON YELLOW FEVER,

WITH A DESCRIPTION OF THE BACILLUS
ICTEROIDES.

Delivered before the University of Montevideo on June 16th, 1897.

BY PROFESSOR G. SANARELLI,

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[TRANSLATION.]

[AFTER some preliminary observations on the history of yellow fever and on its clinical symptoms, Professor Sanarelli proceeded to give the results of his own investigations as follows:]

CLINICAL AND ANATOMICAL INVESTIGATIONS.

The material of my studies I procured partly at the lazaretto of the Island of Flores; where during last summer I installed a small laboratory for the investigations on the sick, or on the cadavers of individuals coming from the Brazilian ports, and who were taken ill during the voyage; in part at the hospital of St. Sebastian of Rio Janeiro, where, thanks to the kindness of the excellent director, Dr. C. Seidl, and of his able colleagues, Drs. Fajardo and Couto, I was able to instal myself conveniently, and to devote more than a month to clinical, anatomical, and bacteriological researches.

BACTERIOLOGICAL INVESTIGATIONS.

The bodies of those who die of yellow fever (icteroid typhus) are either altogether sterile, or are entirely invaded, by certain microbic species, such as the streptococcus, the staphylococcus pyogenes, the coli bacillus, the protei, etc., which cannot in any way be considered as the cause of the malady, or by a mixture of microbes, of which the isolation alone, the classification, and the study require such an amount of labour as to render accurate systematic research impossible.

I believe it superfluous, then, to recount the ways by which I arrived at the recognition of the microbe of yellow fever; I owe this good fortune to the second case of yellow fever I met with in the Island of Flores. This case presented, in a state of relative purity, the specific microbe to which I subsequently gave the name, not altogether proper, but sufficiently expressive, of "bacillus icteroides," because yellow fever is also called icteroid typhus.

I have said in a state of relative purity, because yellow fever presents the prototype of diseases with mixed infections. In the eleven necropsies that I made, I have never met with the bacillus icteroides alone; it was at least associated with

the coli bacillus, staphylococci, or the streptococcus. In the second case, at the Island of Flores, it was only associated with a small quantity of coli bacilli, and in the eighth, studied at Rio Janeiro, with staphylococcus aureus.

In all the other cases, I either found it mixed, in a large minority, amongst numerous common microbic species, or I was not able to find it owing to the cadavers being completely invaded by other microbes, which, as we shall subsequently see, after having succeeded, owing to the action of the bacillus icteroides, in invading the organism, eventually injure or cause the total disappearance of the specific microbe.

I would briefly premise that the bacillus icteroides must be sought for in the blood and tissues, and not in the gastrointestinal cavity, where, contrary to what might *a priori* be supposed, it is never found. In fact, in yellow fever the digestive canal becomes the seat, as in typhoid fever, of an exaggerated pullulation of the coli bacillus, which is met with in a state of almost absolute purity.

According to the results of my researches, the isolation of the specific microbe of yellow fever is only possible in 58 per cent. of the cases, and in some rare cases may be effected also during life. The reasons why in every case of yellow fever one cannot isolate the specific agent are easy to understand. In the first place, at the beginning of the disease the bacillus icteroides multiplies very little in the human organism, a small quantity of the toxin, as we shall see later, being sufficient to develop in man the very grave picture of the complete disease. In the second place, the toxin, either by itself, or indirectly by means of the profound lesions that it determines, above all in the digestive mucosa and the liver, facilitates in an exceptional way secondary infections of every kind. Such secondary infections may sometimes assume the type of true and special septicæmiæ, with coli bacillus, streptococcus, staphylococcus, etc., capable of killing the patient by themselves alone. At other times they occur mixed, so that, in the last stages of life, they may transform the individual into a true culture of almost all the intestinal microbic species.

Finally, as the result of my observations, that the bacillus icteroides is found in the circulating blood and in the interior of the tissues, and that it is never found in the gastrointestinal contents, it must be held, contrary to what is at present supposed, that the virus of yellow fever does not reside in the digestive tube, and that therefore its poison, instead of being absorbed through the intestinal walls, is manufactured in the interior of the organs, and in the blood itself.

THE BACILLUS ICTEROIDES.

This bacillus at first sight presents nothing morphologically characteristic. It is a little bacillus with rounded extremities, for the most part united in pairs in the culture, and in small groups in the tissues, from two to four-thousandths of a millimetre in length, and as a rule two or three times longer than broad. It is very pleomorphic. A search for it in the tissues does not give good results, excepting in the cases in which the death of a patient occurs without secondary septicæmiæ. Even in the cases which on bacteriological examination give the purest results, it is not easy to see it in the sections of the tissues owing to the number being sometimes extremely small. Yet, by employing suitable methods, one can find it in the organs, usually united in little groups, always situated in the small capillaries of the liver, kidneys, etc. The best means for demonstrating not only its presence, but also the special tendency it has to be localised in small groups in the blood capillaries, is to place a fragment of liver obtained from the body whilst fresh, in the incubator at 37°C. for twelve hours; this favours the multiplication of the specific microbes.

The bacillus of yellow fever develops sufficiently well on all the ordinary nutritive substances. In plate culture in ordinary gelatine it forms roundish colonies, transparent and granular, which during the first three or four days prevent the appearance of leucocytes. The granulation of the colony becomes continuously more marked, and usually a central or peripheric nucleus, completely opaque, is delineated. With time the entire colony becomes opaque, but does not liquefy gelatine. Streak cultures on gelatine solidified obliquely, forming brilliant opaque little drops similar to drops of milk.

In meat broth it develops slowly, without forming a pellicle or flocculent deposits. On solidified blood serum it grows in an almost imperceptible manner.

The culture on agar-agar, unlike what is observed with the greater part of the known pathogenic microbes, presents for the bacillus *icteroides* a diagnostic means of the first importance. When the colonies develop in the incubator they assume an aspect which does not differ from that of many other microbic species—that is, they are roundish, grey, a little iridescent, transparent, with a smooth surface and regular margins. If instead of making them grow at a temperature of 37° C. they are left to grow at a temperature of 20° to 22° C., the colonies are like drops of milk, opaque, prominent, and with pearly reflections, completely different from those developed in the incubator. This different manner of development can be utilised by exposing the cultures for the first 12 to 16 hours to the temperature of the incubator, and then keeping them for 12 to 16 hours more in that of the room. The colonies then show a flat central nucleus, transparent and bluish, and surrounded by a prominent and opaque zone, the whole resembling a drop of sealing wax. As this character, which for the present may be considered specific, can fortunately be obtained, even in 24 hours, it serves to establish, in the most rapid and certain manner, the bacteriological diagnosis of the bacillus *icteroides*.

Besides these morphological characters, which are sufficient to differentiate the microbe of yellow fever from all those that are at present known, the bacillus *icteroides* is endowed with some interesting biological properties. It is a facultative anaërobe, does not resist Gram's stain, slowly ferments lactose, more actively glucose and saccharose, but is not capable of coagulating milk; it strongly resists drying, dies in water at 60°, and is killed in 7 hours by the solar rays, but lives for a long time in sea water.

PATHOGENIC PROPERTIES IN ANIMALS.

The specific microbe of yellow fever is pathogenic for the majority of domestic animals. In fact, whilst birds are completely refractory, all the mammals with which I have experimented are more or less sensitive to the pathogenic action of the bacillus *icteroides*.

It kills *white mice* in 5 days, causing a general septicæmia, with fatty degeneration of the liver.

In *guinea-pigs* it produces, in very small or large doses, a cyclical febrile disease, which always ends in death after 8 to 12 days. The infection can take place by any path, even by the respiratory passage. The microbes, as soon as they penetrate into the organism, chiefly collect in the spleen, where they remain during the evolutionary cycle of the malady, without notably multiplying. After 6 to 7 days they suddenly invade the circulation, enter into a period of active proliferation, and kill by septicæmia. The lesions found *post mortem* are hypertrophy of the thymus gland, splenic tumour, axillary and inguinal adenitis, and hepatic lesions, solely in chronic cases, which are very rare. Less frequently, enteritis, nephritis, and albuminuria are encountered; finally, hæmorrhagic effusion of the serous membranes is observed very rarely.

The *rabbit* is still more sensitive than the guinea-pig to the action of the ictteroid virus. Whatever be the dose of this virus, and in whatever way it penetrates into the organism, it infallibly kills after a cyclical disease, which lasts 4 to 5 days after infection by the subcutaneous tissue; 2 days only if the inoculation was made directly into the blood. The evolution of the infective process is in this case identical with that described above in the guinea-pig. In regard to the constant anatomical lesions, they are represented, as in the guinea-pig, by splenic tumour, hypertrophy of the thymus gland, and adenitis. Besides this, the ictteroid virus is capable of determining in the rabbit nephritis, enteritis, albuminuria, hæmoglobinuria, and various hæmorrhagic manifestations in the serous cavities.

But the animal that lends itself better than any other to exhibit the strict anatomical and symptomatological analogies of experimental yellow fever with human yellow fever is the dog. Injection must be effected by the veins, and the diseased process which results is almost immediately manifested with such violent symptoms and such complex lesions as to recall the clinical and anatomical picture of human yellow fever. The most prominent symptom in experimental yellow fever of the dog is vomiting, which begins directly after the penetration of the virus into the blood, and continues for a long time, as if the animal were under the influence of an energetic emetic. After the vomiting hæmorrhages appear, the urine is scanty and albuminous, or there is suppression, which precedes death a little. Once I observed grave jaundice. At the necropsy highly-interesting lesions are met with, inasmuch as they are almost identical with those that are observed in man. Above all, the profound steatosis of the liver strikes the attention. The hepatic cells, even when examined fresh by means of a little osmic acid, appear completely degenerated into fat, like those of individuals who die of yellow fever. The amarylligenous toxin is in reality, as we shall see later on, a true specific poison of the hepatic cells, like phosphorus and arsenic. A complete steatosis of the organ can be produced by injecting directly into it, through the abdominal walls, a fresh culture of the specific bacillus. Besides the liver, the renal tissue, which is the seat of an acute parenchymatous nephritis, and which must be considered as the immediate

cause of the anuria and the uræmic intoxication, presents a grave fatty degeneration. In fact the blood of dogs which die of experimental yellow fever contains a quantity of urea equal to that which is met with in animals completely nephrotomised, or in the severest cases of human yellow fever. The whole digestive apparatus is the seat of the gravest hæmorrhagic gastro-enteritis that can be imagined; comparable solely to that provoked by poisoning with cyanide of potassium. This hæmatogenous gastro-enteritis is then perfectly analogous to, perhaps more severe than, that which is observed in man. In the majority of cases the bacillus *icteroides* is always found in the blood and organs, in variable quantities, but in a state of absolute purity. Sometimes, however, I found it associated with the coli bacillus and the streptococcus, as in man.

As I have also observed this tendency to secondary microbic invasions in studying amarylligenous intoxication in dogs, obtained with filtered cultures alone, it must be concluded that the amarylligenous poison either by itself, or through the alterations that it provokes in the different viscera, and above all in the liver, which, as is known, is universally considered as an organ of defence against microbes, favours the secondary infections in the dog, having perhaps their point of departure in the intestinal canal itself. This constitutes an important point of bacteriological contact between yellow fever in the dog and in man.

The experiments performed in *monkeys* also present great interest, inasmuch as they demonstrated the possibility of obtaining in these animals fatty degeneration of the liver, still more grave than that observed in man. In one case the liver was completely transformed into a mass of fatty substance similar to wax. In the monkey, as in the dog and man, the disease frequently ends with the bacteriological appearance of a mixed infection, with staphylococcus or streptococcus.

Goats and *sheep* are also very sensitive to the ictteroid virus, and the same complex phenomena, indicated as specific in other animals, are repeated in them. Besides the grave fatty degeneration of the liver, which is never absent, nephritis, anuria, uræmic intoxication, and mixed infection are observed.

From the results of this first part of the research regarding solely the morphology, biology, and the comparative pathology of the bacillus *icteroides*, certain fundamental conclusions concerning the etiology and the pathogeny of human yellow fever may be drawn:—

1. Yellow fever is an infective disease due to a well-defined micro-organism, capable of being cultivated in our ordinary artificial nutritive media.

2. This micro-organism, which I have provisionally called bacillus *icteroides*, can be isolated not only from the cadaver, but also during the life of the patient suffering from yellow fever.

3. Its isolation generally presents almost insurmountable difficulties, due partly to the constant intervention of secondary infections, and partly to the relative scarcity with which it is encountered in the organism.

4. Such secondary infections, nearly always due to determinate microbic species, as the coli bacillus, the streptococcus, the staphylococcus, etc., may burst into the organism even a long time before the death of the patient, and thus death is sometimes due more to them than to the action of the bacillus *icteroides*.

5. It is probable that one of the causes which give to the yellow fever of man its protean character is the nature and the manner of development of these secondary infections.

6. The yellow fever infection, as much in man as in the lower animals, represents a disease with a cyclical course. During this period the specific microbe is found in the organs in very small numbers, and it is solely at the end of the cycle, about the seventh or eighth day, that it multiplies rapidly, and invades almost suddenly the whole organism, generally accompanied by other microbes, probably coming from the intestines.

7. Only in cases which terminate in this manner—that is to say, which regularly complete the disease cycle—can the specific microbe, diffused in the blood and organs, be found with comparative facility. When an intercurrent septicæmia, or a precocious uræmic poisoning, puts an early end to this disease cycle, it is extremely difficult, if not altogether impossible, to isolate the bacillus *icteroides*.

VISCERAL LESIONS.

The bacillus *icteroides*, when it has once penetrated into the organism, not only determines a general intoxication, but produces specific alterations: In the liver, rapid fatty degeneration of the histological element; in the digestive canal hæmatogenous gastro-enteritis; in the kidney acute parenchymatous nephritis, which is one of the earliest lesions, and that to which the anæmia which is very quickly established must be attributed.

CAUSES OF DEATH IN YELLOW FEVER.

The patient suffering from yellow fever is in fact contem-

poraneously threatened by three imminent dangers, and the bacteriological examination of the cadaver may approximately place in evidence the principal cause of death:

1. It may be due to the specific infection principally, when the bacillus *icteroides* is found in the cadaver in a certain quantity, and in a state of relative purity. This happens only in the cases which run their special disease cycle to the end.

2. It may be due to the septicæmias successively established during the course of the disease, when the cadaver presents an almost pure culture of other microbes.

3. It may also be due, in great part, to renal insufficiency, when the cadaver is found almost sterile; the percentage of urea in the blood is very high, and death takes place before the malady has reached the end of its evolutionary cycle.

It is difficult to pronounce during the life of the patient on the prevalence or not of the uræmic symptoms over the specific, because the most salient symptoms of the yellow fever intoxication are easily confounded with those of renal insufficiency.

This frequent and inevitable complication is perhaps the principal cause why there is no typical pyrexial curve. It is indeed very probable that certain normal and subnormal temperatures observed with great frequency during the state of delirium or in the full evolution of the disease, and some sudden and inexplicable terminations of the diseased process are due, besides the action of the amarylligenous poison, in great part, to the intervention of uræmic intoxication.

The so-called "black vomit" is due to the action of the gastric acidity in the blood which is extravasated in the stomach, in consequence of the grave toxic lesions of its mucosa. The act of vomiting is directly provoked by the specific emetic action, that the toxic products of the bacillus *icteroides* circulating in the blood possess.

The hæmorrhagic symptoms are due above all to the hæmorrhagiparous property possessed by the bacillus *icteroides* in common with other microbes, and in the second place to the profound and rapid fatty degeneration produced in the vessel walls.

TOXINS.

The small numbers in which the bacillus *icteroides* is usually found in the human organism, and the violence of the symptoms which are immediately provoked in dogs by injections of cultures relatively little abundant, into the veins, make me suspect the existence of a very active specific poison. This poison is obtained, like the diphtherial, by simply filtering the broth culture of the bacillus *icteroides* 24 days old.

The amarylligenous poison bears heating to 70° almost with impunity, but boiling sensibly attenuates it. If cultures sterilised with ether are employed, the toxic power is much more active.

ACTION OF THE TOXINS ON ANIMALS.

I have studied the action of this specific poison in guinea-pigs, rabbits, dogs, cats, goats, the ass, horses, and man. It has an action little marked and little characteristic in those animals in which the reaction to living virus is little specific: such are the small rodents, in whom death is caused only by strong doses of the poison; small quantities, as a rule, only cause transitory loss of flesh. In dogs the toxins, introduced into the veins, produces the same lesions as the virus. Ten to fifteen minutes after the injection a general rigor occurs, an abundant lachrymal secretion begins, and is followed by impetuous and continuous vomiting, at first of food and then of mucus, so that in a short time the stomach is completely emptied, and the animal lies extended and helpless. Frequently hæmaturia is observed. If the dose was moderate the dog recovers quickly from the violent attack, which may be compared to the poisoning produced by an active emetic, but if the quantity of toxin be very large, or it is repeated in successive days, continuously increasing the doses, the dog finally succumbs, presenting the same anatomical lesions that have been described as due to the action of the living virus. Bacteriological examination demonstrates the existence of mixed infections due as usual to coli bacilli, to streptococci, or to staphylococci.

The cat is very resistant to the icteroid toxin, as to the virus. In fact, truly formidable doses of either the one or the other can be injected without obtaining other consequences than a diminution of weight, more or less marked, followed by inflammatory processes in the part. This animal is the most resistant of those I have so far had occasion to experiment upon.

In the goat the icteroid toxin exactly produces, with the exception of vomiting, the same lesions as those described in dogs and in man. The great tendency to hæmatolysis (hæmoglobinic exudations, hæmoglobinuria), and the extreme sensibility of the kidneys to the amarylligenous toxin are noticeable above all in the goat. The death of the animal is due in great part to the profound lesion of this viscus, since the notable quantity of urea which is met with in the fluids represents an important presumptive evidence in favour of a grave uræmic intoxication.

My experiments on the ass were limited to one only. The same patho-

genic mechanism, with very few differences, was observed; that is, there were inflammatory and degenerative processes in the liver and kidneys, lesions of the mucosa, hæmorrhagiparous phenomena in the parenchyma, the serous cavities, the mucosa, the glandular organs, as the mamma, and lastly the final picture dominated by uræmic intoxication, and by the invasion of the microbes in the organism.

The horse is extraordinarily sensitive even to injections of small quantities of the toxin. It may be said, then, in a general way that the higher we ascend in the zoological scale the more developed is the sensitiveness of animals towards this potent and strange poison. Subcutaneous injections, even of small doses of the filtered culture, always determine much local tumefaction, followed by fever, which lasts twelve to twenty-four hours. The swelling is extremely painful, and disappears slowly. When the injection is more abundant, or if, instead of injecting the filtered culture, cultures sterilised with ether, which are much more active, are injected, the tumefaction produced becomes voluminous, and is always followed by the appearance of vast subcutaneous œdemas which extend in the sloping parts of the belly, reach the limbs, and sometimes end by disturbing for several days the movements of the joints. Sanguinolent ulcerations, which suppurate and are difficult to heal, are nearly always determined in the surface of the enormously distended skin. Both the œdemas, and the tumefactions which are produced in the part injected, do not disappear for many days, during which the animals very frequently present an almost continuous fever. Endovenous injections are much more easily tolerated, but have grave inconveniences. After each injection the animal regularly has a violent attack of dyspnœa, and has a general trembling, which obliges it to lie down. Fever appears, and for some hours the animal remains somewhat dejected. However, the following day the temperature becomes normal, and, as a rule, there is no other incident. In the course of my vaccination experiments I have had to lament the death of some of the horses; one of them was of the creole race, which is much less resistant than the half breeds to toxins in general, and above all to the diphtherial and amarylligenous toxins. The necropsy of this creole horse, which a little before death had some slight hæmorrhages, showed much tumefaction of the spleen, slight degeneration of the liver and kidneys, albuminuria, and some foci of enteritis.

TRIALS ON MAN.

In 1816 Dr. Chervin, of Pointe-à-Pitre (Antilles) drank repeatedly large quantities of black vomit without feeling the least disturbance. Some years before other North American colleagues, Drs. Potter, Firth, Cathrall, and Parker, did everything possible to inoculate themselves with yellow fever. After having uselessly attempted experiments on animals they experimented on themselves, inoculating the black matter at the very moment in which the moribund patient rejected it, placing this matter in their eyes, or in wounds made in their arms, injecting it more than twenty times in various parts of the body, respiring the effluvia of its evaporation, making pills of it which they swallowed, inoculating themselves with the saliva or the sweat of the patients, in short, devising every sort of daring means for experimentally transmitting yellow fever. All these experiments were without result, and in the United States during many years it was believed that this terrible malady was non-contagious. We are now in the position to explain perfectly the cause of such surprising failures. We have seen that the bacillus *icteroides* has not its seat in the stomach, and that if it accidentally reaches it, carried with the hæmorrhages, it is certainly found there in very great dilution as in the blood.

My experiments on man amount to five. For reasons readily understood I have not employed living cultures, but simply cultures in broth of fifteen to twenty days, filtered through a Chamberland bougie, and then for greater precaution sterilised with a few drops of formic aldehyde. In two individuals I have experimented on the effects of subcutaneous injections, in the other three the effect of endovenous injections. These few but very successful experiments have been sufficient to illuminate with a truly unforeseen light all the pathogenic mechanism until now so obscure and badly interpreted.

The injection of the filtered cultures in relatively small doses reproduced in man typical yellow fever, accompanied by all its imposing anatomical and symptomatological retinue. The fever, congestions, hæmorrhages, vomiting, stæstosis of the liver, cephalalgia, rachialgia, nephritis, anuria, uræmia, icterus, delirium, collapse; in short, all that complex of symptomatic and anatomical elements which in their combination constitute the indivisible basis of the diagnosis of yellow fever. This fact is not only striking evidence in favour of the specific nature of the bacillus *icteroides*, but it places the etiological and pathogenic conception of yellow fever on an altogether new basis.

THE PATHOLOGY OF YELLOW FEVER.

The dominating theory which represented the digestive canal, especially the stomach, as the crucible of amaryllism

solely because the gastro-intestinal phenomena were those which more vividly struck the clinician, being eliminated at a blow; it being once demonstrated that all these striking phenomena are due only to the specific poison manufactured by the microbe circulating in the blood, yellow fever immediately enters into the same class of diseases as that in which, some time since, I placed another great disease process, which before my researches had always been very badly understood—typhoid fever.

All the symptomatic phenomena, all the functional alterations, all the anatomical lesions of yellow fever are only the consequence of an eminently steatogenous, emetic, and hæmolytic action of the toxic substances manufactured by the bacillus icteroides.

It is perhaps for this reason that, owing to its general symptoms, the ataxo-adyamic characteristic manifestations, the tendency to hæmorrhages, the icterus, etc., yellow fever has been also compared to poisoning by the poison of certain serpents.

Another point of contact between the two diseased processes is in the hæmotogenous gastro-enteritis, which, in cases of poisoning, is up to now erroneously considered to be due to a kind of eliminating effort of the organism.

THE MODE OF INFECTION.

By what way the specific microbe can enter the organism, where it manufactures its poison in it, is very difficult to establish. In countries where yellow fever prevails, evidence sufficiently demonstrative to establish the transmission by water has not been collected. On the contrary, there exists an inexhaustible series of facts, which point strongly to atmospheric transmission. The solitary example, always quoted by authors, in relation to the diminution of yellow fever in Vera Cruz, after that city was furnished with good potable water, can have only a relative value, like all affirmations of the kind.

The remarkable resistance to drying which I have demonstrated in the bacillus icteroides warrants us in assuming a diffusion of the amarylligenous virus, both by means of the air and by means of water. Further, contagion by the respiratory passages has been demonstrated to be possible by the same experiment in animals. As to the mechanism of contagion by water it is now placed beyond doubt that the epithelium of the digestive passages, when it is intact, does not as a rule, permit the passage of any species of pathogenic germs.

But it must be remembered that in countries subject to yellow fever, the slightest disturbances of the digestive functions, as the abuse of alcoholic and iced drinks, the abuse of fruit, etc., above all in the newly arrived, constitute, like depressing causes in general, so many points of entrance of yellow fever.

Moreover, one must not forget that the newly arrived in tropical countries are subject to a slight catarrh of the biliary passages, which, together with the inevitable overwork of the liver that accompanies it, may also facilitate the attachment of the bacillus icteroides arrived in the intestines, in some part of the hepatic organ. Now that we know well the formidable effects of the amarylligenous poison, we can readily understand how its producer can find, without much difficulty, a mode of resisting, and of diffusing itself in whatever organ it penetrates, with or without other co-operating causes. Nothing, in fact, is more easy than the penetration of the bacillus icteroides into the intestines, from the moment that it forms a part of the microbic flora of the yellow fever localities.

The extreme tendency to lesions of the hepatic organ in warm countries is not only one of the conditions very readily disposing to amaryllism, but, this once established, it will be the principal cause of those secondary infections which impress a physiognomy, sometimes strangely intricate, on the bacteriological conditions of yellow fever, and which undoubtedly contribute in a notable manner to augment the frightful mortality of this disease.

SECONDARY AFFECTIONS.

The experimental study of these secondary infections has enabled us to observe a series of biological phenomena which throw an altogether new light on the reciprocal relations be-

tween the agent of amaryllism and those of the secondary infections.

The icteroid bacillus, either through the action of its specific poison or through the grave hepatic lesion which is its more immediate consequence, favours at a given moment the entrance into the organism of the septic microbes, which not only end the disease long before the specific agent would, but are also injurious to this latter, immediately invading its dominions, suppressing its vegetative faculty, and perhaps also its vitality.

It is for this reason that these phenomena of the microbic antagonism between the amarylligenous bacillus and those of septic infections, instead of being useful to the patient, who represents the field of action, have the effect instead of hastening the end.

YELLOW FEVER ON SHIPS.

The behaviour of yellow fever on board ship differs from that of cholera, as when once introduced on board, it explodes, rapidly attacking all those who, so to speak, can be attacked. The gravity of this explosion varies according to the quantity and energy of the cholera vibrio, and according to the predisposition of the subjects; but having once produced this explosion, the cholera vibrios do not seem to encounter in the ordinary conditions of materials on ship-board, a very favourable ground for their existence. This species of intermediary between man and the cholerigenous agent being wanting, especially if a good measure of disinfection has been practised, the disease is extinguished.

Yellow fever, on the contrary, once installed on board a vessel, is there long and tenaciously maintained, more particularly in the hold, magazines, merchandise, and in all close and restricted parts. The notion, indeed, is commonly held that old and dirty ships are the most unfit to use in countries where yellow fever is endemic.

Those who specially occupy themselves with naval hygiene consider as yellow fever vessels ships insufficiently aërated, provided with very small openings, where in the upper parts the vitiated air stagnates, and in the lower there is a foetid humidity. Humidity, heat, and want of light and ventilation, therefore, seem the coefficients special to the preservation of the bacillus icteroides.

But in the present state of our knowledge it is not possible to attribute to these various coefficients any specific value, inasmuch as they represent so many conditions which may militate in favour of all microbes in general. It is, therefore, necessary to seek in some other concomitant element the cause which favours in an almost specific manner the nautical habitat of the bacillus icteroides. A simple phenomenon, which at various times during these studies, has occupied all my attention, has afforded a new explanation of the probable cause of this mysterious longevity and resistance of the bacillus icteroides on board ships. This is in the fact that the common moulds of the atmosphere are the great protectors of the bacillus icteroides.

The microbe of yellow fever, although it is endowed with a great resistance towards the natural physico-chemical agents, nevertheless is not indifferent to the substances necessary for its nutrition. It is certain that during its saprophytic existence outside the organism, as in the hold of a ship, it would not be able to obtain nutritive principles of great value; this is so true that very frequently it is not even capable of multiplying on a plate of ordinary gelatine.

THE INFLUENCE OF MOULDS ON THE BACILLUS.

But if it happens that a mould develops near it, the products of material exchange of this hyphomycete or the transformation affected by it are sufficient to nourish the bacillus icteroides, and to enable it to live and multiply, otherwise it would be condemned to a more or less early death.

This property of moulds can be experimentally demonstrated, by simply depositing the spores of any mould in the midst of a gelatine plate, previously sown with icteroid microbes, but which has remained for a long time completely sterile, as often happens. Directly the mould commences to develop its mycelium, a crown of little punctiform colonies of the bacillus icteroides immediately appears around it in the gelatine. In proportion to the increase of the mould, these colonies continuously become more numerous, rapidly

extending their zone around the central thicket formed by the mould. After some days the gelatine plates, where the moulds are accidentally or artificially developed, present an extremely curious aspect. Around each mould the colonies of the bacillus icteroides, which might be thought dead, or totally incapable of developing after so long a time, constitute a species of constellation, the more innumerable the nearer to the mould. It may be said, then, that moulds exercise a kind of radial influence, within which only the development of the icteroid colonies is possible. This radius of influence is more or less extensive according to the species of mould, and the space it occupies, but it is always perfectly regular, uniformly distributed, and equidistant from the centre represented by the thicket of the mould.

Outside this radius of influence, which is always strictly limited, the development of the microbic colony sharply ceases, and the remainder of the gelatine remains sterile until some new spore causes the formation of new mycelia, which in their turn are immediately surrounded and enclosed by a new pullulation of icteroid colonies.

It is very probable that such a faculty constitutes a specific character possessed by all the moulds in general, since the six species that I have accidentally isolated from the air of the laboratory have shown themselves, although in diverse degrees, equally capable of favouring the revival and multiplication of icteroid microbes otherwise incapable of development. Further, it is possible that there exists in Nature, especially in localities where yellow fever is installed with great vigour, some mould at present unknown, endowed with a helping power truly specific and much more notable. This strange phenomenon of parasitism, this strange form of microbic saprophytism possibly represents the principal cause of the ready acclimatisation of yellow fever on board ships.

It is, indeed, highly probable that, especially in the holds of badly ventilated vessels, the constant heat and humidity, considered in their physico-chemical effects, are the conditions which maintain so long in life the microbes of yellow fever accidentally arrived there. In the hold of vessels, notwithstanding the heat and humidity, other pathogenic microbes, as those of cholera, typhus, etc., do not prosper nor maintain their activity for a long time. In respect to yellow fever, heat and humidity and scanty aëration may therefore be considered above all as the conditions indispensable for the development of moulds, and then as indirectly favourable to the vitality of the bacillus icteroides.

This phenomenon of commensalism, very analogous to that which Metchnikoff has already some time ago indicated for the cholera vibrio, also explains, and agrees with many other well-known practical observations furnished by the epidemiological history of yellow fever, and on which I believe it is useless to dwell further.

We must then consider moulds as the natural protectors of the specific agent of yellow fever, because it is solely through their intervention that the latter can find the force to live and multiply, whereas the unsuitableness of the nutritive means or the unfavourable action of the developing temperature would render its existence altogether impossible. The intervention of this factor, apparently so insignificant, constitutes perhaps the principal cause of the acclimatisation of yellow fever, not only on board ships, but also in certain localities where it appears to find conditions extraordinarily propitious to its sad dominion. In fact one of the conditions considered indispensable to the development of yellow fever, that is, humidity, is, together with heat, the condition most propitious to the development of moulds. It is above all to the defect of ventilation and the excessive hygrometric state of the atmosphere that the unhealthiness of Rio Janeiro is held to be due. During the great epidemic of yellow fever of Montevideo in 1872 the inhabitants of houses looking north only were attacked with an inexplicable preference. Both the houses and the side of the streets looking north in Montevideo are distinguished for their truly exceptional humidity.

It is, then, probable that the factor of humidity, whether on board ships or on the coasts or the interior of countries, represents the principal coefficient of a biological phenomenon rather than that common meteorological influence, the action of which is always identical in the etiology of almost all the epidemic diseases. On the other hand, the

notable resistance presented by the bacillus icteroides towards the principal factor of natural disinfection, that is to say, drying, and its great longevity in sea water sufficiently explain the ready acclimatisation of icteroid typhus and its obstinate persistence, especially in the maritime localities afflicted by the immigration of its specific agent.

This is the point to which I have had the fortune to bring our knowledge, after a year and a half of indefatigable work, concerning a terrible disease, the most grave and most urgent sanitary problem in all America. Much more still remains to be accomplished. To-day we can recognise the specific agent of yellow fever; we have it in our hands; we have minutely studied its life, customs, necessities, relations with external agents, and with other minute beings; we have succeeded in revealing the very complicated mechanism of all the numerous diseased manifestations that it determines in the human organism; finally we have placed this malady, which up to a few months ago represented a fearful mystery, on the same level as all the other great infective diseases.

The useful results for public prophylaxis, and for clinical treatment, it is not necessary to indicate here. The principal basis of social defence against diseases is the knowledge of their specific cause.

Asiatic cholera, typhoid fever, and many other grave diseases no longer inspire the terror of other kinds, because science, founded on the study of their specific agents, can nowadays protect us against their diffusion and their acclimatisation, adopting wise sanitary measures, and effecting hygienic improvements of various kinds, from whose good effects some cities have been almost restored from death to life.

However, besides the prophylactic ideal, which hygienically speaking is far superior, because it is always better and easier to prevent maladies than to cure them, or to make them disappear when they have manifested themselves, there exists another ideal—therapeutics.

Well, given the nature of the diseased process which we have studied, I do not believe it is difficult to realise also this ideal, and I have a firm conviction that very soon it will be possible to apply to man a preventive and curative treatment of yellow fever.

THE CROONIAN LECTURES

ON

THE MEANS BY WHICH THE TEMPERATURE OF THE BODY IS MAINTAINED IN HEALTH AND DISEASE.

Delivered before the Royal College of Physicians of London,

By W. HALE WHITE, M.D., F.R.C.P. LOND.,

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LECTURE III.

[ABSTRACT.]

CALORIMETRY.

DR. HALE WHITE in his third lecture dealt with the calorimetric method of studying the question whether the production of heat is increased in fever. He described the ordinary water and air calorimeters, and pointed out their defects and the fallacies to which they were apt to give rise. He then described the form of differential air calorimeter which he had devised in co-operation with Dr. Haldane, Dr. Washbourn, and Mr. F. G. Hopkins. In principle it consisted of two chambers exactly similar, in one of which hydrogen was burnt, while in the other the animal on which the experiment was to be made was placed. Each chamber had a double wall. The space between the two skins was airtight and filled with air. Each of these air spaces was connected with a manometer of special design. During an experiment, the jet of hydrogen gas was kept burning in the one chamber while in the other the animal was placed. At the beginning of an experiment a note was made of the upper level of the fluid in the manometer. During an experiment the heat given off from the animal warms its chamber, and