On latent and recurrent infection, and on subinfection / J. George Adami.

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ON LATENT AND RECURRENT INFECTION, AND ON SUBINFECTION*

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It so happened that when the very courteous invitation of your Dean reached me, I was reading the "Life" just published of one whom I knew intimately in the old days at Cambridge—one of the great minds of the Nineteenth century. I refer to Robertson Smith, that extraordinary man whose knowledge was such that not merely was he editor of the Encyclopedia Britannica: he **was** the Encyclopedia Britannica—and over and above all he led that crusade in favor of reverend historical criticism of the Bible which has influenced all Protestantism. His celebrated Heresy trial dragging through many years in Edinburgh while apparently a defeat and leading to dismissal from his chair in Aberdeen, in reality brought about the triumph of honest thought, which has spread and affected all the churches.

Reading that life brought back vividly the unforgettable days, or more accurately nights—"noctes ambrosianae"—when after dinner in Hall we adjourned to the "Combination Room" and thence to his own rooms in the Fellows' Building at Christ's, succumbing to the charm of his conversation. For he knew everything (save music) from the manners and customs of the Esquimaux and native Australians up to the latest developments in Pure mathematics and Psychology. I have heard him correct a zoologist just back from years spent in the Malay archipelago in his statements regarding the fauna of Celebes: have learnt from him how to treat and appreciate Chateau wines—to distinguish between a Haut Brion and a Mouton-Rothschild: have heard from those present how being a guest at Hardwicke Hall and finding himself at the annual tenant's

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dinner, sitting among the farmers he discussed so learnedly the genealogy of celebrated race horses, showing by example how certain strains of blood were essential for speed, that the farmers took him, the Professor of Arabic, for a horse breeder. He was a wonderful man: he loved a fight, but over and above all he loved his friend.

Poor Robertson Smith! he died all too young at 47 even if he had achieved an international reputation long before he was forty.

But it was the history of his illness that determined my choice of subject.

Brought up with extreme frugality in a country manse, Robertson Smith and a still more brilliant brother were educated largely by their father, with the result that when the two went to Aberdeen, there between them they literally swept the board. They worked intensely, and every prize became theirs. They were the most brilliant students of their generation. But nature took its toll. Even before he reached his final year the elder brother's health gave way: he only graduated to die of tuberculosis. A sister who had nursed him in his final illness lost health rapidly and died of galloping consumption. A few years later a younger brother succumbed to the same dread malady. Robertson Smith himself developed persistent colds and a hacking cough: had to give up work in his final year and return home an invalid. So brilliant had been his career that the University gave him his degree practically without a final examination save one oral question asked **pro forma.**

There can be no question that he suffered from tuberculosis at this period: he himself never doubted it—but from now on he mended—so that in a year's time he was able to go to the Free Church College in Edinburgh for his theological studies—and with each year came increasing health. It was some 15 years later that I first came to know him, and in those years he had accomplished much with enormous energy and abundant health. But, the last position given him by an appreciative University—that of University Librarian—meant long hours daily in a stuffy atmosphere and little fresh air. He first began to suffer from what some termed eczema of the cheek, but what was really lupus, and then in the last eighteen months of his life there was slowly progressive bone disease of the lumbar region with excruciating sciatica, tubercular ulceration and finally secondary infection, septicemia and death. The case was a typical one of the condition about which I want to talk to you this morning, that of latent infection.

Latent Infection.

It is only during the last few years that we have come to recognize the frequency of the condition. Nor have we as yet as a profession reached any unanimity as to that frequency. I take it that all medical men from their own experience can furnish several examples of similar latency in cases of tuberculosis—of cases in which

the only adequate explanation is that years previously there had been the primary infection, followed by arrest and apparently perfect health, and then under conditions of strain or bad surroundings the disease lights up again and too often proceeds to a fatal termination. Let me quote for you a family history known to me. In this there was no previous record of the disease, but each summer the family went to the sea-side, occupying year after year a habitant cottage. Subsequent enquiries brought out that the habitant and his family occupied the guest rooms during the winter months, and that one after another all the members of that French Canadian family succumbed to tuberculosis—a history all too common among the habitants of Quebec province. Of the English Canadian family which occupied the cottage in the summer, two of the children—girls—died young, the one certainly of malignant tuberculosis, the other of an obscure illness lasting several months, possibly tuberculous. All the others reached maturity. There appeared to be nothing wrong with them over and above a liability to catch colds easily. But as the family dispersed, one, a girl, presented pulmonary tuberculosis after child birth, another who had been specially athletic as a school boy manifested tuberculous pleurisy and lung disease after two or three years of office work, while another boy after an attack of suspicious pleurisy while a student died in early manhood from renal tuberculosis. In each case it was after some strain or the action of some predisposing cause that the disease showed itself. Quite the simplest and most rational explanation is that the primary infection occurred in childhood when all were exposed to the action of a common causative agent,—house infection—that following upon this there occurred a long period of latency, with relighting of the disease under the influence of unfavorable environment.

Now-a-days, without shadow of doubt, the Tuberculo-cutaneous reaction is demonstrating to us that progressively as we pass from early childhood to youth and early adult life a greater and greater proportion of all individuals harbour the tubercle bacillus until by the 19th year scarce 5 per cent of the population is free from the disease. At the recent International Congress of Tuberculosis, Professor Calmette of Lille reported that during six months in 1911 he had submitted 1226 children to the cutaneous tuberculin test. These children were not attending hospital or dispensary—they were regarded as healthy. He obtained the following results:—

Age.	Number tested.	Infected.
0 to 1 yr.	273	9%
1 .. 2 ..	145	22%
2 .. 5 ..	206	54%
5 .. 15 ..	366	81%
Over 15 ..	236	88%

At the same meeting Professor Harbitz of Christiania gave the results of his post mortem studies on the bodies of 484 children:

First year of life 20 per cent; second year of life 27 per cent; fourth and fifth year 44 per cent; sixth to fourteenth year 75 per cent; fifteenth year 85 per cent were found to be infected with tuberculosis. It certainly looks very much as though in the vast majority of cases we deal with disease which lies latent for a longer or shorter period of years, nay, if this does not sound too paradoxical, a disease which in the vast majority of people lies latent for all the remaining period of life. By which I mean that only 1 in 12 of the total population dies of tuberculosis, whereas 19 out of 20 of those attaining adult life afford this cutaneous tuberculin test. Ergo, the majority of mankind have latent where they do not eventually have healed tuberculosis. As regards healed tuberculosis I do not know of any adequate series of statistics showing the proportion of von Pirquet or allied reactions at 20, 30, 40, 50, 60 years of age. If for example it be found that 95 per cent of those tested give the reaction at 20 years of age and only say 50 per cent react at 50 years of age, this would be striking evidence in favor of the view that over 40 per cent of the population present complete healing of the original infection.

You may know that von Behring and his followers go so far as to lay down that in the vast majority of cases the primary infection occurs in early childhood, during the milk drinking period—that it is of bovine origin—and there are many who hold that such bovine infection is of primary importance. I confess that after all the work of the British and German commissions, of the New York Health Department and others, this long debate might be considered settled. I mean this, that upon ordinary commonplace grounds when children are surrounded by abundant human individuals having open tuberculosis, is it not more reasonable that children should be more readily susceptible to the human type of bacillus than to the bovine, more particularly when it is evident that in man the human type is associated with the more acute disease, or put otherwise that the human bacilli are more virulent for man than are the bovine.

Were the opposite view correct Tuberculosis should be more common in countries in which bovine tuberculosis is the most common. As a matter of fact it is as frequent in Japan where cows milk is not used for feeding children as it is in the States, where year by year fewer mothers suckle their own children, and where increasingly the milk man becomes the foster mother. Were this view correct we have no explanation of the striking reduction of the death rate in Edinburgh, and indeed throughout Great Britain, where it is true very much has been done to segregate human suf-

ferers from the disease and practically nothing to reduce tuberculosis in cattle.

As regards this latent infection in childhood, three years ago I had a striking object lesson. With Dr. Lafferty, the leading physician of Calgary, Alberta, and Dr. Peter Bryce of the Department of Health in Ottawa, I spent a day making careful examination of the girls at an Indian Government School in Alberta. We made a most careful physical examination of 25 girls taken indiscriminately and ranging in age from 7 to 17. Of these 25, 24 gave signs of scattered patches of lung involvement now at apex, now elsewhere. Was this really an indication of latent tuberculosis? The history given by the good Sisters who kept the school was to the effect that the children were in general healthy and active—certainly they appeared so—but if any epidemic of childish illness attacked the school a certain number of the children were apt to show imperfect recovery and succumb later to rapidly developing consumption. So also they told us that it was most distressing to them and appeared to render their work largely useless as regards at least the bodily welfare of their charges, that when the girls upon reaching the age of 16 or 17 went back to the tribe and became married, one after another died in the course of a year or two, the strain of childbirth and the miserable conditions of life no longer in the open air, but in the wretched unventilated shacks with which civilization has displaced the tepee, resulting in death from tuberculosis. The mortality from this cause among the Indians is something appalling.

But here is the point: as with the Japanese, the use of cow's milk for feeding the young is unknown among the Indians. The Government it is true affords beef for food, but throughout the North-West and notably in the foot-hill districts where these Indians live, the "open air treatment" of the cattle (they live in the open the whole year round) has resulted in tuberculosis being an unknown quantity among them. The only possible source of infection among these children is from human beings, and these studies seem to point definitely to the fact that infection occurs in early childhood. Perhaps creeping about the floors of the huts they introduce the infection through the mouth.

I trust that you will not from this think that I seek to minimige the dangers of bovine tuberculosis—Far from it! Those dangers for the infant are very real—When, as Park has shown, it is absolutely demonstrable that in New York City alone several hundred children suffer and die each year from bovine tuberculous infection, it is obvious that the campaign against tuberculosis in dairy cattle must be waged with ever increasing vigor. But it is equally demonstrable that a much greater number of children, and the vas majority of adults, suffer from infection gained from another human being, and I protest against a campaign being so waged as to

blind ordinary people to the commonest means of spread of this frightfully prevalent disease, and to the surest means of its reduction, namely, the segregation of "open" cases of the disease in man.

What, if I may so express it, is the mechanism of these cases? It appears to be that the growth of organisms, their very presence and multiplication within the tissues in the ordinary individual sets up a general, in addition to a local reaction, so that on the one hand by the development of granulation around the original foci of growth the pathogenic microbes are fenced in (they are not necessarily killed); and on the other, should individual microbes by leucocytic or other agency escape through the fence, the increased anti-bacterial power of the system at large leads to their rapid destruction. So long, that is, as the general health is maintained. But now if through any circumstances the general vitality and resisting powers be lowered, once again the specific microbes of these diseases escaping from the regions where they are walled in, can multiply without hindrance and set up a recrudescence of the disease.

We may, indeed, lay down that latency is a function of chronic infection. Take for example Syphilis. There as a general rule, I might say, the natural history of the disease is that, after the active manifestations of the secondary stage, there results a quiescent period of three or four years before tertiary lesions manifest themselves, or indeed twenty years or more may elapse before tertiary disturbances become recognizable. So much is this the case that Sir Jonathan Hutchinson divides the acquired disease, not into three but into four stages, namely the primary, secondary, intermediate stage, or stage of latency or of relapses, and the tertiary stage. In connection with the congenital form of the disease I may note those interesting cases of syphilis congenita tarda in which the infection gained in the womb only shows itself at puberty or later.

Another disease of the same group is Glanders. There, as doubtless you know, the use of mallein has demonstrated to us the existence of "ceased reactors":—horses which have manifested at one period the acute disease, then have apparently recovered so fully that the injection of mallein no longer induces a reaction. It is however well-known to farmers that a "ceased reactor" is always a source of danger: the animal may be in excellent condition for it may be several years, but sooner or later the disease may break out and light up again, and such animals may thus convey the disease to the other animals in the stable.

Carriers.

In Typhoid fever and to some extent in Cholera we obtain latency of a different order. You are all of course familiar with the subject of typhoid carriers. The latency here is not so much with the disease—the typhoid carrier is not liable to a new attack of ty-

phoid fever—as with the bacilli. The bacilli it appears are destroyed within the tissues, or at least in the tissues especially affected in the active disease—the Peyer's patches, mesenteric glands, spleen, and so on. But they continue to multiply in cavities which truly are outside the body—as for example the gall bladder and urinary bladder. Here from time to time they may take on active growth and set up local inflammation, and from here they may re-enter the tissues and set up, not typhoid fever, but abscesses in the neighborhood of the joints and elsewhere.

Recurrent Infection.

Here then we have an intermediate group of conditions leading towards and connected with the next order of cases to which I would draw your attention, namely the recurrent infections

Of these the type examples are afforded by conditions set up by the pyogenic cocci and notably by the streptococci.. I refer more particularly to conditions such as Erysipelas and Boils. The organisms inducing these states are normal inhabitants of the surface of the body, and, unlike most bacteria, when they invade the tissues they induce at most a transient immunity lasting for but a few days or weeks, so that one crop of boils is singularly apt to be followed by another, one attack of erysipelas by a succession. The regions involved in the successive attacks are by no means necessarily the same. In other words unlike what happens in tuberculosis the second attack does not originate from microbes which have been lying latent in the tissues; it originates from a new, a recurrent infection from the surface.

Of this group quite the most important members from a medical point of view are the conditions of Acute Rheumatism. They are characteristically recurrent, and what is more workers are coming round more and more to the opinion that the commonest causative agent is to put it broadly, a member, or series of members of the streptococcus group, be it an attenuated streptococcus, Poynton and Paine's Diplo-streptococcus, Schottmüllers Streptococcus viridans, Horder's saprophytic streptococci, or Rosenow's modified Pneumococci. A point of singular interest is that for long clinicians have associated acute rheumatism with tonsillitis, and now organisms undistinguishable from those isolated from cases of acute rheumatism, are being isolated from the mouth. I will not say that the evidence is conclusive that all cases of acute rheumatism originate from a primary invasion or entrance of streptococci from the buccal cavity. We know for example that one group of closely allied cases—the gonorrheal—have the point of entrance elsewhere, but everything to-day points to the fact that the majority of cases of acute rheumatism are set up by streptococcal organisms, and like erysipelas and boils are well marked examples of recurrent infection by

organisms which are to be found growing normally upon body surfaces.

What now is important to determine is how far chronic rheumatoid arthritis with disorganisation of the joints (or some of the cases included under this term) belongs to the same category, how far it is a continuous low infection with intermittent exacerbations. I only know that from one such case with extreme joint destruction and a history of exacerbations extending over a period of twenty years, we at the Royal Victoria Hospital at Montreal isolated a germ, having the properties of Poynton and Paine's micro-organism. In passing it might be observed that this property of recurrent infection is characteristic of the pathogenic micrococci as a group, with the one possible exception of the Meningococcus. I say possible, because the disease set up by this microbe is so fatal and the known cases in which recovery has been brought about are still so comparatively few that it is unsafe to say whether those which recover show any marked liability to recurrence.

Subinfection.

Lastly I wish to bring before you another group of disorders whose genesis I hold is closely allied to that of the above recurrent infections. The essential course of these recurrent infections is the entrance into the tissues of microbes of pathogenic properties which normally lead a saprophytic harmless existence upon the surface of the body. Are there microbes of still lower pathogenicity than the streptococci, also leading a saprophytic existence under normal conditions, which gaining entrance into the tissues are there responsible, not for frank infections, but for a lower grade of disturbances. It was in 1899 before the Society of Internal Medicine at Chicago that I introduced the conception of what I termed subinfection. To the best of my belief this was a new hypothesis. How has it fared in the meantime! Has it suffered the fate of so many medical hypotheses, or is it "going strong?"

I based myself on the following facts, namely that experimentally it is easy to prove that throughout the intestinal tract leucocytes are constantly passing out through the surface layers into the tissues and that whereas many are destroyed, many can be seen to have passed back bearing ingested fatty globules, and bacteria. Macallum more particularly has demonstrated that if a peptonate of iron be given to a fasting animal, in a very short time leucocytes containing the iron can be detected in abundance in the lumen of the gut, in the walls of the gut, and even in distant organs like the liver and spleen. As a matter of fact in any autopsy on man made within an hour or two post mortem abundant bacteria undergoing degeneration are to be detected in such organs as the Peyer's patches, the mesenteric and the peribronchial nodes. Where the in-

testinal wall is congested and inflamed this passage of bacteria through the agency of the leucocytes is greatly increased, while the greater the precautions taken, the more frequently is it possible to obtain bacterial cultures from the organs of normal animals. Bacteria in short are constantly passing into the system from the intestine and upper respiratory tract, and as constantly being destroyed, notably in the mesenteric and other lymph nodes and in the tissues.

It has been repeatedly proved by observers who have fed healthy animals with pure cultures of microbes, both pathogenic and nonpathogenic, that after a few hours, on killing the animal, these forms so fed are to be isolated from the different organs. More particularly of late years attention has been called by von Behring, Ravenel, and others, to the fact that the tubercle bacilli given with the food are recovered under certain conditions from the thoracic duct and elsewhere. Years ago Nocard showed that obtaining serum under aseptic precautions from various animals to serve as culture media, certain batches were apt to be contaminated, and studying the cause of contamination he found that with scarce an exception the contaminated sera had been withdrawn a few hours after the mid-day meal.

The only possible explanation that I can see for these facts is that through the agency of the leucocytes these contaminating bacteria are carried into the blood, and it must be added, under ordinary conditions such bacteria gaining a scattered entrance are destroyed either by the leucocytic hosts, by the cells of the lymph nodes, or again by the endothelium of the capillaries, and as a result there is no infection. Everything, however, points to the fact that with inflammation of the intestinal mucosa there is more active migration of the leucocytes and more abundant carriage of bacteria into the system. As such carriage is, as already noted, scattered, even under these circumstances there may be no infection, no multiplication of the bacteria within the tissue. This, however, does not mean that there will be no ill-effects: with the destruction of bacteria there is liberation of their toxins. It may well be that the overwork of the phagocytic cells, endothelial as well as leucocytic, in the different organs may lead to their eventual exhaustion, while further the long continued action of the liberated toxins may tell upon the nobler cells of the tissues and bring about their degeneration and atrophy.

In the communication above referred to, I brought forward observations which appeared to me to indicate that both pernicious anemia and the ordinary so-called portal cirrhosis of the liver were of the nature of subinfections, and attributed both these conditions to the increased carriage inward and destruction of more particularly members of the B. coli group. I need not remind you that members of this group are common inhabitants of the intestinal tract.

I did not expect these views to be accepted immediately. It is pleasant to find that slowly but I think surely, year by year more evidence is accumulating in favor of this conception of subinfection, and that more and more workers are expressing themselves as accepting it. Two years ago there were published a series of communications by Dr. A. E. Shipley, now Master of Christ's College, Cambridge, and by Cobbett and Graham-Smith on "Grouse disease". You know of course how the grouse is worshipped in England and more particularly in Scotland, and can imagine the pain and consternation when these most excellent birds meet with a premature-untimely death—through other than human agency. Every spring and autumn with unfailing regularity a certain number of these birds are found dead, and some years the mortality assumes alarming proportions, so much so that at last a Commission was appointed to investigate the subject and to determine the nature of the disease and suggest means of prevention. Preliminary observations showed at once the presence of bacilli of the colon type in the livers and sometimes in other organs of the diseased birds. It soon became evident, however, that these microbes might be present in the organs of grouse which otherwise appeared to be normal. Briefly it was found that the primary lesion was in the paired ceca at the junction of the intestine and rectum. Grouse harbour numerous tape worms and strongylus, but in these diseased birds the ceca were found filled with a mucoid looking material which upon treating with hardening re-agents resolved itself into a mass of thousands of delicate strongyles covering over the inflamed mucosa. Cobbett and Graham-Smith demonstrated most clearly from a study of apparently healthy birds recently killed that there is a direct relationship between the number of these strongyles and the presence of coliform organisms of the liver. Where the strongyles were few in number the liver afforded no cultures: where they were abundant cultures were easily obtainable. Microscopically the strongyles could be seen to penetrate and injure the mucosa. From these observations it is evident that such injury allows the absorption of intestinal micro-organisms, and that we deal not with a specific bacterial infection but with a condition which at first, at most, is a subinfection. Exceptionally strong birds are found to stand a larger infection better than weaker birds; the wet seasons in the first place favor increased multiplication of the strongyles outside the body and by lowering the general health of the grouse favor their growth in the gut and secondarily bring about increased subinfection with decreased resistance and increased mortality. The birds die of privation and malnutrition while their stronger brothers "manage to pick up a living somehow and tide over the period of disease."

At a meeting of the British Medical Association in Birmingham last year, there was an important discussion on the pathological

properties of the B. coli, opened by Dr. Rolleston, and here one speaker after another—including Dock, Woods Hutchison, Sims Woodhead, and others—expressed themselves as favorable to the idea of subinfection.

Indeed since the admirable experimental work of Opie upon the production of hepatic cirrhosis, it is difficult to hold any other opinion. While I have repeatedly been able to obtain the cultures of organisms of the B. coli type from cases of cirrhosis in man, I have been unable to reproduce the disease by inoculation of the growths of the same. Both Weaver and Hektoen of Chicago have, it is true, announced the isolation of strains of B. coli which would produce cirrhosis in the liver of animals. I think I am right in saying that both of these observers were unable to obtain these constantly or indeed other than in occasional cases, and other workers have had the same experience. On the other hand as everyone knows, the common form of cirrhosis as known in man is associated with alcoholism; but observer after observer, with it is true some exceptions, has found that the long continued treatment of animals with alcohol by inoculation or through the digestive tract does not, save in exceptional cases, lead to hepatic cirrhosis.

There is a stronger narcotic than alcohol, namely chloroform, which has pronounced effects upon the hepatic cells, causing necrosis and destruction of, more particularly, the cells of the centre of the lobules. Opie found that employing chloroform alone, this destruction is not followed by fibrosis or cirrhosis; instead of this where the dose given has been the means of death, the dead cells undergo regeneration and in a few weeks the organ assumes its normal appearance. But now he found that if he combined the two processes and treated the animals of the laboratory with chloroform and then made an intraperitoneal or intravenous inoculation of a growth of a culture of B. coli he could with certainty produce well-pronounced cirrhosis resembling that seen in man.

The simplest view, therefore, of the etiology of "gin-drinker's liver" in man, is that alcohol or some other irritant taken into the alimentary canal absorbed therefrom has a deleterious action upon the hepatic parenchyma and at the same time causes inflammatory conditions of the intestinal mucosa; that by the entrance of the B. coli and other organisms into the portal vessels these organisms are carried to the liver and there destroyed, their toxins setting up that low form of irritation which leads to the simultaneous degeneration and destruction of the hepatic cells and overgrowths of the connective tissues of the organ. We do not deal with infection but with subinfection. The liver of hepatic cirrhosis does not show indications of active growth of the bacilli, there are no local foci of bacterial proliferation, no abscess production or diffuse puru-

lent change, nor is the clinical picture that which we associate with infection. The slow, often year long development of the condition can, it seems to me, only be explained along these lines of irritation of the organ by bacteria constantly brought to it and as constantly undergoing destruction.

I am inclined to think that more notice deserves to be taken of the blood changes occurring in portal cirrhosis in man due to the hemolytic action of the toxins of B. coli and allied organisms. It is not a little suggestive and shows the relationship between the causative agent of portal cirrhosis and that of pernicious anemia, that as Kretz and Dr. Maude E. Abbott have pointed out, the majority of cirrhotic livers when examined present increased hemosiderin pigmentation just as do the livers of pernicious anemia. This increase of hemosiderin in the liver can only be explained by increased destruction of the red corpuscles and the liberation of hemoglobin. That the B. coli cause hemolysis in the organ has been strikingly demonstrated in the last few years by the recognition of remarkable cases of what is termed Microbic cyanosis. Wholly independently Stokvis of Amsterdam in 1902, Gibson and Douglas of Edinburgh in 1906, and Blackader and Duval of Montreal in 1907, have described fatal cases in which there is a rapid development of cyanosis so that the patient became purplish. Nothing has been found in these cases save the presence of abundant B. coli in the blood during and immediately after death. We are still ignorant of the precise conditions which lead to this unusual multiplication of bacilli in the blood. Outside the body the bacilli cause hemolysis with liberation of hemoglobin from the corpuscles; these cases show that a like hemolysis may occur within the vessel.

We know now that Pernicious Anemia is a terminal advanced anemia which may be brought about by various means, but I still hold to the conclusion that the commonest form seen in the Temperate Zone is associated with gastritis with a condition of achlorhydria permitting the active multiplication of B. coli, and it may be other hemolytic bacteria in the upper portion of the gastro-intestinal tract; that there is increased evidence of these hemolytic bacteria in the portal blood leading to the destruction of the erythrocytes and so to all the characteristic symptoms of this condition. That there is not an accompanying cirrhosis, following Opie's work, must be due to the fact that there is not simultaneous absorption of substances causing the degeneration of the hepatic parenchyma. It deserves note that, independently, Hunter of London has ascribed pernicious anemia to the constant low infection of the gastro-intestional tract by streptococci present in the suppurative discharge from the gums in conditions of pyorrhea alveolaris. It is noteworthy that streptococci are also markedly hemolytic. On this side of the Atlantic that enthusiastic worker, the late Dr. Christian

Hertex of New York similarly ascribed the condition of the overgrowth of anerobic organisms such as the bacillus Welchii in the lower intestinal tract. He found that in young people presenting a superabundance of these anerobes in their feces there was present a well-marked anemia, and supposed there was an increased absorption of the toxins of these organisms leading to hemolysis. Neither of these two observers quite accept the view of subinfection, but it is interesting to see how they approximate to my point of view—how we all regard the hemolysis as of bacterial origin due to the action of the liberated toxins. For myself, I find that this hypothesis of subinfection is helpful towards a comprehension of these slowly developing conditions of hepatic derangement. I do not as yet go so far as my friend Woods Hutchison and regard gout as in the same category; we still, that is, want evidence of the association of microbes with the gouty lesions.

Terminal Infection.

Lastly, I would note that this condition of normal passage of microbes into the tissues gives us our best understanding of terminal infection. Such terminal infection may be regarded as the lighting up of latent infection when eventually the bacterial powers of the tissues become exhausted. It is in these conditions that bacteria which otherwise would be destroyed undergo multiplication and gain the upper hand. For myself, let me confess that I cannot bring myself to believe that the abundant bacteria found in the various organs a few hours after death are due in the main to a post mortem entrance from the intestinal tract. Rather I am inclined to think that in the main they have entered the blood stream during life, and owing to the greatly weakened state of the tissues they have not undergone destruction. At least it seems to me that this view is deserving of consideration.