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MULTIPLE INFECTIONS

A STUDY OF THE RELATION OF ONE INFECTION
TO ANOTHER *

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It is generally recognized that when a person has one or more infectious diseases, one may influence the other occasionally to the apparent advantage of the patient, but more frequently to his disadvantage. In other words, increased susceptibility to one organism may result from infection with another. This subject has been dealt with in the literature under such titles as mixed infection, metastatic infection, secondary infection and focal infection. It may be illustrated by familiar clinical examples. It is well known, for instance, that latent tuberculosis may become active and rapidly progressive after an attack of tonsillitis, measles or pneumonia. Osler mentions the fact that quiescent maladies, such as congenital syphilis and tuberculosis, may be lighted into activity by vaccination. Urethritis or chronic prostatitis is often unfavorably influenced by the onset of a new infection. Urethritis that is apparently cured may occasionally recur after an attack of tonsillitis, bronchitis or other acute infection. In a patient whom I observed, a urethral discharge in which gonococci were abundant was noticed a few days after a severe attack of tonsillitis. The patient gave a history of having had urethritis two years previously, but since that time had apparently been well and had not been exposed to fresh infection. Chronic cystitis of a mild type may become severe following an attack of diarrhea, cholecystitis or appendicitis. A patient who had specific disease that had been thoroughly treated and had been apparently latent for four years was covered with a copper colored papillary rash and gave a positive Wassermann test at the end of the first week of convalescence from typhoid fever. Another patient had an attack of pneumonia after the appearance of an acute alveolar abscess. Several weeks later he had a recurrence of active tuberculosis that had been latent for many years and had not interfered with the most active mental and physical work.

Chronic infections of a milder nature may also have a deleterious influence on other infectious diseases with which a person may be afflicted. This influence is often quite marked. The ill effect of chronic infections of the nose and throat on persons with tuberculosis is

generally recognized, and proper local measures for the cure of these are looked on as an important part in the regimen for treating tuberculosis in many institutions. Oral sepsis may have an important influence on tuberculosis, and the eradication of oral sepsis may be of material value in arresting the progress of the disease.

Staphylococcal infections of the skin, such as acne and chronic furunculosis, according to Sutton, are often more amenable to treatment after the eradication of infected tonsils, alveolar abscesses, etc. In a patient with *Staphylococcus aureus* septicemia of more than two months' duration, the temperature fell to normal a few hours after the extraction of an infected tooth and remained normal for ten days. The case eventually ended in complete recovery. The roots of the tooth showed *Streptococcus viridans* in almost pure growth when cultures were taken, while repeated cultures of the urine and two blood cultures gave a growth of *Staphylococcus aureus*.

One chronic mild infection may influence the course of other chronic mild infections. For example, tonsils that appear to be chronically inflamed often become smaller and appear relatively normal after the eradication of severe oral sepsis. Chronic infection of the nasal sinuses may often be reduced in severity or apparently cured by the removal of infected tonsils or alveolar abscesses. Persistent cases of pyorrhea often yield rapidly to treatment after the removal of chronically infected tonsils or after the extraction of abscessed teeth. A patient who had been subject to recurrent attacks of slight jaundice associated with slight fever and pain in the region of the gallbladder for several years was apparently relieved permanently by the extraction of one abscessed tooth. Numerous similar examples with which careful observers are familiar could be mentioned.

EFFECT OF CHRONIC SEPSIS ON SYPHILIS OF NERVOUS SYSTEM

The ill effect of chronic sepsis on the course of syphilis of the nervous system is often very great, and on account of its practical importance will be dealt with in some detail. Syphilis of the central nervous system was suspected clinically and verified by lumbar puncture in 6 per cent. of 1,000 cases in office practice in which I made examinations on account of general medical complaints. One or more additional chronic infections thought to be of serious moment were found in nearly all of these. The coexistence of syphilis of the nervous system and chronic sepsis in persons observed in office practice is therefore common and very important. The fact that an infection in no wise related to syphilis may hasten the course and augment

* A portion of this article has been reported in brief by the writer in a monograph entitled "Oral Sepsis in Its Relationship to Systemic Disease."

the symptoms of *tabes dorsalis* is well illustrated by the subjoined cases:

CASE 1.—A man, aged 35, had been treated two years for *tabes dorsalis*. Before treatment was started he had noticed slight ataxia and bladder disturbance and was subject to mild attacks of darting pain in the legs. He improved very satisfactorily under specific treatment, and after he had been free from pain and bladder disturbance for more than a year, he had an attack of acute tonsillitis. With the onset of this there followed a recurrence of the most severe lightning pains that he had ever experienced. Morphine and salicylates to the limit were required to keep him out of agony. Nothing was disclosed except the attack of tonsillitis to account for the sudden recurrence of severe symptoms of *tabes*. A tonsillar abscess developed, and when this was incised, the lightning pains at once ceased almost completely. A few slight pains were noticed until the tonsils were removed three weeks later. During two years since that time, the patient has been practically free from any active symptoms of *tabes dorsalis* and has required very little treatment of any kind to prevent recurrence of his previous symptoms.

Since observing this case I have made a careful search for chronic sepsis in patients with syphilis of the nervous system, and on finding it have eradicated it thoroughly before beginning antisyphilitic treatment. It has seemed apparent from the results obtained that many of the symptoms of early *tabes dorsalis* that one might attribute to progress of the disease, such as lightning pains, increasing numbness, paresthesia, ataxia and visceral disturbances, may be rendered worse by chronic sepsis and may be relieved to a considerable degree by its removal. In fact, one might assert, with reason, that in persons suffering from *tabes dorsalis* the removal of chronic sepsis as a therapeutic measure for arresting the disease ranks in importance barely second to specific medication itself.

CASE 2.—A man, aged 50, with *taboparesis*, had been given thorough specific treatment for years. When he came under my observation he was unable to attend to business, and spent most of his afternoons in bed. All known methods of treatment had been pushed to the limit, and it appeared that very little improvement could be expected from further specific measures. The patient had large tonsils and several abscessed teeth. These were removed, whereupon the patient improved steadily and to an unbelievable degree. Within less than a month he was able to engage again in business. He has continued mild specific treatment, and has remained in active business since that time.

CASE 3.—A man, aged 45, was brought in with a diagnosis of *tabes dorsalis*. Physical and laboratory examination left no doubt concerning this. The onset had been stormy, and for three weeks the patient had been fairly convulsed with darting pains and had hardly been able to control himself. He was so nervous and irritable at the time of the examination that it was almost impossible for him to remain quiet long enough to permit a specimen of blood to be obtained for examination. Lumbar puncture could not have been performed without general anesthesia. The teeth showed an advanced degree of sepsis. The abscessed teeth were all extracted. Within a few days the patient's condition was so much improved that he went back to work. He felt and acted like a well man even though specific treatment had not yet been administered.

Many cases similar to the foregoing could be cited. These are not unusual cases, but represent almost an average experience.

ALLERGY

The problem of multiple infections and the relationship which one infection bears to another is deeper and of greater interest than the simple fact that a

person bombarded by two or more infections is worse off than if he had only one. One infection has an interesting relationship to other infections with which a person may be affected, and may be explained in part at least through phenomena described under the terms allergy, protein sensitization and anaphylaxis.

A true toxin is not formed by any of the micro-organisms that ordinarily take part in the pathology of infection in human beings with the exception of tetanus and diphtheria bacilli. Killed cultures of all other organisms or extracts of the organisms, or the culture mediums in which they have grown may be injected in large quantities into healthy guinea-pigs without immediate gross ill effect. They differ strikingly in this respect from tetanus and diphtheria bacilli, each of which produces a true toxin that is poisonous in high degree when administered subcutaneously even in very minute doses to animals. The products formed by other organisms that cause disease may be extremely toxic, however, through an entirely different mechanism, namely, the development in an individual of a condition known as allergy. This term, introduced by Pirquet, is used to designate the changed condition of human beings or animals, caused by infectious diseases or produced by inoculation with alien proteins, which causes the individual to react in a peculiar way if the bacteria responsible for the infectious disease or if the protein with which he may have been inoculated is reintroduced into the circulation. The ensuing reaction is in some respects protective and beneficial, but in other respects may be harmful and even dangerous.

Allergy and its effects are well illustrated by the action of tuberculin. Killed tubercle bacilli or their extracts, or mediums in which tubercle bacilli have grown, may be injected in large amounts into normal untreated animals without gross immediate ill effect. If even minute quantities are injected into animals or persons with tuberculosis, however, the effect is entirely different. Instead of its being apparently inert it causes a reaction which may result quickly in death. The changed condition of the animal produced by the tuberculous infection which renders it sensitive to the products of the tubercle bacillus is the condition known as allergy. Several striking phenomena follow the introduction of tuberculin into tuberculous persons or animals which never appear in the nontuberculous. These are, first, pain, swelling, redness and sometimes necrosis at the site of inoculation. This is known as the local reaction. Second, a rise in temperature and pulse rate and general symptoms of toxemia, which phenomena are known as the general reaction. Third, inflammatory changes at the site of all active tuberculous lesions. This is known as the focal reaction. This last phase is very interesting and may be used in explaining many of the phenomena observed in multiple infections. It may be slight or may be well marked. It may hasten the breaking down of tuberculous tissue and lead to rapid spread of the disease.

Some persons with tuberculosis become so sensitive to products of the tubercle bacillus that amounts of tuberculin as minute as 0.001 mg. are sufficient to produce severe reactions and to cause local inflammatory reactions at the site of all active tuberculous lesions. Others tolerate larger amounts. A reaction as described above can be produced in tuberculous animals by the subcutaneous injection of living tubercle bacilli as well as by extracts of the organisms. If tuberculous

guinea-pigs are inoculated with living tubercle bacilli, a local and general reaction results within a few hours essentially similar to the reaction produced by the extracts of dead bacilli. If nontuberculous animals are similarly inoculated, no such reaction ensues, but the animal after a period of days or weeks becomes ill and dies of tuberculosis. If a localized tuberculous lesion in human beings (such as a tuberculous joint) is subjected to massage and manipulation, living tubercle bacilli or their products gain entry into the circulation, and a transitory rise of temperature and other symptoms of a general reaction may follow. This may be associated with an increase in the inflammatory reaction at the site of all other active tuberculous lesions (focal reaction).

The foregoing well known facts regarding tuberculous infection and the sensitization produced by it are true of infections in general. An attack of typhoid, for example, renders an individual sensitive to the protein of the typhoid bacillus, an attack of furunculosis renders one sensitive to *Staphylococcus aureus*, etc., so that persons having these diseases usually show a local, general and focal reaction if they are inoculated with killed cultures of the offending bacteria. This may temporarily increase the severity of the infection, the degree of which would depend to a certain extent on the quantity of bacteria injected.

Persons with chronic furunculosis may give a general reaction within a few hours if they are inoculated with an excessive quantity of killed staphylococci, and the furuncles are made temporarily worse. Such persons react similarly when they are subjected to the effect of an increased number of living bacteria due to the development of a fresh furuncle. This often causes both a general and a focal reaction. For example, with the development of a fresh furuncle there may appear fever, malaise, etc. (general reaction) and an exacerbation in the inflammatory process in recent furuncles (focal reaction). In fact, signs of activity, such as itching and redness, may appear in the scars of recently healed furuncles. This may be followed by a discharge of pus containing *Staphylococcus aureus*. These well known principles are true of infection in general and can be used in the explanation of many interesting phenomena. It often explains the reason why with the onset of a new infection signs of irritation and inflammation may appear within a few hours at remote points. Case 4 illustrates this:

CASE 4.—A woman, aged 60, relatively normal for her age, had ten infected teeth extracted. Less than twenty-four hours afterward there developed a severe acute follicular tonsillitis. Several days later the infection began to spread from the gums to the cheeks, pharynx and tongue, and give rise to an extensive ulcerative stomatitis. The point to be emphasized here is the fact that the inflammatory reaction in the tonsils, while relatively distant from the gums, occurred within a few hours and preceded by several days the infection of the neighboring tissues of the mouth. It occurred after too brief a period of time to be the result of direct infection of the tonsil by the organisms disseminated from the alveolar process, and must have been a reaction of tissues sensitized by the organisms already localized in the tonsils. It was analogous in every way to the focal inflammatory reaction in the lungs that may be brought about in tuberculous individuals by the injection of an overdose of tuberculin.

It is by no means uncommon to observe pain in the region of the gallbladder, appendix, stomach, joints, cervical glands, etc., a few hours after the extraction of infected teeth, and such may frequently be inter-

preted as focal reactions caused by the traumatic dissemination of micro-organisms or their products from the alveolar process.

Frequently the clinical manifestations of chronic appendicitis, cholecystitis, gastric and duodenal ulcer, chronic arthritis, etc., clear up rapidly after the extraction of diseased teeth, even though the first effect may have been an increase in the inflammatory processes. Occasionally chronic inflammatory conditions that appear to indicate the need of surgical interference and serious internal diseases that cannot be reached by therapeutic agents partially clear up after as simple a procedure as the extraction of a tooth or the removal of a pair of diseased tonsils. The relief can often be attributed to the fact that sources of bacterial products that have been continuously causing focal reactions in the infected organs have been removed.

This explanation applies very nicely to multiple infections when each lesion is caused by the same micro-organism. It may or may not apply in part to lesions caused by different micro-organisms. This question is an open one about which much might be said. For example, if a person has streptococcic tonsillitis, a latent streptococcic infection in the joints and in the gallbladder, it would be in harmony with accepted theories if an acute exacerbation of the tonsil infection were followed in a few hours by a reaction in the joints and gallbladder that caused pain and other phenomena of a focal reaction. This explanation, as previously mentioned, would not apply in the same way to multiple infection if the various lesions were caused by different micro-organisms, because sensitization against the protein of an infecting organism is thought, and I believe correctly, to be more or less specific. Whatever the theoretical explanation may be, we have this fact, which is beyond dispute: Infection with one micro-organism may lower the resistance against other micro-organisms to a degree that is by no means negligible. I dealt with this above, and mentioned clinical examples. One further illustration even more striking may be added here:

CASE 5.—A patient, aged 35, apparently in good health, had a severe attack of erysipelas, evidently streptococcic in origin. A few days after this a very insignificant pustule no more than 2.5 mm. in diameter which showed *Staphylococcus aureus* on culture began to spread with great rapidity and within a few days gave rise to an extensive phlegmon which persisted for two weeks. In this instance the streptococcic infection certainly had lowered resistance against *Staphylococcus aureus*.

TYPES OF IMMUNITY

There apparently exist two types of immunity—a specific immunity and a nonspecific immunity. Nonspecific immunity has been made use of in the cure of disease by Miller and Lusk, Jobling and Petersen and others, who have injected alien protein of different types (including killed typhoid bacilli) in the treatment of arthritis and other infectious diseases. While the results obtained were not invariably a complete success, they were sufficiently striking to warrant the observers in concluding that nonspecific immunity is often an important factor in the cure of disease. The inoculation of infected persons with an alien protein, such as typhoid bacilli or albumose, may cause general reactions that render the patient's condition temporarily worse. Often it also causes focal reactions in the infected areas. For example, in persons with arthritis the joint pains may often be more severe a few hours

after the intravenous injection of typhoid bacilli. Persons with *tabes dorsalis* frequently have sharp, darting pains in the legs after similar intravenous injections. The reactions that are produced by the injection of alein proteins are often very similar to reactions that follow inoculation with the specific organism that causes the person's disease. It is not inconceivable that frequently repeated inoculations with a nonspecific virus might cause repeated reactions in inflammatory lesions due to other organisms and in this way do harm and cause an exacerbation of the disease. It is possible that one infection may exert a deleterious influence on lesions caused by other micro-organisms in some such way as this and might in part explain the cure of one infection by the removal of another infection in no wise related to it.

PRACTICAL CONSIDERATIONS

This paper has been written because of its practical bearing on the treatment of infections. Whether or not the explanations given are the correct ones, these facts stand, I believe, proved and beyond dispute: 1. In persons suffering from multiple infections, each infection may increase the severity of the others whether due to the same or to different organisms. 2. Removal of one infection may, under favorable conditions, be followed by spontaneous healing or improvement in the others. A physician often is faced by a combination of infections, some of which are removable, and others not. A consideration of problems of the relationship between infections often aids in the practical handling of the situation. If minor infections are promptly taken care of, those that are more serious may take care of themselves.

CONCLUSIONS

1. When a person has several infections, each may increase the severity of the others whether due to the same or different infecting micro-organisms.
2. Acute exacerbation of one chronic infection may stir up other apparently latent infections into activity.
3. The removal of one infection may under favorable conditions be followed by spontaneous healing or improvement in others.
4. If minor infections are properly taken care of, those that appear serious may yield more easily to treatment.
5. Chronic sepsis exerts a serious influence on the course of *tabes dorsalis*, and its removal is frequently followed by amelioration in the symptoms of this disease.

Effects of the War on the Next Generation.—The general physical standard of the men who have joined the colors is necessarily on the average distinctly better than that of the men who have not joined. Only men above a certain level of physique are accepted; men of smaller build or weaker constitutions are rejected. A heavy loss of life has occurred, and is yet to occur among the men who are fighting with our armies. No corresponding wastage is occurring among those who are not fighting. The result must be that the average physical standard in this country of males of the ages of say 20-40 will be much lower after the war than it was before the war. This lowered standard will be reflected in children born in subsequent years; and will begin to be recorded at school medical inspections about the year 1921, when the children born in 1916 are entering on their school life.—Dr. D. Morley Mathieson, M.O.H., South Shields, England, *Medical Officer*.

THE TREATMENT OF LYE STRICTURES OF THE ESOPHAGUS*

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In 1910, Dr. Jackson made earnest appeal for legislation to protect innocents from lye products sold for domestic use. Careless and misleading labels and indiscriminate distribution of caustic cleansers have been responsible for many of these accidents and food and drug laws do not penalize the manufacturer or agent. They are put on the market to be used by housewives and certain it is that the more careless the housewife the more likely she is to use the stuff and, also, the more liable she is to have more children than she can safeguard.

These overworked women and their children deserve what protection the law can give them against the commercial shark and it seems to become the duty of the medical profession to keep hammering away until they are heard. Caustic alkalis and cleansers should be caution labeled and the sale restricted as are all poisons.

There are a few important features of lye corrosion which should be mentioned. The mouth secretions usually protect by dilution the throat and hypopharynx and, as a matter of clinical observation, the real escharotic effect is usually in evidence at the cricoid or about the depth of the bronchial region and above the hiatus.

It seems that at these points the caustic is arrested briefly, or owing to the somewhat delayed spasm excited by the irritant, the bolus is retarded in the lower esophagus and enters the stomach slowly. This accounts for the fact that comparatively few of these victims exhibit stomach lesions, the acid secretions neutralizing as fast as it reaches the organ. The esophagus is a senseless kind of an organ, that is to say, deficient in sensible nerves and inclined to throw spasmodic fits much to the detriment of its own welfare. But we must label this a conservative physiologic action in that it aids in protecting the more complex, vital organ, the stomach. Most of these victims vomit rather promptly and thus does the stomach repay the self-sacrificing esophagus by furnishing the antidote, acid secretions.

CASES OF LYE TRAUMA

I have seen two fatal cases which I will briefly mention to make clear the serious effects of lye trauma in the stomach.

One, a lad, aged about 12, who had swallowed lye at 2 years of age. The stricture was not complete and he had existed on liquid nourishment for ten years. He was diminutive and emaciated to a skeleton—no hair, no teeth, a pitiful little old man. Gastrostomy was done and an effort made to build him up before dilatation of the stricture was attempted, but there was evidently atrophy of the gastric mucosa, and he died in about a month from inanition.

The other fatal case was that of a girl of 5 years who had swallowed lye six months previously. The stricture of esophagus was of moderate degree, but she could not digest anything and died in a few weeks of inanition.

A third case is reliably reported to me. Lye was swallowed at the age of 5. No esophageal lesion followed, but life has

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