SECONDARY MIXED INFECTION

IN SOME OF THE

ACUTE INFECTIOUS DISEASES OF CHILDREN.

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SECONDARY MIXED INFECTION IN SOME OF THE ACUTE INFECTIOUS DISEASES OF CHILDREN.

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Mr. President, and Fellows of the Gynæcological Society: The humoral pathology of our forefathers met its end in the post-mortem room, and under the microscope. It would not be surprising if an equal revolution should now follow the investigations of the bacteriological laboratory. Our present accurate knowledge of chemical elements and principles has been attained by careful, conscientious experiment, often carried out on an preconceived erroneous theory. In the same manner, our knowledge of mycological pathology has been advanced by experimental investigation undertaken to sustain false or imperfect theories. Thus the idea of a specific pneumonia was, for a time, disputed on the ground of bacteriological research demonstrating pneumonias due to various other forms of infection. It is needless to say that the value of these researches is in no way diminished because the signification of their results was at first imperfectly understood or misinterpreted.

I.

We may safely say that among the earliest manifestations of the struggle for existence, there was developed between individuals relations

which ultimately terminated in true parasitism. In the course of time these relations became essential to the existence either of the parasite, of the host, or of both.

Not only among the lowest forms of animal and vegetable life did parasitism arise, but, also, between forms high in the scale of development, and those of the lowest and intermediate forms. We may see a form of parasitism existing to-day between two of the most undifferentiated organisms. Thus, the *Mycoderma aceticum* depends upon the presence of the *Sacharomyces cervisiæ* to prepare a small quantity of alcohol for its nourishment. Among the infusoria, the *Paramecium aurelia*, at least, has a parasite. It seems strange that a form of parasitism may not only be destructive or harmful to the host, but, from an adaptation of the parasite, the host may at last become entirely dependent upon it for the perpetuation of its own species. This is admirably illustrated by the relation existing between some of the flowering plants and insects. The secretions of the plants, and, especially, of their flowers, become the necessary food of the insect; and, because these insects cannot depend upon the perpetual and uninterrupted flowering of the plants, they have learned to prepare store-houses, and, also, as the more certain means of perpetuation, to live in large, highly specialized colonies. They have become modified in their forms, their habits, and their social life by their condition of parasitism. The host also reacts to the constant presence of the parasite. Even whole orders have been so modified that fertilization is absolutely impossible without the presence of the insects. Those plants that furnish only occasional food remain independent, others that are constantly associated with the parasite are somewhat modified, but not dependent upon it; while those forms which from long and constant association, or from change of environment which can only be endured by the modifications which render the insect fertilization necessary, become, at last, entirely dependent upon its existence for their perpetuation. Among the highest forms of life even, parasitism may become necessary to the existence of the host species. In all mammalia, the young exist for a considerable time as parasites upon the mother. In the Bonelliæ, the parasitic male occupies, during nearly the whole of its existence, the sexual organs of the female.

Many parasites are, on the other hand, very detrimental to the existence even of the host. Certain *Unios* are invaded by *Nematoda* that multiply in the mollusk's heart until circulation is so impeded that a sufficient activity of the branchial cillia is not maintained to furnish an adequate supply of food. Death results to the mollusk, and the parasites are carried into the intestinal canal of the scavenger fishes to complete their existence as sexual worms. The echinnoccus is also a destructive parasite, at least in some mammalia. It is remarkable how a virtually non-destructive parasite may incidentally become a source of danger to its host. In the powerful muscles of the unionidæ of certain streams

tributary to the Fox river, I found very generally a peculiar parasitic *Dystoma*. Specimens thus affected were abundant where the stream passed through a village, but very rare elsewhere. The explanation was soon forthcoming. About the muskrat houses away from civilization, were piles of shells which these animals had emptied, besides many unopened and living specimens. Almost all the open shells were found to belong to individuals in which the muscles had been weakened by the invasion of the parasitic *Dystoma*. We see from these illustrations that parasitism may be either destructive to the host or necessary to the existence of the host species, or it may occupy an intermediate relation.

When we speak of a destructive parasitism, we understand that the host species must not thereby be entirely exterminated, because this would bring the condition suddenly to an end. To take a remote illustration, the destructive parasitism which exists between the Carnivora and Herbivora falls short of the extermination of the latter order from various obvious and well-recognized causes. We conclude from a consideration of the evolution of parasitism that (1) a destructive parasitism may not be an obligate parasitism. For, let us for a moment suppose the existence of an obligate parasite which invariably and rapidly destroyed its host; with abundant opportunity for the spread of the parasite there would soon result extermination of the host species, and most certainly an extermination of the parasite. But should a few individuals escape the attack of the parasite through the favor of locality, then would the host species multiply, but there would remain no chance of resurrecting the parasite.

2. A destructive obligate parasitism may exist when the causes determining the initiation of the parasitism are the same as those determining the perpetuation of the host species.

Syphilis is a form of comparatively destructive parasitism which depends on the reproductive act, as a rule, for its spread from one individual to another.

3. A destructive obligate parasitism may exist when its relations are such that it appears only after the reproductive period has passed, or after the reproductive act has been accomplished. This theorem is illustrated in the animals among whom one of the parents becomes the host of the offsprings, and dies in their care, or where the destruction of the male is essential to the fecundation of the female.

4. An obligate parasitism signifies an ancient and long continued parasitism.

5. Most obligate parasites are not only non-destructive, but even helpful.

These theorems are so nearly axiomatic that a discussion of them at this time seems almost unnecessary. Hence, when we observe a very destructive form of parasitism in a species, we almost immediately conclude that it is occasioned by a facultative parasite, at least, a facultative

parasite so far as this species is concerned. All apparent exceptions, at least, so far as I know, are susceptible of explanation. Tuberculosis, which seems to be a destructive obligate parasite of man (although it does not conform to all the requirements of a destructive parasitism), is, in fact, only an obligate parasite of the warm-blooded animals as a whole. Among a number of these, tuberculosis is a comparatively harmless affection. In the Aves it results in the production of new connective tissue showing very little tendency to break down (Etudes Experimentales et Cliniques sur la Tuberculose, D. H. Martin. Vol. II, page 365, 1887).

6. The less destructive a parasite is to the host, the fewer the means of offense and defense which the host species offers to the attack of the parasite; and, vice versa, the more destructive the parasite and the longer it has continued, the greater the resistance which the host species manifests. The obligate character of measles and scarlet fever indicates an ancient and continued relation with man. Nevertheless, from the comparatively harmless character of measles, scarcely any individual immunity has been developed. All individuals, of whatever age, who have not been protected by a previous attack, suffer from the slightest exposure. Not so, however, with scarlet fever. Age alone renders the individual immune in most cases, while many of the youth suffer repeated exposures without falling victims to the disease. This acquired immunity stands in direct ratio to the destructiveness of the disease.

Let us now consider some of the relations of the facultative and destructive parasites of man.

7. As a converse of what has already been premised, we should conclude that all destructive parasites were facultative parasites, and depended upon unusual circumstances to permit or induce them to assume a parasitic existence. Generally they lead an independent existence, or, at least, are only messmates of their host. In point of fact, our most dangerous and destructive enemies are the ever present bacteria of our intestinal and respiratory tract, and one of the most important subjects which the study of parasitism forces upon us, is a consideration of the causes which determine the localization of infection. All destructive forms of parasitism necessarily depend on accidental moments to open the doors which ages of evolution have closed against them. These avenues may be thrown open as a whole by causes which diminish the general vitality of the host, as inadequate or perverted nutrition or innervation; or a point of diminished resistance may be affected by local causes. Among the latter, we are accustomed to think of traumatism as the most potent. Perhaps a more careful consideration of the effect of local infection upon the tissues will lead us to conclude that the most important factor determining the localization of infection is an antecedent and comparatively harmless infection.

Tetanus is a most destructive infection in man, but it is clinically and experimentally shown to be invariably a hanger-on upon a much less destructive pyogenic infection. Indeed, it has been impossible, so far, to cultivate the bacillus of tetanus on any soil alone, but only when growing with other bacteria.

In this relation, the kind of infection is a matter worthy of study. Some forms of infection thrive only in the blood channels, and they might properly be termed *hæmatophytic;* while the greater number invade the lymph spaces and their smaller intercellular prolongations, and therefore might be termed *lymphophytic.* Among the former are the *Spirillum* of relapsing fever and the *Plasmodium malaria.*

Foremost among the facultative parasites of man, both in the number of individvals they destroy, and in relation to the present subject, are the pyogenic bacteria. Of the three or four forms of suppuration ordinarily met with, that produced by the *Staphylococcus aureus* of Ogsdon is the most common. It is pre-eminently a parasite of the cell, producing multiplication of the nuclei, and latter coagulation and peptonization of the protoplasm. This peptonizing power is manifested in the nutrient gelatine by its liquifying that solid medium.

However, the study of no other pyogenic microbe is so interesting from a theoretical and clinical point of view, as that of the *Streptococcus pyogenes.* It appears frequently as a simple infection, but most often as a secondary or mixed infection. Unable to invade the healthy and uninfected human body, it follows in the train of the acute infectious diseases, and through the doors they throw open, it gains access to the body. Though it is unable to compete with other suppurative bacteria in readiness of attack, and being therefore more rarely met with clinically, its unusually varied and often masked destructive powers commend it to the consideration of every physician and surgeon, and its exhibition of various degrees of virulency, and its peculiar reaction on the tissues of different species and different individuals even, recommend it to the study of the zoologist. Its remarkably small size and its power of linear advance through fission give it a peculiar advantage over the other pyogenic microbes after an invasion has once begun, which modifies all of our ordinary notions of suppuration.

The *Streptococcus pyogenes* is found in abscesses which are often slow in formation, and which present some of the symptoms of cold (tubercular) abscesses, in that they are very often unaccompanied by any rise of temperature. The tissues about the abscesses are not much inflamed or infiltrated, and the abscesses can be taken up in the fingers and moved about with the overlying skin. Sometimes, if not generally, the abscess wall is not distended under any pressure, so that doubt may exist as to the presence of fluctuation unless great care and a delicate touch are exhibited. The same conditions render the diagnostic use of the hypodermic needle more difficult. The overlying skin

has a normal color until the *paniculus adiposus* is destroyed and the nutrition of the skin impaired. Then it becomes tawny, and, as invasion approaches, it dies, and the contents of the abscess are discharged through the resulting defect. Occasionally after an abscess of this kind has been observed for some time, it unaccountably disappears, and a casual observation discovers no trace of it except a little looseness and movability of the surrounding tissues. In such a case, a dissection will show that the abscess has opened into an adjoining connective tissue space, has perforated some fascia, and sunk into it, or been forced into some distant and remote part of the body by atmospheric pressure, or by the mechanical force of some adjoining motor apparatus.

The contents of the streptococcus abscesses present the greatest variety of appearance; in one case, resembling closely macroscopically the staphylococcus pus; in another, colored with the pigment of muscle, bone or blood; in another, made up of a thin dirty fluid in which floats the debris of the destroyed tissues. The walls of the abscess are not covered with a granulating tissue, but are ragged and necrotic. They are themselves invaded to a considerable depth with the invading microbe, and the increase in size of the abscess is due to their progressive destruction. The facia of the muscles and the fibrous sheaths of the blood-vessels present considerable resistance to the advance of this destruction, and, therefore, it is not unusual to see at the bottom of the abscess or in its center a bundle of large blood-vessels, or a whole muscle desected out as if for demonstration. Microscopical examination of the pus shows a small number of leucocites and a large amount of unrecognizable detritus, the result of tissue necrosis and fatty degeneration. With proper staining, the streptococci are seen as small spheres, four to ten in a chain. They occupy not only the leucocites, but are found between the cells composing the wall ofthe abscess, and also in the intercellular lymph spaces. The connective tissue spaces and the lymph spaces are invaded to a considerable distance. This may become very general, and involve vast areas without the formation of abscesses. The perimycium and the endomycium are semetimes found crowded with the streptococcus. (Ziegler, I, p. 366.)

When the streptococcus is cultivated on the nutrient gelatin, the growth is very significant. There is soon seen a mass of colonies along the line of the needle, which spreads out on the surface of the gelatin, forming a tulip-shaped growth. The gelatin remains solid all the time, that is, it is not peptonized. A corresponding reaction is observed on the tissues. While the staphylococci produce a liquifaction of the gelatin and a circumscribed suppuration, the streptococci produce a less active tissue reaction. The suppuration is of a modified kind; the exudate is sero-purulent, serous, or fibrinous, or all of these combined. In some animals (rabbits) the reaction is an inconsiderable inflammation,

while in others it is a mild suppuration (mice). They may be injected into the jugular vein of rabbits without producing any serious consequences.

II.

While no satisfactory demonstration of the pathogenic micro-organisms, which no one doubts are the etiological factor of the "acute infectious diseases," has been made, we may safely conclude that such a demonstration only awaits a better method or greater diligence than has already been used. Sahli says that it is not wonderful that many investigators have failed to discover the prime cause of diseases which have been recognized clinically to be infectious. And he remarks that they may either be too small to be seen, or may be insusceptible to the staining methods which have been tried.

In this discussion it will be assumed that all of the acute exanthemata are due to micro-organisms, whether they have been demonstrated or not.

It is very well recognized clinically that scarlet fever, measles, whooping cough and mumps are due to obligate parasites of man, or, at least, of the warm-blooded animals. We should therefore conclude that in these diseases, as we have already found in typhoid, the pure and unmixed infection would be productive of a very small mortality.

MEASLES.

The investigations of Cornil and Babes establish the fact that in measles numerous diplococci are uniformly present in the interstitial lymph spaces of the lungs, as well as in the larger lymph channels and concentric glands. These bacteria resemble somewhat the gonococci, but are surrounded by a clear, unstained capsule like that of the pneumococci. Later in the disease, the same bacteria are found in the blood vessels everywhere. While it cannot be said that this diplococcus is the demonstrated etiological factor of measles, we may safely consider it so until later and more perfect researches confirm or refute its claim. One thing is certain, the pathogenic micro-organism of measles attacks the lining membrane of the respiratory tract, and its connecting mucous tracts. In these a self-limited inflammation is set up, which, however, diminishes the resistance of the whole respiratory tract and its annexa. Secondary infection is therefore apt to follow in these regions (Henoch, page 688), especially those forms which occupy the lymph spaces. In the upper respiratory tract and the adjoining mucous membranes, secondary infection with the ordinary pus microbes frequently sets up suppurative otitis media, suppurative conjunctivitis, keretitis, laryngitis and pharyngitis. In the same regions diphtheritic inflammations are occasionally observed. Suppurative broncho-pneumonia and true specific pneumonia are observed as secondary infections in the lower air passages. "Measles is regarded by all authors as one of the frequent

causes of secondary pneumonia in the child." (See, page 80.) It occasions more than one-fourth the cases of broncho-pneumonia in children. This pneumonia is a suppurative process, and is occasioned by the assumption of a pathogenic parasitism by the heretofore harmless saprophytic bacteria in the secretions of the respiratory passage. Babes found no other bacteria in the products of such cases of broncho-pneumonia. Pneumonia should always be feared when the thermometer shows a rise of temperature after the first remission, or when the dyspnoea, cough, or circulation show any departure from what we consider a normal course of this disease. In some cases of broncho-pneumonia, cough and hectic continue for a long time, and upon post-mortem examination multiple small abscesses are found in every part of the lung, and, perhaps, in the mediastinal glands, with dilitation of the bronchioles and atelectasis. But pneumonia and pulmonary oedema are not always due to local origin. In certain cases they arise, as in scarlet fever, from the flooding of the venous current with suppurative bacteria from an abscess originating near the respiratory openings, or in distant bones and joints. Such cases are not infrequently reported. (Henoch, page 696.)

Adhesive pleurisy is observed over the affected lung, while serous and suppurative pleurisies are relatively rare. The rupture of a suppurative broncho-pneumonic cavity into the pleural cavity has occasionally resulted in a pyo-pneumothorax. (Henoch, page 638.)

When infection with the *Bacillus septicæmiæ hemorragicæ* takes place, all the symptoms of hemorrhagic infection follow in many or all parts of the body. The temperature is generally high, and all the secretions and excretions are mixed with blood. Sometimes the patient withstands this drain, and then falls into a typhoid condition. It has appeared as late in the disease as the third week. (Henoch, page 697.) All other forms of mixed infection are apt to follow.

When a suppuration in the lung or a local phlegmon elsewhere occurs, the infection may be taken up by the lymphatics, and emptied into the blood current, where characteristic symptoms will result. A streptococcus abscess is likely to be followed by pyæmia, or, at least, by a glomerulo-nephritis, while other forms of infection produce malignant septicæmia. Ulceration sometimes takes place in the mucous membrane of the eye, mouth, and throat. Diarrhœa, or more properly, dysentery, is a remarkably frequent complication of measles. It is sometimes so excessive that it leads to collapse and death. Upon post mortem, an intense inflammation of the colon is found, with ulceration of the follicles and superficial lymphatics, and the enlargement and even breaking down of the tributary mesenteric glands. (Henoch, page 690.)

But the most dreaded and frequent of all secondary infections which result from this disease, is tuberculosis. All authors notice the

frequency not only of pulmonary and laryngeal tuberculosis, but the remarkable disposition of tubercular disease to appear in the joints and and other organs on the arterial side of the lungs after this disease. This unusually numerous following of tubercular joint diseases is due to the formation of tubercular foci in the lung at the point of acquired diminished resistance and the transportation of the bacilli directly from the lung to the fated joints where traumatism has provided a suitable habitat. The tubercular infection is stored up in the lung tissue until degeneration of the primary focus allows a further dissemination. If this is the mechanism of this sad complication, we should expect it to occur as a rather late sequela. This is uniformally the case.

As measles predisposes to all the lymphophytic forms of infection, we should expect to find it frequently combined in the same individual with those obligate parasitic diseases which are of this nature. Indeed, this is clinically shown to be the case with whooping cough. Association of measles with pre-existing disease usually makes a graver prognosis, and it is especially to be feared in those children that have suffered from exhausting diseases, such as diarrhœa, pneumonia, or tuberculosis. Measles in most of these cases appears as a terminal disease.

One of the rarer forms of secondary infection which occurs with measles is acute pemphigus. (Kleutfel, Steiner, Loeschner, and Henoch, page 692.) It appears either alone or with hemorrhagic infection, and, usually, rather early in the disease (3d to 8th day). Demme has demonstrated the presence of a bacterium which he thinks is the especial cause of Pemphigus acutus. Noma and erysipelas are sometimes observed, and gangrene may follow any extensive or acute form of infection. (Henoch, page 696.) Nephritis is not an unusual concomitant of the various forms of secondary infection, and disease of the kidneys should never be considered as anything but a symptom of septicæmia. It is probably due in all cases to capillary embolism in the tufts of the glomeruli, either by living bacteria or dead products of their growth. The various forms of nephritis which accompany or follow measles are natural consequences of various forms of infection. In the mild and early septicæmia of measles the nephritis is mild, as in typhoid fever, pneumonia, and erysipelas. In each of these cases the etiological moment of the disease has been demonstrated to be the true cause of nephritis. When a streptococcus infection follows measles, there may be a streptococcus nephritis exactly resembling that so frequently occurring after scarlet fever. Occasionly hematuria is observed as the only sign of septicæmia hemorrhagica. Most cases of suppurative pneumonitis are found post mortem to be accompanied by secondary bacterial nephritis; and there is no doubt that many cases of vicious or imperfect nutrition after measles, accompanied by occasional traces of albumen in the urine, are due to this cause.

III.

No form of secondary infection is so mournfully interesting as that which occurs after scarlet fever. Although scarlet fever is not so contagious as measles, the fatalities which follow it exceed those of measles by almost 50 per cent. The class affected is one which appeals to our sympathies in the highest degree. While the older members of the family are immune to this contagion, the helpless children are almost universally susceptible, and the remote consequences of the disease are obscured by the triviality of the onset. Diphtheria alarms by its rapid and terrible destruction, while the terrors of scarlet fever are put off for months, or even years. Therefore it behooves the State to defend its helpless youth by salutary laws, efficiently executed, and by a conscientious, educated medical profession.

During the last twenty years the death rate from scarlet fever has been diminished in the State of Michigan from 4.85 per 10,000 inhabitants per annum to 2.75. It is easy to estimate approximately the number of lives thus saved to the State, but it stands to reason that a much larger number of individuals have been saved from nephritis, otitis, and resulting deafness, cervical adenitis and subsequent tuberculosis, and many of the rarer accidents of the disease. With a death rate of two or three per 10,000 inhabitants, the charitable institutions of the State are still filled with pitiable, helpless, and expensive citizens; and many are endured and supported at home by private charity. The saving of life alone, by the proper isolation of this disease, is not the only thing to be considered. We must also take into account the diminished necessary charitable appropriation from the State treasury, and the indirect support, through private charities, of individuals who would otherwise become helpless and a charge to the State. There can be no doubt that the number of helpless, pitiable, and vicious individuals now supported at the public charge is sufficient to demand an earnest consideration of this subject from every humanitarian and economist.

Scarlet fever begins as a septicæmia with a local lesion in the pharynx. We have every reason to suppose that it is due to the infection of a lymphophytic micro-organism. It seems to be an obligate parasite of man, but also a facultative parasite of some domestic animals. Netter has shown that the mouth, in a very large per cent. of individuals, is constantly occupied by the Streptococcus pyogenes, which has been shown to be also a lymphophytic microbe (Baumgarten). It would be nothing more than natural to expect that the primary lesion in the throat would predispose to infection with the ever-present streptococcus. This, we find to be very frequently the case. No complication of scarlet fever is so frequent as that which the clinicians have termed "cervical involvement." This cervical involvement, we are told, appears any time after the appearance of the primary throat le-

sion. The intercellular mucous tissues of the pharynx are found crowded with chain cocci, which always occupy the intercellular spaces, and are usually non-destructive directly to the surrounding cell elements. My own examinations are in accord with what has been reported from all parts of the world. In seven cases of post-scarlatinal abscess in the region of the neck, which I have examined during the past three years, three have been accompanied by abscesses elsewhere. In all of these cases, I found the unopened abscess, and by aseptic operation made inoculation in nutrient gelatine. In every case, there resulted a pure culture of the *Streptococcus pyogenes*. Three of the seven cases were accompanied by abscesses elsewhere; one in the neighborhood of the right seventh rib and the cheek, one in one of the phalangeal joints, and one in the axilla. All of these abscesses contained the *Streptococcus pyogenes* alone, except the one in the cheek, which contained besides the *Streptococcus aureus*. Indirect cell division rapidly appears in the wall of the blood-vessels, and escape of the elements of the blood greatly increases the mass of the tissue invaded. Multiplying, as the streptococci do, by fission, and doubling their length every few minutes, they are able to force themselves rapidly forward in all directions from the point of primary invasion. Very early the cervical glands contain the multiplying streptococci, and appear greatly enlarged. Until the surrounding tissues are directly invaded, there is little periadenitis. In this respect the streptococcus lymph adenitis resembles that of tuberculosis. The whole cervical region on both sides of the neck may become infiltrated and indurated in a most incredibly short time. The formation of pus is, however, slow; and, at most, after weeks or months the intercellular spaces are filled with a sero-purulent exudate. The sheaths of the large blood-vessels are dissected up for a great length. The infiltration may advance to the origin and insertion of the muscles of the neck and pharynx, and when suppuration occurs, the pus may be discharged spontaneously into the throat. Large areas of skin may be separated from the underlying connective tissue, and in this way, its nutrition is cut off, and necrosis follows. Great black sloughs are apt to occur, which may extend nearly around the neck, following the line of a bandage, or the area of counter-irritation. When the slough is removed, the most perfect anatomical dissections are presented to view. Gravitation abscesses may occur, which, upon rupturing into the pericardium or pleura, result in all the sad consequences of infection of these large cavities. When the infiltration of the connective tissue of the throat has been sufficient to shut off the nutrition of the part, gangrene has followed, with the enormous enlargement of the pharynx (Thomas, page 217). Among the milder symptoms of this infiltration are dysphagia, aphagia, and dyspnœa. Œdema of the glottis, destruction of the epiglottis, and exfoliation of cartilage are not unknown

(Gee, page 341). Not unfrequently the large blood-vessels of the neck are open by necrotic erosion, and sudden and fatal hæmorrhage follows. When these serious and terrible appearances are combined in one clinical picture with the emaciation, the otitis, the suppurating joint and bone diseases, the terrible diarrhœa, or the nephritis, we have a picture from which the bravest physician would fain turn his face.

If such serious and alarming destruction about the seat of the primary lesion is rarely observed, the more insidious and delayed consequences of streptococcus colonization are sadly frequent. I shall be able to call attention in this limited time to but a few of the more important.

The number of mutes and of totally or partially deaf persons as the result of scarlet fever is very great. About one-third the inmates in the various public institutions are reported in this category. Of course, there are many who are incapacitated by defects in hearing without loss of speech. This number is still larger. These unfortunate individuals often receive credit for defective intellect instead of impaired audition. This is especially the case in the public schools, where teachers have large numbers of pupils for a few weeks or a few months only. The stupidity and viciousness of many a pupil is the result of a failure on the part of parents and teachers to appreciate this defect. These children become useless and disagreeable, if not expensive and criminal citizens. They are directly or indirectly a burden to the State. It is worth our while, therefore, to study, even at some length, the cause of such a calamity as this.

Coryza is not as frequent a symptom of scarlet fever as of measles, but an inflammation of the naso-pharynx is often observed which produces a copious secretion. That this is due to the streptococcus infection of the tonsil or pharynx, or extension of the infection along the pharyngeal muscles, there is no reason to doubt. The greatest danger lies in infection of the tissues along the Eustachian tube and the closure of its nasal end. Then follows destructive inflammation of the middle ear and its annexa, rupture of the drum, and protracted otorrhœa. Actual destruction may interrupt, or cicatricial contraction may impede, the transmission of sound to the internal ear, or more extensive infection of the bone may actually destroy the internal auditory apparatus. The infection of the petrous portion of the temporal bone may interrupt audition by destruction of the auditory nerve. The petrosa is traversed by a number of other nerves and blood-vessels, which may be destroyed with the destruction of the bone. Thus results paralysis of that portion of the face supplied by the facial. The glandular apparatus may cease to operate, and mastication and taste become impaired. But these deformities are scarely to be considered in comparison to the danger to life which follows infected thrombosis of the intercranial sinuses, in close proximity to the petrosa. Into any of these larger blood-vessels,

thrombi may protrude from the smallest nutrient vessels of the bone. About the protruding thrombus, the blood plaques collect until the the sinus is occluded. This white thrombus is infected, and, in time, becomes a generator of ptomaines, the absorption of which is manifested by constitutional symptoms. Later on it is broken down and scattered into all parts of the body, or gives rise to local suppuration, meningitis, or cerebritis. Frequently the infection of bone advances to the periosteum and gives rise to no serious symptoms until by contact the meninges are infected from contiguous extension. It is even possible that distant portions of the brain may be infected through wandering phagocytes and the membranes remain intact.

There is no doubt that the majority of cases suppurative otitis media arises by extension from the naso-pharynx to the eustachian tubes (Wolf, *Centralblatt fuer Bacteriologie und Parasitenkunde*, 3, page 545). The observation of Zaufal (*Baumgarten's Jahresbericht*, 3, 1887, page 417) of the rare coccus of Friedlander and the capsule of Frankel in the secretions of the ear, and also in the coincident secretions of the nose, in extra clinical evidence (See also Rohrer, *Centrlbl. f. Bact. u. Parasitenk.*, 3, p. 644). Habermann (*Baumgarten's Jahresbericht*, 1, p. 83), in commenting on the etiology of tubercular otitis media, mentions the probability of the transportation of tubercular sputa up the Eustachian tube by coughing. Clinically this method of origin has long been recognized. Nevertheless, there can be no doubt that disease of the petrosa may arise by metastatic infection, and such a possibility should always be considered.

Pneumonia is a rather rare complication of scarlet fever, and has not received as much attention as its theoretical importance in relation to nephritis and other lesions on the systematic side of the circulation would command. Early in the disease there is a catarrhal pneumonia as there is a catarrhal nephritis (Friedlander). This early pneumonia is due to the septicæmia of the pure scarletinal infection, and is usually coincident with the exanthema. The secondary pneumonia is the only form to be considered. It occurs rather late in the disease, usually in the second or third week. It is due to the infection of the venous side of the circulation with bacteria which have entered the walls of the pharynx and escaped through the cervical lymphatics and been poured out through the thoracic duct. The kind of pneumonia resulting depends upon the character of the infection. If it is a form which will produce local destruction in the lungs, small abscesses may be formed which may discharge through the bronchi or into the pleura. More often the infection is with the lymphophytic streptococcus. Then a bronchopneumonia follows, which, though alarming, is not necessarily fatal. It may continue a very long time, even months, and is apt to be followed by tuberculosis. That this is the correct explanation of this complication the researches of Thaon and Pipping leave no room for doubt.

In extremely rare cases a true specific pneumococcus pneumonia may occur in a patient recently affected with scarlet fever. This is, however, a remote chance, and I am unable to cite a case in which its demonstration has been made. Then, too, a patient suffering from diphtheria as a secondary infection is apt to have a diphtheritic pneumonia from extension of the disease downward by aspiration. However serious these accidents may be, they are too rare to require further mention.

It is evident that a streptococcus pneumonia, however slight the local symptoms may be, is a very serious matter when we consider the remote consequences. The bacteria, of whatever kind, escape the capillaries of the lung and enter the arterial side of the circulation. Most of them are quickly included in phagocytes, and their multiplication is arressed. It is well known that a traumatism is frequently the determining cause of the localization of infection. The function of the heart valves furnishes this factor. Upon their edges the streptococci first gain a foothold and thrombosis sooner or later begins. These infected thrombi are carried off in the arterial circulation and scattered in every part of the body. The valves themselves may become rapidly incompetent, and compensatory hypertrophy of the heart may result. Moreover, through the coronary arteries, the tissues of the heart may be directly affected, and coagulation necrosis and fatty degeneration, with resulting aneurism or sclerosis, follow, with serious interference to the heart's function. But the larger portion of the blood passes to the aorta, and infection may be carried to every part of the body. The spleen becomes enlarged, and shows its characteristic septicæmic appearance. The liver, kidneys, serous cavities and the brain do not always escape. Some of these forms of infection will be noticed in detail.

In all the acute infectious diseases, nephritis appears as a constant and early symptom. In typhoid it is noticed in the first week, and the typhoid bacillus is then found in the urine by means of cultures. In small-pox, measles, typhus fever, and sometimes in whooping cough, an early nephritis has been observed. In these cases, however, no etiological factor has been discovered. The early nephritis in scarlet fever appears as a slight albuminuria in the early part of the first week. Purdy, however, mentions a case which came to section in the middle of the second day of the disease, in which all the evidences of glomerulonephritis were present. In these cases the lesions of the kidneys are usually slight, and they interfere very little with the course of the disease.

Quite a different thing, however, is the post-scarlatinal nephritis. It appears about the end of the third, and only rarely later than the sixth week. Its appearance stands in no relation to the severity of the scarlet fever infection. The hyperexia of the disease disappears from the seventh to the eleventh day, and a week or more of convalescence inter-

venes before the gradual or sudden onset of nephritis. Some have noticed a slight irregularity of the temperature chart in those cases which later develop nephritis. Others assert that nephritis is apt to follow in case the cervical glands which have once subsided enlarge again. I shall endeavor to show that this disease is frequently due to capillary embolism in the tufts of the glomeruli resulting from the presence in the circulation of the Streptococcus pyogenes.

We have already seen that the sub-mucous tissue of the pharynx and naso-pharynx, the cervical lymphatic, the lungs, the heart, the joints and bones, and especially the tissues about the middle ear, are invaded by the streptococcus with unusual frequency as a complication of scarlet fever. Let me add to these researches the direct examination of the blood. Escherich gives a complete account of the investigations which have been published up to date of his essay on the presence of bacteria in the blood of patients suffering from scarlet fever. It appears that all authors have found the streptococcus in unusual numbers. Riess, Loeffler, Babes, Fraenkel, Cooke agree in the morphology of the microbe which they found by culture methods in the blood in the early weeks. There can be little doubt that it is one or another of the varieties of the *Streptococcus pyogenes*.

Streptococcus invasion gives rise in other instances to glomerulo-nephritis. Baumgarten (p. 339) gives an account of such a case, from which I copy the accompanying figure. It occurred in a case of pyæmia beginning in an abscess of the face. The drawing is made from a section stained with methyl-blue. Both the afferent and efferent capillaries are distended with cocci. The distinct beaded form of the coccus can be made out in some of the central loops where there is less crowding. The nuclei of the vessel wall are unstained, showing that coagulation necrosis has taken place.

Bamberger, Aufrecht, Litten and Perret find nephritis due to bacterial origin, and have proposed such names as *mycotische Nierenerkrankung*, *nephrite parenchymateuse aigue*, and *nephrite bacterienne primitive*. An inspection of the history of these cases as given by Perret shows, however, that those of Aufrecht were certainly secondary, one to dysentery, and the other to suppurating tuberculosis. Mannaberg (Zur Ætiologie des Morbus Brighti acutus. *Centralblatt fuer Klinische Medicin*, *1888*, *No. 30*) examined bacteriologically eleven cases of acute nephritis. In eight of these the streptococcus was found. Three gave negative results. The quantity of streptococci stood in direct proportion to the severity of the disease. In four of the cases in which the streptococcus was found, there were complications which furnished an entrance for the bacteria, and secondary bacterial nephritis followed. In one case "croupous pneumonia," in one eczema, in one syphilis maculo-pupulosa, and in one diphtheria accompanied the symptoms of nephritis. The biological character of the streptococcus

differed slightly from that of the *Streptococcus pyogenes* or *erysipelatis*, and Mannaberg considers it a distinct species. His researches not only show the streptococcus to be a frequent cause of nephritis, but illustrate the variability of the species. Mircoli (Primaere mykolische Nierenentzuendungen der Kinder. *Centralblatt fuer Bacteriologie und Parasitenkunde*, III, p. 336) describes a form of epidemic primary bacterial nephritis which attacked fourteen children in a village of three thousand inhabitants. Of these three died and microscopical examination of kidney showed acute parenchymatous nephritis originating about embolic foci of diplococci and chain cocci.

Babes describes various forms of bacteria which he found in the blood-vessels of the kidneys in the nephritis following sepsis, rheumatism, yellow fever, and scarlatina. In pneumonia a form of nephritis is occasionally observed in which Klebs and others have found the pneumococcus of Friedlander. Nephritis frequently follows anthrax infection, and in these cases no one doubts that the anthrax bacillus is the prime etiological factor.

The fact that few investigators are able to demonstrate the bacteria in sections of the kidney, the urine from which has been shown by culture methods to swarm with them, is accounted for by Schweizer (*Virch. Arch.*, CX, and *Centralblatt fuer Bacteriologie und Parasitenkunde*, III, p. 244). He says that they are removed by the osmotic currents which are set up in the processes of hardening, staining and mounting.

In a single case of post-scarlatinal nephritis in a boy I removed the urine under every indicated precaution and immediately inoculated nutrient gelatine. The resulting cultures were exhibited to this Society at a recent meeting. Since that time inoculation has been made in the anterior chamber of the eyes of rabbits, and suppuration has twice resulted. In another case of post-scarletinal nephritis in a girl from whom the urine could not be taken with that care which is necessary to an accurate observation, the inoculated tubes were liquified and poured out upon plates, and although numerous other colonies were seen, the great majority proved themselves to be the *Streptococcus pyogenes*. These meager researches obtain any value only because they are in accord with the investigations of the most reliable bacteriologists.

The frequency with which the streptococci are found in cases of pyo-nephrosis is a matter not entirely foreign to our subject. I have myself demonstrated the *Streptococcus pyogenes* by culture in one case operated upon by myself and another operated upon by Dr. Fenger.

It may not be as conclusively demonstrated as could be required by those who have not paid the strictest attention to the progress of pathological mycology during the past three years, but I believe the following theorems will be sustained by subsequent research.

1. Nephritis and the concommitant albuminuria in the acute infectious diseases, erysipelas, typhoid fever, pneumonia, carbuncle and

puerperal septicæmia has already been shown to be due to embolic infection in the arterial tufts of the glomeruli and the resulting defect, and there is reason to believe that the same pathology prevails in the early nephritis of measles, scarlet fever, diptheria and rheumatism.

2. In all cases of secondary infection after the acute infectious diseases when nephritis arises it is due to the escape of the products of secondary infection into the systemic side of the circulation and the consequent embolism in the kidneys, and the resulting local disturbance.

3. The presence of bacteria corresponding with the primary disease or with the secondary infection in the kidney and in the urine is in no other manner explained.

4. In post-scarlatinal nephritis the ætiological factor is the *Streptococcus pyogenes* or a microbe which cannot at present be distinguished from it.

I can only refer incidentally to secondary infection with other than the pyogenic bacteria.

All authors mention the occasional appearance of hæmorrhagic infection (Smith, p. 509; Thomas, p. 210, 225, 227). In these cases there is hæmorrhage from all the excretory and secretory organs of the body. The skin, mucous membranes and conjunctiva are separated from the underlying tissue by larger or smaller extravasations of blood. Coincident hæmhorrhage in the kidneys gives rise to a hæmaturia which is entirely distinct from that which occurs in the ordinary streptococcus nephritis. In the intermuscular fascia such extensive extravasation appears as to give rise to symptoms of acute anæmia. Riess has made a most perfect demonstration of the infection in the blood. Abercrombie says, "Changes in the blood-vessel take place in scarlet fever, measles and whooping cough, but especially in diphtheria, resulting in hæmorrhage." And he looks upon cerebral hemorrhage in children as frequently due to this cause. Such hæmorrhage within the cranium may result in sudden death (Henoch, p. 256) or permanent paralysis with the formation of scar or cyst, and subsequent general cerebral sclerosis manifested by epilepsy and insanity. The young are most often affected with this form of infection, but a fatal case of septicæmia hæmorrhagica after scarlet fever is reported by J. L. Smith (p. 509) in a man 32 years old.

Secondary infectin with noma, diphtheria, pemphigus and erysipelas, present no unusual anomalies. Perhaps the relation of diphtheria to scarlet fever has already furnished a sufficient ground for discussion.

The most interesting and frequent secondary infection of all, yet remains to be noticed. Should the little patient escape all the dangers of suppurative otitis, streptococcus pneumonia and nephritis, and the pyogenic infection of bones and joints, the general and local resistance of the tissues may be so greatly impaired that he falls an easy victim to

the attack of the tubercle bacillus. The enervating influence of the general disease is greatly aided in this matter by the lymphophytic infection of the pharyngeal cavity by the streptococcus. The tonsils and folds of the pahrynx furnish a reservoir for tubercular food, and that temperature is maintained which is most favorable to tubercular growth. Is it a wonder, then, that tubercular cervical lymphadenitis is such a frequent sequelæ of scarlet fever? In measles pulmonary tuberculosis follows, but in scarlet fever we are accustomed to look for a precursor of scrofula.

In following back the history of tubercular infection outside the lungs, I have been surprised to find that a history of scarlet fever could frequently be elicited which had escaped the recognition of the attending physician and the family at the time. There is every reason to believe that tubercular infection of the young rarely appears as a primary disease, but always or almost always follows the train of measles, scarlet fever, typhoid fever, diphtheria and especially of cholera infantum.

IV.

MUMPS.

Mumps clinically answers all the requirements of a parasitic disease. The aged and infants are immune to its attacks. It is generally looked upon as a trifling and ridiculous affection, but it is followed by complications scarcely less formidable than those already noticed. Every physician of experience has noticed the occasional enlargement of the cervical lymphatics after mumps, and has doubtless recognized its tubercular nature. Pyogenic infection also appears not only in the parotid and other salivary glands, but in the adjoining tissues, and destruction of the auditory apparatus occasionally follows through suppurative otitis media (Henoch and Eichorst).

Infection of joints is not unknown, though fortunately very rare.

My own experience with the secondary infections in mumps is confined to two cases. One case of bilateral epidemic parotitis was followed by tubercular infection of the cervical and submaxillary glands, with subsequent breaking down and discharge through the skin. The scars resulting from the protracted discharge were so deforming that surgical relief was sought. The other was a case of right-sided parotitis, which was followed by tubercular infection of the gland itself or a portion of it. The patient was living at the time in Scotland, and was under the care of Sir McLeod. His advice and prognosis shows that he recognized the nature of the disease at the time. Later it broke down and ran the ordinary course. I saw the patient soon after arriving in this country from Scotland, and several years after the onset of the disease. He was a robust young man. Near the old scar, and apparently in the body of the parotid, there was a firm, hard tumor half an inch in diameter. I diagnosed tubercular disease, and advised imme-

diate removal of the tumor and the old scar, which had a very repulsive appearance. The patient's family would not consent. Six months later the tumor was two inches in diameter and much softened down. It was then opened, and has continued to "discharge" ever since. In both of these cases there is not the slightest doubt there was a secondary infection at the point of diminished resistance. One may ask where the bacilli entered the body. We can suppose that the patient was entirely free from tuberculosis until the parotitis gave entrance to the bacilli through the gland or some adjoining tissue which was no longer protected by the secretions of the gland. *Fœtor ex ore* is often produced on account of the inability to keep the mouth clean (Eichorst, p. 189). My second case would seem to be an example. Or we can suppose the infection of the cervical glands, with latent tuberculosis, which sprung up when the local inflammation and the general depression of mumps gave a favorable opportunity.

The ordinary train of secondary infections is observed by all systematic authors as sequelæ of epidemic parotitis, pneumonia, endocarditis, ostitis, arthritis, nephritis, and local infections. Nuritis especially, especially retinitis, seems to be remarkably frequent.

I regret that time does not allow me to consider the serious secondary infections which have been observed in whooping cough and diphtheria. Just one word in regard to the summer diarrhœa of infants, and I am done. Like puerperal fever, this is a disease which does not depend upon a single etiological factor. Beginning as an intoxication from the absorption of the products of putrefaction in the intestinal canal, it goes on as an infection of the mucous membrane of the bowel when the physiological resistance has been diminished by general intoxication and perverted nutrition. Later than this, a general infection of the blood and lymph may follow, with all the sad consequences of septicæmia. When the little sufferers escape the primary disease, they fall easy victims to the attack of tuberculosis, which their milk so abundantly contains.

With this brief and imperfect review of the subject I leave the matter with the following suggestions:—

1. That, as there are no known means of averting the dangers of secondary infection, every effort which the State and the medical profession can use should be exerted to isolate and prevent the primary disease.

2. That when a patient is suffering from any one of the primary diseases, every effort should be made to sustain the vitality and strength of the patient at the highest point, and exclude and eliminate all avenues by which the secondary infection is known to arise.

3. That, as the evidence now stands, all the complications of these diseases are due to secondary infection, and the examination of pathological products by the aid of bacteriological methods offers the greatest, if not the only hope of that thorough knowledge which is necessary to a proper therapy.

ADDITIONAL NOTES ON SECONDARY MIXED INFECTION.

BY BAYARD HOLMES, M. D.

Perhaps nothing is more difficult to the beginner than to stop when his theorem is demonstrated. The importance of secondary infection as a factor in nearly all the complications of disease is continually forced upon me and I cannot resist bringing the subject again before my readers as if enough had not already been said.

In confirmation of my conclusions in a late number of this magazine on secondary infection in some of the acute infectious diseases of children, I beg to be allowed to call attention to a recent publication of Babes* which unfortunately fell into my hands too late to be incorporated in my original thesis.

These investigations were carried out some time ago and attempted to show the bacteriological condition of the dead bodies of children. It was repeatedly demonstrated that the cadavers of children that had suffered no previous disease were free from bacteria for a long time in winter and from four to ten hours in summer. The condition was very different in case they had suffered especially from one of the acute infectious diseases. In these cases Babes found the spleen, kidneys, liver, lungs, and blood infected with numerous colonies of streptococci putrefactive bacteria, capsule-cocci, more rarely staphylococci and various bacilli. Without doubt the most of these stood in a relation of sequence to the general and primary disease. Of special interest is the study of the manner of localization and spread of the secondary infection and the peculiar sequence of the infection after different primary diseases. For example, in eight cadavers, every one contained one or more bacteria in the internal organs. In two cases of diphtheria, the bacillus of diphtheria was found ; in one case of septic omphalitis, the bacillus of green pus ; in six cases of different kinds, the *Streptococcus pyogenes;* in one, the *Staphylococcus aureus;* and in five cases, various putrefactive bacilli. In many cases it was possible to recognize the point at which the different secondary invasions of the body had taken place. For example, in a case of sepsis after scarlet fever in which streptococci were found in every part of the body and in places mixed with a few saprophytic bacilli, a pure streptococcus pneumonia was found in the lower part of the left lung, while a number of foci were found in the upper part of the right lung swarming with bacilli alone. Thus in one part of the lungs was a pure culture of the streptococcus

*Bacteriologische Untersuchungen ueber septische Processe des Kindesalters, von Dr. V. Babes, Director des bacteriologischen Institutes in Bukarest, mit 21 farbigen Abbildungen im Text. Leipzig, Veit & Comp. 1889.

and another part furnished the bacilli. From these separate foci the infections spread to every organ on the systemic side of the circulation.

In another case of sepsis after scarlet fever, a submaxillary gland was found degenerated and filled with streptococci and putrefactive bacteria. In a third case, the same conditions were found in an interbronchial gland. In both these cases microscopical examination and bacteriological investigation showed that the gland and the surrounding lymph channels were crowded with streptococci and putrefactive bacteria, and the same forms were found in almost every organ of the body.

It is a most significant fact that out of thirty-four deaths from scarlet fever not one of the cadavers was found free from septic infection. The largest internal organs were found full of septic bacteria and often furnished more than one kind. I would call attention especially to the cases of nephritis after scarlet fever (loc. c. pp. 4–17.) Let me give a brief abstract of a few.

1. Eight-year-old boy. Hæmorrhagic scarlet fever with severe pharyngitis. The submaxillary connective tissue infiltrated, resistant, reddened. Temperature of sepsis Urine scanty, with abundant albumin and hyaline casts. Post mortem: Spreading out from the submaxillary tissues, were numerous sinuous abcesses which were filled with a thin pus. The tributary mediastinal glands were enlarged to the size of hazel nuts and some of them were cheesy. The spleen was enlarged, congested and softened. The kidneys were moderately enlarged and pale, and the capsule stripped off with difficulty. The cortical substance was pale, brownish, friable, and œdematous; the pyramidal portion, reddish. Out of the papillæ, pus-like semi-fluids were easily pressed. Safranin or scarlet staining demonstrated rose red masses in the intima of the larger blocd vessels of the kidney. The tissues about these vessels were moderately infiltrated with mononuclear and polynuclear round cells. Marked changes were found in the glomeruli especially. Both the perithelial and endothelial cells were multiplied and enlarged. The Malpighian tufts were crowded in places with polynuclear leucocytes. Some of the glomeruli were very small and atrophic with destruction and sclerosis of the capsule and especially of the tufts, while others were very much smaller than normal though no changes in their structure could be recognized. Bowman's capsule was thickened in most cases and frequently contained red blood corpuscles. The epithelial cells of the capsule were enlarged and multiplied. Round cells were frequently observed around the hilus of the glomerulus and infiltrating the surrounding intercellular spaces. The epithelium of the convoluted-tubules was granular and swelled, staining by Gram's method and afterwards with safranin demonstrated no bacteria. Cultivations made from the kidneys, spleen and other internal organs in artificial nutrient media as well as inoculations in animals demonstrated the presence of the *Streptococcus pyogenes* in all of these organs, beside two bacilli that proved pathogenic to mice.

2. An eight-year-old girl suffered from albuminuria and anasarca the second week after scarlet fever. Three days before her death she was attacked with croup. At the post mortem, chronic bronchial catarrh and bronchiectasis, with croupous bronchitis, was demonstrated in different parts of both lungs. The kidneys were greatly enlarged, the capsule easily stripped off. The cortal substance was somewhat thickened, yellowish brown and granular. Cultures were made from the croupous products of the lungs, from the enlarged bronchial gland, from inflammatory products of the lungs, as well as from the œdematous subcutaneous connective tissue and from the kidneys. In all of these, except in the croupous products of the lungs, a pure culture of the Streptococcus pyogenes was found. In this locality alone Loeffler's bacillus was also present.

3. In a five-year-old girl, anasarca appeared while desquamation was still going on,

ten days before death. The urine was passed in moderate quantities. It was turbid and highly colored. Specific gravity, 1.030. Much albumin, hyaline casts and blood. The post-mortem showed chronic tuberculosis of the bronchial glands, sclerosis of the apex of the right lung, and fibrinous and serous pleuritis on the right side. The kidneys were much enlarged; their surface yellowish white; the capsule easily stripped off, leaving the cortex glistening. The cortical substance was very thick, friable and œdematous. By microscopical examination, many groups of the larger blood-vessels, especially of the pyramids, showed amyloid degeneration of their walls; and, in the same neighborhood, the smaller blood-vessels were filled with thick, hyaline, fibrinous masses. In other small blood-vessels in the same neighborhood, were found thick masses of streptococci. Similar masses filled some of the blood-vessels leading to the glomeruli. The endothelium of the vessels was often multiplied and detached from the walls. The glomeruli were changed in different ways. They were either simply atrophic and sclerotic, or they were surrounded and compressed by a sclerotic capsule. The tufts were for the most part amyloid degenerated. Their lumen was obliterated and filled with hyaline masses. In other places the vessels were most changed at the hilus of the glomerulus. In some glomeruli there was no amyloid degeneration, but the capsule as well as the tuft was transformed into young, spindle-celled connective tissue. From the shedding of the epithelium of Bowman's capsule, a spindle-celled proliferation was observed. Similar changes were found throughout the kidneys.

From all the pathological products cultivations were made in blood serum and agar. From the kidney there developed, in the depth and on the surface of the agar, small glistening points composed of streptococci, while from the pneumonitic foci and from the pleuritic products developed, beside the streptococci, scarcely distinguishable colonies which were composed of capsule-cocci. These latter bacteria killed guinea pigs in twenty-four hours, while the streptococci produced only insignificant local inflammation and œdema. A mouse inoculated with the streptococci remained healthy.

4. In a nine-year-old girl that had been one and a half months recovering from the scarlet fever, anasarca suddenly appeared seventeen days before she came to the hospital. On her admission desquamation and left-sided pneumonia were observed. The urine contained at that time a little albumin and a few hyaline cylindrical casts. At the post mortem, the upper lobe of the left lung was found in the condition of gray hepatization. The changes in the kidneys were very slight. They were scarcely at all enlarged. The cortical substance was pale, rigid and breakable. The pyramids were reddened. The left heart was enlarged and its walls thickened. The cell multiplication in the larger blood-vessels of the kidney was slight, though there appeared in the neighborhood of numerous glomeruli wide zones of mononuclear round cells. The glomeruli themselves were unusually rich in cells, and they filled the capsule completely. The epithelial cells of the capsule itself were multiplied and granulation tissue was found between it and the tufts. Numerous conical infarcts were found pointing from the surface of the kidney. These were composed of cells, degenerated and lifeless, and inclosed by a granulation border. From the kidney and spleen a pure culture of the streptococcus was found, while from the pleuritic exudate was cultivated a lance-shaped capsule bacterium. From the lungs there was also raised a third kind of bacteria. It grew on the surface and in the depth of the agar as a golden yellow point, and it was proved non-pathogenic.

7. A seven-year-old boy was attacked with a hæmorrhagic tonsillitis, which soon took on a diphtheritic character eleven days before his death. In the submaxillary region a tumor as large as a hen's egg developed which suppurated three days before his death. The surrounding tissues were filled with a phlegmonous exudate. At the post mortem the abscess and phlegmon in the submaxillary region was found filled with ichorous pus. The blood-vessels in this region, especially the veins were filled with infected thrombi hæmorrhagic infarcts were found in the lungs and spleen. The latter organ was greatly enlarged and softened. Suppurative peritonitis was present, and the kidneys were doubled in volume. The capsule was stripped off with difficulty, and left a smooth surface with here and there depressions, evidently resulting from exposed foci. The

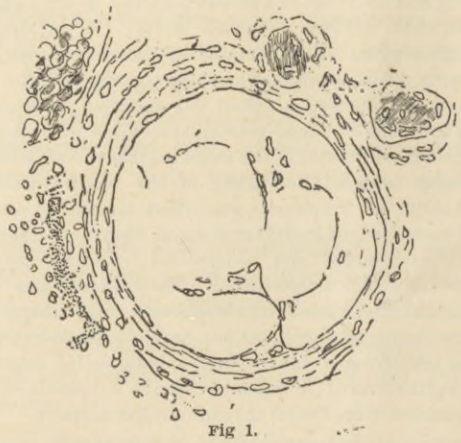

Fig 1.

Fig. 1. From the amyloid kidney of case 3. Drawn from the colored engraving of Babes. In the centre is seen the glomerulus with the amyloid tuft and thickened capsule. In the upper left-hand corner is a portion of an enlarged vein. In the upper right-hand corner are two urinary tubules, with the thickened walls. In the lower left-hand corner and extending upward are seen masses of streptococci filling a little blood-vessel, the walls of which are fast becoming granulation tissue.

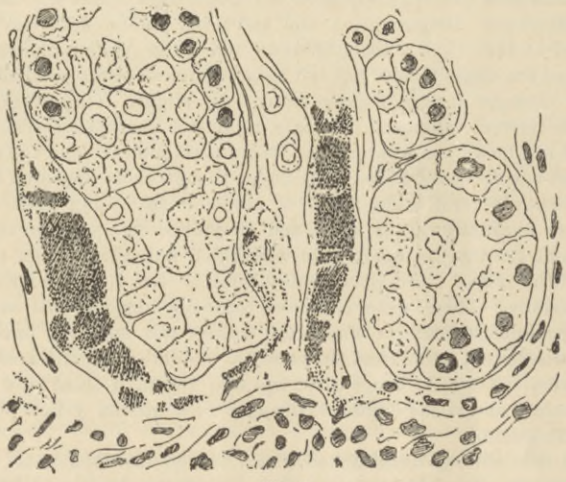

Fig. 2.

Fig. 2. From the colored drawing of Babes. Case 7. From a case of post scarlatinal nephritis. In the centre and on the left-hand side of the drawing are seen two connecting blood-vessels filled with streptococci. It will be noticed that the epithelium of the urinary tubules in the region of the occluded vessels is lifeless, the nuclei taking no stain, while a little farther away the nuclei are intensely stained. In the lower part of the figure multiplication of the connective tissue is noticed.

cortical substance was yellowish-white, markedly injected in places and very much thickened. It was succulent and friable. The pyramids were livid, and appeared whipped out at the base. The larger blood vessels of the kidney were surrounded with a thick mantle of granulation tissue, for the most part composed of polynuclear cells. In the interior of the large veins were found masses of streptococci attached to the wall. In the small blood-vessels, especially in the medullary substance, they filled the lumen completely (See Fig. 2). Where the blood vessels were filled with red corpuscles, the streptococci could be seen reaching forward in long chains. In the region of these foci the epithelium of the urinary canal was coagulated and the nuclei had disappeared. In the interior of Bowman's capsule, as well as in many of the urinary canals, were found blue hyaline masses. The epithelium was everywhere swelled and fatty degenerated. Between the urinary canals there was frequently observed a rich proliferation of the connective tissue.

From the infiltrated submaxillary tissue a white mouse and a guinea pig were inoculated. Both died with all the symptoms of sepsis, the mouse after one and the guinea pig after ten days. Another mouse inoculated from the infected mouse also died on the next day. From the internal organs of the latter animal a pure culture of the streptococcus was cultivated. A direct culture from the infarcts in the spleen, from the submaxillary phlegmon, from the pleuritic exudate and from the kidney gave a pure culture of the streptococcus Besides the streptococcus there was also found in the suppurated pleuritic exudate a micrococcus in the form tetrads without capsules. These were stained by the method of Gram. They were about seven to eight-tenths micromillimeters in diameter and grew in thin flat flakes on the surface of the agar and gelatine. Mice inoculated with them died in from two to four days with septic symptoms.

Animals inoculated with the streptococci taken from this case by means of a platinum needle presented reddening and oedema in the region of the inoculation. Mice died two to six days after inoculation, with septic symptoms, while guinea pigs died in from two to six days, with an inflammatory oedema spreading out from the inoculated ear. At the post-mortem of these animals the spleen was always found greatly enlarged and there was a serous or fibrinous exudate in the serous cavities. The streptococcus retained its pathogenic action for six generations or for two months and a half while later cultures produced only local inflammation and rarely resulted in the death of the animals inoculated. A single other culture was continuously planted for two years and was found as virulent as ever at the end of that time.

I should like also to call attention to an article by Raskin in a recent number of the *Centralblatt fuer Bakteriologie und Parasitenkunde.**

She prefaces her remarks by calling attention to the investigations of Heubner, Litten, Croocke, Henoch, Burkhardt-Merian, Virchow, Friedlander, Bokai Babes and others. She points out the uniform testimony of all these investigators as to the presence of the streptococcus in the pathological products found in connection with scarlet fever. She calls attention also to the investigations of Klein and Babes and considers their conclusions at length. Both these authors found the streptococci in the blood of scarlet fever patients and considered them the cause of the disease. The researches of Klein and his school were familiar to all my readers. Raskin says that from a theoretical point of view the streptococcus infection must either be secondary to scarlet fever and in no casual relation to it or it is the ætiological factor of the disease. Her own researches would seem to demonstrate the former proposition.

*Klinsche experimentelle Untersuchungen ueber Secundar-infection bei Scharlach, Von Dr. Marie Raskin in St. Petersburg. *Centralblatt fuer Bakteriologie und Parasitenkunde.* V. Band. No. 13 and No. 14 March 28th, 1889.

She has examined in all ninety-two cases of scarlet fever. Thirty-one of these presented the following complications: Seven cases, suppurative lymph adenitis; four cases, diphtheria of the pharynx; one case, laryngeal diphtheria with broncho-pneumonia; two cases, suppurative joint inflammation; one case, serous joint inflammation; one case, fibrinous pleurisy; four cases, pyæmia; three cases, septicæmia; seven cases, otitis media—one of which was complicated with facial erysipelas. In twenty-three cases the blood and pus was examined microscopically and by cultures. In those cases that ended fatally sections of the internal organs were examined. In twenty-eight cases the scales, and in six the skin, and in sixty-four the blood alone was examined. All of these examinations were conducted with the strictest attention to the possibilities of air and contact infection.

Raskin comes to the following conclusions from her clinical and experimental researches:—

1. The malignant complications of scarlet fever, viz, suppurative lymphangitis, purulent otitis, suppurative synovitis, broncho-pneumonia, pleuritis, pyæmia and septicæmia and perhaps also diphtheria and serous synovitis, are produced by secondary infection with a streptococcus; and, moreover, other bacteria also may take part in the production of some of these processes; for example, the pyogenic staphylococci in otitis, the *Micrococcus pyogenes tenuis* in pyæmia, and a septic bacillus in septicæmia.

2. The streptococci enter the body through the primarially inflamed fauces; they spread by way of the lymph-channels and are thence poured into the blood streams.

3. When the streptococci are once in the blood, three possibilities remain to be considered: a. They may disappear without any other effect than a more or less pronounced modification of the temperature. b. They may multiply rapidly in all parts of the body and produce death by general septic infection. c. Or, what is more frequent, they may produce death by pyæmia.

4. The streptococcus which is found associated with scarlet fever, appears to be a variety of the well-known *Streptococcus pyogenes or erysipelatis.*

5. It stands in no casual relation to scarlet fever.

These conclusions are perfectly in accord with my own ideas published in the February and March numbers of The North American Practitioner, and in connection with the investigations of Babes they furnish all the evidence necessary to the demonstration of every one of the theorems laid down in that essay.

The recently published researches of Prudden and Northrup on the ætiology of diphtheria* gain a new significance when considered in connection with the subject of secondary mixed infection. Although the article is fresh in the minds of all my readers, I hope I may be pardoned in giving a very brief outline of the work and then be allowed to suggest a possible reconciliation with other well established facts.

In all but two out of twenty-four cases of diphtheria examined, a streptococcus was found in large numbers in the pseudo-membrane. In most of the cases where examination was made of the kidneys, spleen

*On the Etiology of Diphtheria, an Experimental Study, by T. Mitchell Prudden, M. D., Director of the Laboratory of the Alumni Association of the College of Physicians and Surgeons, New York. *The American Journal of the Medical Sciences*, April and May, 1889.

and liver, a pure culture of the same streptococcus was raised. In the examination of the throats of thirty-one well and sick children not affected with diphtheria, only twice was the streptococcus found and then in the scrapings from the throats of children suffering from scarlet fever. From the scrapings from the throats of twenty-four healthy children, not a colony of streptococci. In only two cases of diphtheria, Nos. XVI and XVII, were no streptococci found in the pseudo-membrane. The author would explain this either by imperfect observation or on the supposition that these were cases of "croup." While the streptococci were usually present in enormous numbers in the pseudo-membrane and the surrounding tissues, they were found only sparingly in the viscera. "This condition of affairs, taken together with early severe symptoms of systemic infection and the lesions of parenchymatous degeneration of the viscera, especially the kidneys, which are apt to occur in diphtheria, would seem to indicate that the systemic changes are due to the absorption of some soluble poison (ptomaine) produced where the streptococci are most actively growing, namely, at the seat of the local lesion, or possibly, as will be seen later in the lungs." (l. c. May, p. 459). Prudden concludes that the streptococcus is the essential ætiological factor in diphtheria and names it *Streptococcus diphtheriæ.*

To begin with, the entity of diphtheria is not established. The very fact that it is so destructive of life would point to its facultative origin. It is an axiom that a destructive *obligate* parasitism cannot exist for any length of time where the means of localization are not greatly limited. If we assume that diphtheria is a distinct entity and an acute infectious disease of man, and therefore an obligate parasite of man, we must cut off from its essential features all those destructive complications which make it such a terror to every medical man and parent. Then true uncomplicated diphtheria is a simple and non-destructive disease, which is malignant only as there is added to it the secondary infections which are so dreadfully frequent in other cases under the surroundings of modern civilization. Should such a demonstration be made by future researches, many facts would be brought into concord, viz., various manifestations of the disease in different places and at different times in the same place; the discovery of different forms of microbes by different investigators, the lack of coincidence in the appearance of the streptococci in the blood, and the symptoms of systemic infection; the appearance of the same or a similar streptococcus in the secondary infections after scarlet fever, measles and mumps.

Nothing has been said as to the reliability of the work of Dr. Prudden. It bears intrinsic evidence of its thoroughness and conscientious care. It is very difficult for us to appreciate the amount of labor these researches have required. It is a matter of true courage to deal daily with poisons which are not to be compared with the most

deadly chemicals. Our gratitude is the least we can offer such devotion. The appearance of the streptococci, under the circumstances mentioned, is not to be doubted for a moment. The demonstration is adequate. Only one thing would it be possible to oppose, namely, the conclusion.

It seems to me possible that the true ætiological factor of diphtheria (if such an acute infectious disease is extant) is a parasite which will not grow on any artificial nutrient material. The bacteria so far found in the false membrane, and in different organs of the body, are saprophytic microbes which have the power of becoming pathogenic only when the primary invasion has prepared a way in a point of diminished resistance. This, I believe, is the role of the streptococcus which Prudden has found so uniformally. If this is not the case we are brought face to face with the fact that streptococci, which cannot be distinguished from each other by any known morphological, culture or staining methods, or by inoculation on animals, produce in one case suppuration (*Streptococcus pyogenes*), in another erysipelas without suppuration (*S. erysipelatis*), and in another, diphtheria (*S. diphtheriæ*).

This brief discusssion points to a time when all our resources will be directed toward securing as efficient antiseptic conditions in medical cases as we are able to promise to-day in surgery and obstetrics.

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