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THE HORMONAL TREATMENT

OF

GONORRHEAL VULVOVAGINITIS.

James M. Brown.

A Thesis submitted to the Faculty
of the College of Medicine, in
partial fulfillment of the
requirements for the Degree of
Doctor of Medicine.

Omaha, Nebraska, April 2, 1937.

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Introduction.

When one regards the importance of vulvovaginitis in children as a disabling and distressing condition, one is struck by the remarkably scant and incomplete attention this disease has received in the literature. Quite recently, however, added impetus was given to the more intensive study of the problem by the introduction of a new and radical method of therapy, which in the enthusiasm of the first reports on its clinical application and disease response, promised to be an approach to the therapeutic control or possibly the cure of this disease.

No greater calamity can befall a household, than the wholesale infection of the female children, with the gonococcus. That such accidents occur too frequently is clear to most workers engaged in dispensary practice. It is true that epidemics occur with greater frequency in institutions caring for large numbers of female children, but widespread infection occurs in homes of families who are ignorant of its manner of introduction, who are astounded by the medical man's apparrent inability to adequately cope with the disease and who eventually are ready to spend anything to be rid of the scourge which threatens to blight the youthful lives of their offspring.

Yet the medical profession as a whole, until recently, has failed to treat the condition of gonorrheal vulvovaginitis as a serious menace to the health of our children. Indeed it is a disease which has been too long neglected by the health administrator, the pediatrician, the gynecologist, the venereologist and the general practitioner. This, of course, is readily understood when one reads the discouraging reports of attempted therapy. Up to the present time, all methods of therapy available to the profession, were but crude attempts at the control of a disease condition, which had heretofore resisted all types of therapy. The true concept of the disease was, for the most part, lacking, or at least, poorly understood by many clinicians. Their therapy was directed to the topical displacement of the organism which, characteristically, was not a surface grower.

Today, however, marks a new era in the treatment of this resistant disease. With the introduction of hormonal therapy to the profession and the subsequent experimentation, which has, to a large extent, placed it within reach of the general practitioner, the management of the disease promises to be a simpler and more logical procedure than had heretofore been experienced. Today the literature is replete with glowing reports of the successful management of the disease by the application of this

new type of therapy.

This subject was not chosen for discussion because the type of treatment is new nor because today, hormonal therapy is the vogue, but because the disease has, for so long a time, been poorly managed and understood by the major portion of the medical world. It is a problem which will be met with in the practice of medicine, by all who choose a general practice and by a few of those entering specialities. Its appeal lies in the fact that it is a disease attacking innocent children who, usually, are not responsible for their affliction. These children certainly are entitled to the best therapy obtainable.

It is hoped that the subject matter is treated in such a way that the casual reader may enjoy it, the interested reader may profit by it and the learned reader may agree with it. It is the expressed wish of this author, that practical application of the contents of this paper may be made.

Definition.

Gonorrheal Vulvovaginitis is an acute or chronic inflammatory disease of the lower genital tract, occurring in female children, who have not reached the age of puberty, caused by the gonococcus and characterized by vaginal discharge.

According to Williams (1), the term vulvovaginitis, is inadequate. He says, " The term vulvovaginitis is neither accurate nor sufficiently descriptive, for in mild cases of vulvitis the vagina is rarely, at least markedly involved, while in the prolonged, complicated cases, the many lesions to be met are not sufficeintly covered." Other authors have suggested that the term vulvovaginitis, be reserved for localized affections of the vulva and vagina, while the disease seen in the female infant caused by the gonococcus, be designated as gonorrhea puellarum.

Whatever the arguments be in regard to the name of the disease, it is characteristically defined as being limited to the lower genital tract of female children who have not yet reached puberty. This factor is important in the conception of this condition and, as will be shown later, constitutes the basis for estrogenic therapy.

History.

Gonorrhea is one of the oldest diseases known to man though the exact period at which gonorrhea began to affect mankind is not definitely established. It was a well known and prevalent disease among even the most remote civilizations. In the ancient Hebrew race, it was a recognized scourge. Reference to a condition, now interpeted to have been gonorrhea, is made in the book of Leviticus XV,ii and iii, which was written about 1400 years before the coming of Christ. " Speak unto the children of Israel and say unto them, when any man hath a running issue of his flesh, because of his issue, he is unclean. "

In the classical writings of such men as Hippocrates, Aristotle, Seneca, Plato and others, which appeared 300 years before Christ, there are numerous references to this condition. From the many descriptions contained in the historic writings of the Egyptians, it is quite evident that they too, were familiar with the disease. The prolific writings of Celsus support the fact that the disease was common in ancient Rome. Posedonius, writing in the year 70 B. C. notes of Cleopatra, (2) that she had published articles on the diseases of women, included among which, is a beautiful description of gonorrhea in the female.

The true nature of the affliction, however, was not suspected until the writings of Avicenna appeared in the tenth century. At this time, it was suggested, by that writer, that the disease was of an inflammatory nature. Following this first inkling as to the pathological character of the disease, there are not many references to gonorrhea until about 1500 A. D. though Maimon, in 1240, recognized the difference between seminal fluid and gonorrheal discharges. During this passage of time, gonorrhea had become confused with syphilis. Even the great Paracelsus was laboring under the popular misconception of the disease, for in 1530, he enunciated his doctrine that gonorrhea was the initial symptom of syphilis. The roots of this flowering misconception were more firmly implanted in the minds of the profession, by the work of John Hunter which appeared in 1770. At this time that illustrious investigator began an experiment, which was to forever end the existing controversy. He inocculated himself with pus from a case of acute gonorrhea. Unknown to him, the patient likewise was a syphilitic. (3). Four or five days following the innoculation, Hunter developed gonorrhea and eventually a chancre. From this, supposedly scientific experiment, he erroneously concluded that the "poison" for both diseases, was the same.

Following this, Benjamin Bell, who had viewed the experiment with some skepticism, and who at no time, had been firmly convinced that the two conditions were different manifestations of the same disease, began an investigation of his own. He innoculated two of his students, one with the pus from a known case of gonorrhea, the other with material from a chancre. Fortunately the test cases were pure cases of the two diseases. The students subsequently developed the disease to which he had been subjected. This is the first recorded evidence of the duality of the disease.

The final evidence was soon collected, when Ricord, in the early part of the nineteenth century, following the researches of Bessereau, commenced the work which resulted in complete and unmistakable proof that the two diseases were distinct and seperate, clinical entities. Bacteriological proof was wanting until Neisser of Breslau, (1879), discovered and demonstrated microscopically, the organism producing the disease. He called the bacterium, the gonococcus, and gave the disease the name Gonorrhea.

Specific reference to gonorrheal vulvovaginitis of children is not definite in the older literature, but in a review of the aspects of gonorrheal therapy it at once becomes evident that the condition was recognized. As early

as the fourteenth century the School of Paracelsus struggled with the problem of adequate therapy in the treatment of vulvovaginitis, making use of local applications of such medicaments as antimony, silver and arsenic. Hahnemann (4), probably realizing the low percentage of cures effected by this, or for that matter, any treatment, suggested that the disease, if left alone, might eventually show spontaneous cure.

Almost all of the methods of treatment, having their inception in the middle ages and continuing down to the present time, consisted of local applications of various forms, with few exceptions of occassional attempts at systemic therapy, such as oral administration of mercury and chalk in conjunction with local treatment of the same compounds, employed by Simpson (5) in 1850, and a silver compound introduced and advocated by Carmichael and Wallace (6) in the latter part of the nineteenth century. Cleansing douches and tampons as a sole method were proposed and employed as were ablutions of milk and water. Silver nitrate and other silver preparations admixed with different bases found favor with some of the profession. For the most part, however, the local application of antiseptic preparations were advised and used including such medicaments as mercurial compounds, salicylic acid, iodoform packs and varying strengths of potassium permanganate solutions.

Modern methods of therapy continued much along these same lines excepting more stress was placed on such secondary factors of therapy as rest in bed, hygeine and diet, with the free intake of fluids. Among other local measures employed were the application of protargin in mild solution as advised by Traussig (7), the instillation of hydrogen peroxide solution followed by the injection of yellow oxide of mercury, as employed by Millstone (8), the instillation of Dakin's solution in olive oil, as advocated by Norris and Mikelberg (9), and the injection of ointment of mercurochrome as suggested by Dorne and Stein (10).

In comparatively recent times, new methods of therapeutic approach made their appearance. Local injections of cow's milk were used by Hagen (11), and specific remidies as autoserums, intravenous gonococcal vaccines, picric acid, acriflavine and methylene blue were advocated by Culver (12).

Physical methods of therapy next came into vogue, Walther and Peacock (13), treating thirty-eight cases with diathermy alone. Antiseptics of the aromatic series, such as oil of santal, capaiba, and hexamethylamine tetramine, preferrably by mouth were employed by Hinman (14).

What measure of success attended the use of these variously named methods of therapy, in the hands of many physicians, can best be judged by the fact that further efforts were continued by a host of other investigators in

the last decade. Sanitary methods exclusively, as douches of sterilized water, were considered by von Pourtales (15) as responsible for his success in controlling the disease. Many of the local methods heretofore described, in modified form, often with the use of the same or pharmacologically similar substances, were reported. Combinations of these various methods were likewise employed with but doubtful success.

We hear little of the reasons advanced to account for the failure of response of these variations in therapy. It was not until quite recently, when endocrine therapy as a whole, had acquired a practical and simple basis, that attention was focused on the possibilities of its application to diseases of the genital tract. Extensive animal experimentation was undertaken and from this grew definite and important theories, among them being that the vaginal tract had a specific response to various hormonal substances. In 1928, Allen (16), working with sexually immature, female monkeys, found that the character of the epithelial lining of the vaginal tract could be altered by means of estrogenic substances. This change was demonstrated as consisting of an increase in the number of epithelial layers. Vaginal smears taken in conjunction with these experiments, showed a proportional increase in the partly or completely cornified epithelial cells.

Lewis (17) ventured still further, choosing human subjects for experimentation. Drawing inferences from Allen's experimental data, he reasoned that if the character of the epithelial lining of the immature vagina could be temporarily altered to resemble the thicker structure of the adult type, the habitat of the invading microorganisms might be made unfavorable to their growth. He argued, that if the transformation could be successfully effected in the case of the immature monkeys, it was quite within reason to suppose that it could similarly be effected in a child. He based his conclusions on certain well established facts viz. the lining membrane of the childs vagina is thin and delicate while that of an adult is thick and cornified, and the infecting organisms multiply only on the thin, delicate membrane, eventually penetrating within the cellular interstices and subepithalial space.

Thus, a new method of therapy, estrogenic therapy, was introduced in the control of gonorrheal vulvovaginitis of children.

Age, Incidence and Transmission.

This particular disease is of world wide prevalence. It affect the poor and squalid, living in crowded city quarters more than the upper classes, though class distinction is no barrier. It is primarily a disease of groups and

is therefore seen more commonly in institutions harboring female children of the age group usually affected. Sporadic cases are not, however, infrequent and in a general office practice, one is liable to see occassional cases of this disease.

The period of greatest susceptibility has been stated to be the first five years of life. Writers in this country are inclined to place the age of greatest incidence at a later date, when the child first goes to school. Stalkner (18) states that in his series of cases, six years seemed to be the average age at which the disease was contracted. In explanation of this he further states that it is at this time that children usually start to school, attend crowded assemblies such as the theater, and use community toilets. He says that it is at this time also, that little girls are too small to seat themselves easily and their vulvas become contaminated from the toilet seat. Irrespective of isolated claims as to the greatest age incidence, the disease can occur at any age from birth up to the time of puberty.

Birth infections, vulvovaginitis neonatorum, are not nearly as frequent as gonorrheal ophthalmia neonatorum, but cases have been reported by Epstein and others. These rather infrequent birth infections of the vulva, are said to occur oftener in breech presentations and this appears quite logical, for in this method of delivery, the infant's

genital apparatus is directly exposed to contamination from a gonorrheal mother, which is not necessarily the case if the presenting part were an occiput.

The disease is seen quite frequently in epidemic form in such institutions as hospitals, orphanages and girls schools where closely allied domicillary association is a necessity.

The transmission of the disease is of utmost importance for in this condition, if in no other, fomites are real offenders. By far, the most common mode of transmission is by indirect contact. This is in contradistinction to the accepted mode of transmission of adult infections. Therefore in the true sense of the word, gonorrheal vulvovaginitis, is not a venereal disease. Direct contact due to sex violence, and in cases of precocious sex indulgence in older children, constitute but a minor percentage of cases. However cases due to sex crimes do occur principally because of the erroneous idea, among many of the lower classes, that gonorrhea may be cured by sexual contact with a virgin.

The sporadic cases seen in office practice, are usually traceable to some infected, adult member of the household, the child being contaminated by such articles as bed linen, wash cloths, towels and other common domestic necessities. The joint occupancy of one bed by a child

and an infected adult, is held to be one of the greatest offenders in the spread of this disease. This is readily explained by the ease of vulvar contamination in such a situation, by recent vaginal discharge in which the organisms have had but little time to be exposed to the deleterious effects of drying and thermal changes. Under these conditions the offending microorganisms might be as advantageously placed as had they been purposely introduced by means of a platnium loop. In hospitals and similar institutions caring for female infants, the transmission of the disease to epidemic proportions has been laid to the attending nurses hands, thermometers, bed pans, enema points, catheters, bath tubs, toilet seats, wash cloths and in the case of the smaller children to diapers. A single admission of an infected individual to an institution may later prove to be the source of an extremely virulent infection. Welde (19) in his studies of the transmission of the disease, concluded that flies occassionally, could transmit the infection. This, however, is not considered a very plausible source because of the effect of drying on the gonococcus. An interesting source of infection is described by one German author. He claims that the public bath was responsible for an epidemic wherein 236 girls were

infected with gonorrhea. Stamm (20) reports the experience of the Jewish Maternity Hospital in Philadelphia, in which sixty-eight infants delivered in that institution became infected. After endless search for the possible source of infection, a diseased laundress was found to be the offender. In this instance the transmission was unquestionably traced to the bed linens. This particular epidemic closed this hospital for a number of months and cost the institution almost $20,000.

The exanthemata definitely predispose to genital tract infection, in girls. It has been noted that some children contract vulvovaginitis, for the first time, during the attack of an exanthematous disease. In other cases, a latent infection becomes manifest during an acute eruptive disease. In support of this Stein (21) reports a case of gonorrheal vulvovaginitis following chicken-pox and another following measles.

Prophylaxis.

This aspect of the problem must appeal to the health administrator rather than to the clinician, though in the handling of the individual case, the clinician, by his instruction and advice, must necessarily play a part. It is the wish of most men dealing with this disease, to make the condition of gonorrheal vulvovaginitis, reportable to the proper health author-

ities. They firmly believe the elimination of the disease will not be accomplished until it is "brought out in the open."

The control of isolated cases in the home presents a very difficult problem. The source of the infection is difficult and often impossible to find, and preventative measures prove equally baffling.

Traussig (7) presents some recommendations for prevention which briefly summarized are:

1. The routine instillation of a drop of 2% silver nitrate solution in the vestibulum vaginae of all new born girls whose mothers present evidence of a gonorrheal infection.

2. Making gonorrheal vulvovaginitis in children, a disease notifiable to the responsible health authorities.

3. Instruction of parents of infected children, through the health visitor, regarding preventative methods to limit the infection. Such methods would include the use of seperate towels and wash cloths, sleeping in seperate beds, care as to a thorough cleaning of contaminated clothing and insistence on the infected child refraining from using the common lavatory.

4. Investigation, by the health visitor, as to

the probable origin of the infection in each case, with the view to excluding this factor from contaminating other children in the same home.

5. The adoption of the U-shaped toilet seat, with low bowl, and other precautionary measures to prevent the spread of infection through public lavatories, in schools, playgrounds, etc.

In elaboration of this last named recommendation Traussig says, " I consider this last named suggestion the most important of all and there is no valid reason why it could not, to a large measure, be put into operation at once. Paper coverings for lavatory seats, have been used for cleanliness in some of the large hotels, and their employment in public places, such as schools, playgrounds and so forth, would diminish the chance of infection. As, however, children could not be relied upon to apply such papers properly, it would be safer to use the U-shaped seat in addition. The heighth of the bowl should not be over eight inches, where the lavatory is to be used by children of school age. The presence of an attendant in the school lavatory, especially during recess, would add materially in the discovery of girls having a discharge, in the proper use of the paper covers and in the general cleanliness of the lavatory."

Since Traussig made these recommendations, some of them have been put into effect with surprisingly good results. Today the U-shaped lavatory seat is practically universal especially in schools catering to pupils in the age group where chance infection with the gonococcus will produce this disease. Puplic toilets, are today equipped with this type of lavatory cover and the incidence of gonorrheal vulvovaginitis is decreasing somewhat, though there yet is a too great incidence of the disease.

As the epidemic form of the disease, is seen, as has been mentioned elsewhere in this paper, in institutions caring for large numbers of female children in the pre-pubertal age, these institutions are taking precautionary measures to exclude the possibility of future epidemics. Such precautionary measures are worthy of some note in a paper such as this and summarized are as follows;

1. The examination of vaginal smears of all female children before admission. If these smears contain gonococci, admission is refused.

2. Rigid isolation of all cases diagnosed after admission. This of course, includes seperate lavatory accomodations, utensils, clothing, toilet apparatus, etc.

3. The detailing of special nurses to care for all cases infected with the genococci. These nurses do not

handle any but the patients with this disease.

Since the wholesale adoption of these more strenuous methods of control, the incidence of institutional epidemics have shown a definite decrease. There is much, yet to be done in this matter of prophylaxis. Like so many of our other disease, the incidence of gonorrheal vulvovaginitis, can be reduced to a minimum, with but little concentrated effort.

Etiology and Bacteriology.

That the gonococcus is responsible for the disease called vulvovaginitis is readily and easily demonstrated. The gonococcus can be recovered in from ten to fifty percent of all cases in vaginal smears, and in many cases in pure culture. This is according to the findings of Ruys (22) who reports the etiology of this condition.

The bacteriology of vulvovaginitis is quite varied, however. The gonococcus is usually seen in the diplococcus form, the pairs being characteristically flattened along the surfaces facing each other. This gives the cocci a peculiar coffee-bean or biscuit shape. Stained directly from acute cases of vulvovaginitis, the microorganisms are found both intra and extracellularly, a large number of them crowded within the leucocytes. They are never found within the nucleus. The intracellular position, which is of considerable diagnostic importance, is lost,

to a great extent, in the secretions from chronic cases of the disease.

The gonococcus is non-motile and does not form spores. It stains readily with the analine dyes in aqueous solution. Gram's method of staining, however, is the only one of differential value, the gonococcus being Gram negative in carefully prepared smears. In exudates from the vagina, the morphological picture is not so reliable, owing to the presence, in this region, of other gram negative cocci. In a like manner, negative morphological examination in chronic vaginal discharges, cannot be relied upon, owing to the scarcity of the gonococci, hence thorough cultural investigation is indicated, if a positive diagnosis is desired. In those cases where the time element does not permit the study of the causative agent in culture, the clinical symptoms presented should always lead to a diagnosis of gonorrheal involvement and proper therapeutic steps taken on the basis of such a diagnosis. It is infinitely better to effect a cure of a non-specific vaginitis with specific therapy, than to neglect a gonorrheal involvement because of inadequate diagnosis.

The gonococcus is one of the most difficult of organisms to cultivate. Bumm (23) obtained the first growth of this bacterium on human blood serum which had been previously heated to partial coagulation. The medium most

commonly employed at the present time, consists of a mixture of two or three parts, meat infusion agar, with one part uncoagulated human ascitic fluid, hydrocele fluid or blood serum. One percent of glucose may be added which gives slightly better growth, according to some investigators. The gonococcus will develop sparsely under anaerobic conditions, but it has a marked preference for aerobiosis. Clinically, at least, the gonococcus, by its predilection for areas air free or nearly so, exhibits the quality of a facultative anaerobe. This fact is borne out by the investigations of Park and Williams (24) and Ruediger (25).

As in the case of so many other organisms, it has been found that the gram-negative diplococci, which are responsible for the production of the clinical condition, referred to as vulvovaginitis, are not a single type, but must be regarded as representing a group, including many closely allied forms or related groups, all of which may be seperated antigenically. Such subgrouping of species formerly regarded as homogenous has been a very natural development of the more intensive study of serum reactions incident to diagnostic agglutination and complement-fixation, and to the control of specific therapy. Torrey (26) and Teague and Torrey (27) have shown that the gonococcus group is not homologous, but that agglutination and

agglutinin absorption, divided it into at least, three seperate subgroups. Watabiki (28) made a similar study of the gonococcus group, and studying a limited number of strains, confirmed the heterogenous nature of the group by referring to them as "comparative but not distinctive differences between individual strains." In 1915, Louise Pearce (29) made a comparison between gonococci isolated from adult males and from cases of vulvovaginitis of children. She came to the conclusion that strains from these two sources, constituted fairly definite, serologically, distinct groups, that there was, at least, a relative distinction between the two groups. Hermanies (30) studied eighty-five strains of gonococci from various sources and concluded that gonococci fall into distinct types with little relationship to each other. His eighty-five strains fell into six fairly distinct groups. The work of Torrey (31) failed to support the contention presented by Pearce, that gonococci producing vulvovaginitis were different from those producing the infection in the adult. Stein (32) and others report that they did not find any marked differences, serologically, between gonococci recovered by culture in their series, and the various stock strains of gonococci, against which the reactions were made. On the other hand Bonarscu (33), carrying out the reactions of agglutination, precipitation

and deviation of complement, using serums from rabbits innoculated with gonococci, isolated from female children and adult males, against strains of gonococci of different origin, brought to light a difference in behavior in the gonococcus of the adult from that of the children. Though this problem is not as yet settled, from an academic point of view, clinically it would seem proven that the gonococcus recovered from the majority of cases of vulvitis in children, represents a less virulent type than the gonococcus of adults.

Histology and Histopathology.

Before any attempt is made at the comprehension of estrogenic therapy, in its application to genital tract diseases, it is quite essential that certain differences, occurring between the immature female genital tract and that of the adult, be clearly understood. We are more concerned with the histological differences existing in the lining membrane of the lower genital tract, rather than the gross anatomical differences existent between the two structures, though, as will be subsequently shown, these differences are of major importance in the prevention of sequellae, which are of rather infrequent occurrence in gonorrheal vulvovaginitis in children.

The two Mullerian ducts of the embryo, lined with

columnar epithelium, fuse to form the Fallopian tubes, uterus, cervix and vagina of the adult. The epithelium of the Fallopian tubes becomes converted to a ciliated, columnar epithelium; that of the body of the uterus, to a low columnar epithelium; that of the cervix, to a non-ciliated, high columnar epithelium and that of the vagina to a squamous type of epithelium. This change in the character of the vaginal epithelium is not due to a direct conversion of the original columnar epithelium, but to a replacement of it by squamous epithelium, growing from below upwards, in the region of the uro-genital membrane. Simple, tubular, glands appear in the endometrium, and compound or racemose glands, in the mucous secreting, cervical epithelium. The vaginal mucosa does not contain any glands. The vaginal aspects of the cervix is covered with squamous epithelium similar to that of the vagina.

This delicate, squamous epithelial lining of the normal child's vagina, is made up of from one to six or eight layers of cells, lying on a distinct basement membrane. There is no apparrent differentiation of these epithelial layers, into zones, as is indicated in the adult type of lining membrane, by an overlying zone of cornified or partly cornified, cells. Certain other differences in the tract, for the most part develop-

mental or anatomical, are believed by Schauffler and Kuhns (34) to be of the utmost importance in regard to the disease vulvovaginitis, in immature female children. These investigators point out the fact that the glands of Skene, while they may be observed, in a rudimentary form, early in development, do not develop characteristics favorable to the growth of the gonococcus, until the approach to puberty is noted. In a like manner, the glands of Bartholin, though present as early as the sixth month of life, do not achieve sufficient complexity to harbor the invading gonococcus, until sexual development is complete, or nearly so. Again the racemose glandular system of the endocervix is quite tardy in developing, frequently being apparrent only as scattered, rudimentary, blunt, glandular, crypts, up to as late as the fifteenth year. In a similar manner, the immature vagina is merely a potential cavity held in a state of constant closure, by its elastic and muscular coats, and replete with stagnant crypts and rugae. Its walls are held tenaceously approximated, in marked contrast to the flattened, gaping vagina of the parous adult.

The conclusions to be gained from these observations are obvious and can be summarized; 1. since the rudimentary glands of Skene and Bartholin of the immature individual offer no harbor of infection for the invading bacteria,

it is not to be expected that infection of any clinical importance will occur, 2. the immature endocervix will practically never be infected by the gonococcus for the simple reason that the cervical glands are not present in a form to provide a substantial habitat for the organisms, and 3. the contracted, cryptiform, rugeose vagina of the immature individual, constitutes virtually an ideal harbor of infection. This last named factor, together with others that will be later discussed, offers a perfectly satisfactory explanation of the occurrence of a primary vaginitis, as the most usual manifestation of these gonorrheal infections in sexually, immature females.

It is common knowlege, that the gonococcus requires for its growth and the development of its pathogenic characteristics, a suitable site of infection. In exposed locations where it is subject to even mild noxious agents, or in competition with almost any other bacteria, the gonococcus becomes impotent and perishes. It is only within the deep stagnant recesses, such as are provided in the glands of Skene and Bartholin or the racemose Nabothian glands of the cervix, or the deep intricate plicae of the Fallopian tubes, that these organisms find their ideal habitat. Accordingly these foci are the common sites of infection in the adult female.

In spite of prevalent misconception to the contrary

the gonococcus is faithful to its bacteriological characteristics in the immature female tract. Its pathogenic action on the genital apparatus of female infants and children is not now believed to be due, as has been urged, to changes in its bacteriologic properties or to the hypothetical lowered resistance of invaded tissues, but to these histological and developmental differences, herein described.

The infectin organisms, do not, as has popularly been supposed, lie on the surface of the vaginal epithelium, but rather penetrate deep beneath the surface covering. Here in the cellular interstices and the subepithelial spaces the invading diplococci find the ideal enviornment for their further growth and development. Here the gonococci, increase in virulence and in number, overcoming eventually, the resistance offered to their continued growth, by the natural defense forces of the immature genital tract, and produce the disease referred to as specific or gonorrheal vulvovaginitis.

Realizing the histological pattern of the female genital apparatus of children, a consideration of the estrogenic response of this structure can be more fully appreciated. The basis for the application of the ovarian follicular hormone, in this condition, lies in the histological response to the substances applied. The estrogenic

materials per se are not gonococcocidal yet with the therapeutic application of these substances, surprising and almost miraculous results are obtained in the majority of cases reported to date. True, in the treatment of cases ofthis disease, with these therapeutic agents, there have been a few cases in which the results have been disappointing, though in the majority of these failures, the fault was in their application rather than a failure to produce the desired histological response.

With the administration of adequate doses of the estrogenic substances certain histological changes, which are readily and clearly demonstrated by biopsy of vaginal mucosa, take place. According to Phillips (35), the upper layers of the vaginal epithelium become cornified and increase in thickness from the normal five layers or thereabouts to as high as thirty or more. There is a pronounced sloughing of this outer cornified layer, the so called functionalis layer. Furthermore there is a tremendous activity demonstrable in the basal cell layer, with numerous mitotic figures appearing in the cell nuclei and a heaping up, of what might be called swollen cells, in the intra epithelial layer, or that zone midway between the functionalis and basalis layers. This sloughing of

the functionalis is demonstrable in vaginal smears taken shortly after the application of these substances. Ordinarily vaginal smears of an acute gonorrheal vulvovaginitis will show only the typical gram-negative, intracellular diplococci, with many polymorphonuclear leucocytes and considerable cellular debris but no cornified or typical mucosa cells. The smears taken after the administration of an adequate amount of the estrogenic hormones are entirely different. Instead of an overwhelming majority of polymorphs, the smears now contain an abundance of cornified or partly cornified epithelial cells. The diplococci are not now as readily demonstrated as in the previous smears. This phenomenon of the sloughing of the functionalis layer is referred to as the " estrogenic response" and is an indication of the adequacy of this type of therapy. It is thought that the sloughing of the epithelium carries with it the infecting gonococci which are imbedded in the uppermost layers of the epithelium. Furthermore by keeping the reaction up over a moderate period of time (several months), one hopes to create a more resistant vaginal wall and thereby prevent reinfection or relapse.

Recent investigation into the histological response of immature vaginal mucosa to estrogenic hormones, conduct-

ed by Lewis (36), seem to indicate that the mucosa after treatment does not, as was previously thought, resemble the epithelial lining of the adult female, but rather the treated mucosa resembles that of a newborn infant. At birth the vaginal mucosa shows a basal layer of compact cells with nuclei which take a deep stain in prepared microscopical sections. This cell layer is thrown into folds and varies in depth throughout the length of the vaginal canal. Superimposed upon it we find a remarkable series of vacuolated cells which often contain nuclei. Mitotic figures are frequent in this layer. This zone consists of vacuolated cells, twenty to thirty or more layers in depth. In some sections it is readily seen that the superficial surface is covered with two or three layers of very delicate, elongated, flattened and nucleated squamous cells. There is this difference between the treated vaginal epithelium and that of the newborn female, in that there has as yet been no definite layer of cornified cells demonstrated in the newborn mucosa. Shortly after birth the vacuolated cell layer desquamates and the epithelial lining takes on the normal structure of the immature female canal heretofore described. That the above changes in the vaginal epithelium of the newborn is due to a substance elaborated by the placenta and

carried by the fetal-maternal circulation to the infant in utero, had been shown by Halban (37) in 1904.

That these changes, which have been described as being due to the hormonal effects on the vaginal lining, were entirely and solely responsible for the splendid results noted with this type of therapy, is probably not true. Indeed it is not the only change wrought by their application and therefore evaluation of individual factors cannot be made unless the entire picture is presented. Lewis and Adler (38), who have done as much or more in the investigation of this problem, recently presented a paper in which they claim to have proven that the alkaline reaction of the normal child's vagina is likewise changed under hormonal therapy and in the opinion of these investigators, this factor has as much to do with the results obtained in this disease control as any other previously mentioned.

Long ago Doderlein called attention to the presence of the bacillus named for him, in the normal vagina, and considered its acid forming properties as responsible for the acid reaction of the secretions of the adult vagina. It was later shown that the acid reaction was due, to a great extent, to the destruction of the superficial, glycogen-containing cells of the lining membrane. In the thin, vaginal mucosa of the child, but little glycogen is

contained in these cells. On the other hand, the superficial cells of the adult vaginal mucosa and of more importance to us, the vaginal mucosa cells of the child adequately treated with the estrogenic substances, are loaded with glycogen. These cells, as a result of bacterial and enzymatic action, produce a markedly acid reaction as they break down. These findings are in keeping with the reports of Cruickshank and others. (39).

Hall and Lewis (40), treated immature female monkeys, hypodermically, with estrogenic substances and found that the vaginal secretions, which are faintly alkaline (pH 7.5 to 8) in the normal animal, became suddenly, strongly acid (pH 5.4 to 5.7) as soon as the vaginal response to the hormone occurred. In normal children, the reactions of the vaginal mucosa are nearly neutral (usually between pH 6.8 and 8.4). When adequately treated with the ovarian follicular hormone, the reaction of the vagina, likewis became acid in character (pH 4.8 to 6). These findings have been confirmed by the researches of Lewis and Weinstein. (41).

As has been mentioned previously in the discussion of the bacterial aspects of the disease, the gonococcus grows best in a faintly alkaline medium (pH 7.2 to 7.6). If the medium is rendered acid very gradually over a period of days or weeks, these organisms will rarely

adapt themselves to a medium as acid as pH 6 to 6.2. Usually the culture dies before this point is reached. With the appearance of the estrogenic reaction in the vaginal mucosa, Lewis (36) has definitely shown that the vaginal reaction become markedly acid, giving readings nearly always below pH 6 and in some instances, giving readings as low as pH 4.5.

This highly acid enviornment is extremely detrimental to the gonococcus which at best is capable of withstanding only slight changes in the acidity of the medium in which it is growing, be it the laboratory test tube or the mucosa of the child's vagina. The eradication of this disease through hormonal attempts of therapy, is due then, not alone to the remarkable changes in the character and thickness of the lining membrane of the normal vagina but is more likely due to the combination of this factor and the disturbance of the acid-base balance of the vaginal mucosa.

Clinical Picture and Diagnosis.

Vulvitis is the main symptom of the disease. The onset is acute and is usually ushered in by a sensation of itching or warm irritation of the vulvar orifice. Redness, heat and swelling are apparrent. The skin in this area is exceedingly delicate and the gonococcus is able to penetrate deeply without much difficulty. The

infrequency of vaginitis in the adult and its great prevalence in children, is most striking and the behavior of the gonococcus in each case varies according to the resistance or receptivity of the vaginal mucous membrane.

The hymen offers no abstruction to upward spread, and the vaginal mucosa, in contrast to that of the adult, is peculiarly susceptible to attack. The lower third of the vagina bears the brunt of the infection and as the case advances the inflammatory process may spread to the fornices or to the vaginal surface of the cervix. The endocervix is seldom affected for the canal is rudimentary and the os is closed. Upward spread to involve the endocervix occurs occassionally, however, in gonorrheal as well as the non-specific types of vaginitis.

The whole mucosa becomes intensely inflammed and is bathed in thick, creamy pus, which overflows and oozes from the vestibule to the exterior. This thick, yellowish discharge is seen covering the labia. The vestibule and hymen are red, inflammed and edematous, while the labia are swollen, tender and glued together. Excoriation of the vulva accompanies a surruonding intertrigo. Suppurating scratches, encrustations, bleeding surfaces of denuded skin areas, superficial ulceration and occassionally condylomata accuminata may be seen on the labia and surround-

ing skin in neglected cases.

The discharge is at first thin and ichorous but later becomes thick, yellowish or greenish-yellow, profuse and offensive. It tends to collect behind the hymen, only the overflow appearing at the vulva. Its flow, therefore, can be often greatly augmented by expulsive efforts on the part of the patient. As time goes on the discharge becomes mucinoid, thin and very scanty. In chronic and frequently in early cases, the mucous membrane appears healthy and non-inflammed, the secretion is mucinous, epithelial and non-purulent, but gonococci can be recovered in culture from secretions which appear negative in smears.

In the majority of cases there is no pronounced discomfort, the first few days. There may be some vesical irritability and frequency of urination the act being accompanied by sensations of burning and stinging. As a result a condition of voluntary retention may follow and be presented as an early symptom. The child complains of a local itching and a feeling of being chafed. On the other hand many cases are symptomless, the child complaining of no local symptoms whatever. In acute cases there may be severe pain between the legs which is aggravated by walking, and later on, purulent excoriations, heat and intense itching, the results of scratching.

Acute inflammatory symptoms usually disappear within twenty-one days, when the discharge becomes scanty, thin and serous in character. At this time symptoms are exceedingly mild and are frequently overlooked. The disease runs a long and tedious course. The rectum shares involvement in the vast majority of cases and as a focus of superinfection, is ideally situated. Indeed it is so rare for the rectum to escape involvement, that rectal implication should, in all probability, be considered a phase of the disease rather than as a complication. Severe constitutional symptoms invariably indicate the onset of metastatic or direct extension complications, but these, fortunately, are rare indeed. The child's general health seldom suffers. The disease characteristically, tends to run a chronic course with frequent relapse the rule. Long gonococcus-free intervals are followed by periods of organismal activity, accompanied by pus production.

This description of the clinical behavior of this disease makes it evident that a diagnosis based on clinical findings alone is liable to be a mistaken diagnosis. The findings in any non-specific vulvovaginitis are similar to those presented, and a differential diagnosis must necessarily include other diagnostic measures. In the diagnosis of an infant leucorrhea it behooves the medical attendant, to make a diagnosis of gonorrheal or non-specific

vulvovaginitis, for, though the treatment might not vary materially, the ultimate handling of the case in any event, is entirely different. Hence the diagnosis becomes increasingly important.

Most men rely on the vaginal smear for the diagnosis of this condition and a report from the laboratory stating the presence of gram negative, intracellular diplococci, morphologically resembling the gonococcus, in a smear is sufficient evidence to substantiate a diagnosis of gonorrheal vulvovaginitis. This ordinarily will serve in the acute cases of the disease but in chronic cases vaginal smears alone are not sufficient, for seldom, if ever, will the diplococci be demonstrated in the slide. Some authors believe that a smear of the cervix and particularly the endocervix is indicated in the long protracted case. This procedure need not necessarily be difficult. With the use of the vaginoscope, the smears are readily obtained. Some sacrifice the hymen for this procedure but in the opinion of many this is not always necessary. For the chronic cases the complement-fixation reaction is of some value, only however, if it is positive but is ofdoubtful value in those cases in which it is negative. Ruys (42), in a recent article claims that the diagnosis should not be based on clinical evidence plus positive smears, alone but that in the

majority of cases cultural methods should be resorted to. She is of the opinion that a far better technique in staining smears than the use of Gram's method is the employment of von Laghems modification of Gram's technique. In her series of 292 cases she could demonstrate the gonococci by means of culture and staining methods, in only fifty-seven cases. From this she infers that perhaps the diagnosis of gonorrheal vulvovaginitis is made too frequently, on too little positive evidence outside of vaginal smears. Clauberg (43) likewise is in agreement with Ruys. From seventy cases, in which the diagnosis of gonorrheal vulvovaginitis had been made, he could not demonstrate, by culture, the gonococcus in any of them. Gradwahl (44), cultivated gonococci in only two of twenty-five cases of clinical gonorrheal infections. However, as it is better to err on the side of too frequent diagnosis of this disease rather than to missthe diagnosis completely, the finding of the typical bacteria is sufficient evidence on which to base a diagnosis. Highly scientific methods of procedure, are not within the reach of every practitioner, hence simpler and perhaps as good methods must be relied upon. In most clinics the smear is considered a proper method of diagnosis.

Treatment.

The estrogenic substances are those which produce estrus directly and not through the stimulation of organs capable of exciting estrus through their activity. They are the active principles of the growing ovarian follicle, though they are found in many of the other tissues of the body, notably the placenta, the amniotic fluid and the urine of pregnant women. There are many other substances capable of producing estrus indirectly through their activating effect on the ovarian follicles of which the active principles of the anterior pituitary lobe, the so-called gonadotropic substances, are the most important. This article, however, is limited to the estrogenic substances alone .

The term, estrogenic substance, has been chosen as a generic term, in preference to the others commonly employed, to avoid any possible misleading implications as to chemical constitution and source of function and to emphasize the fact that such principles produce estrus and not menstruation, which is a different thing.

In a paper such as this, it seems impossible to avoid the use of trade names of the estrogenic substances now available for clinical use. Indeed, unless they are employed, this article might mean little to the average

reader and as it is this author's expressed desire to present, as nearly as possible, a practical and concise treatise on this subject, it seems advisable to include those names which will be met with later in the practice of modern medicine.

The better manufacturers appear to be making an honest effort to supply the profession with substances of genuine estrogenic potency and their laboratories have shown a commendable willingness to cooperate, both with the clinician and the laboratory worker, in the investigation of estrogenic therapy. The following preparations of estrogenic substances are the ones most widely used in this country and include those used in the case reports to be included a little further on in this discussion.

1. Theelin. (P.D. & CO.) An aqueous solution of crystalline theelinof Doisy in 1 cc. ampules of 167 International units.

2. Theelin in Oil. (P.D. & Co.) In 1 cc. ampules with a potency of 1000 International Units.

3. Amniotin. (Squibb). In 1 cc. ampules each containinf either 2000 or 8000 International Units in corn oil.

4. Progynon. (Schering). In 1 cc. ampules of 25 rat units of estrogenic substance in aqueous solution.

5. Progynon. (Schering). In 1 cc. ampules of 10000 or 50000 International units in sesame oil.

The unit of dosage commonly employed in this country is the Allen-Doisy rat unit, defined as the quantity of active principle, divided and given in three injections, at four hour intervals, necessary to induce estrus within three days, as judged by the presence of cornified cells in vaginal smears, in ovariectomized, sexually mature rats of a standard weight. (140 ± 20 Gms.). (45). The International Unit, now coming into use, is that dosage necessary to produce an effect, under identical conditions, equal to that of 0.1 microgram (0.0000001 gm.), of a standard preparation of crystalline theelin. According to a report issued by the League of Nations (46), the International Unit is about one third the Allen-Doisy rat unit.

The problem of individual dosage and the proper administration of these various substances will necessarily confront everyone and as that is not as yet definitely established, an outline of therapy will be included from which individual variations may be made. The treatment of gonorrheal vulvovaginitis is the same whether it be an acute or chronic infection, although it has been noted, and subsequent reports will bear this out, that chronic infections repond more rapidly to this type of hormonal therapy.

The patient should be placed under treatment as soon as a diagnosis has been established. The choice of estrogenic preparations to be used will be left to the individual. The treatment should be continued, with daily administration, until negative vaginal smears are obtained. There are three accepted methods of administration each with its advantages and its limitations. They are hypodermically, orally and vaginally, in supposibories.Oral administration has an obvious advantage in the treatment of children and from all clinical and experimental data, seems to be entirely effective. The accepted, adequate daily dosage is one hundred rat units if the drug is given hypodermically, while about five times this dosage is required if by, oral administration. The vaginal supposirtoies contain about seventy-five rat units and this is adequate if this route of administration is chosen. In addition to the administration of the estrogenic substances, some authors, notably Engel (47) believes that the vaginal canal should be thoroughly cleansed, daily, with any of a number of suitable solutions. He employs a 1:5000 solution of potassium permanganate. This is probably an unnecessary procedure and being odious to most children, is better not done.

The change in the clinical picture is striking,

almost dramatic. From the typical, thick, purulent, flux of an acute gonorrhea to a slight, dry, cheesy, white discharge. Microscopic smears of the vaginal discharges yeild equally striking results in most cases. Before the administration of estrin, the smears are typical of acute gonorrhea, full of pus cells and gonococci. After, even a few days treatment, the pisture is often changed to that of an adult leucorrhea, masses of epithelial cells and gram-positive bacilli of the Doderlein type, with often not a single or gonococcus appearing in the film. The general health of the children under this therapy, is usually not affected. They are prone to gain weight with surprising rapidity. There is often a accompanying swelling of the breasts, and there may be some slight hypertrophy of the labia, but to date there have been no cases of vaginal bleeding reported. The labial swelling is readily reduced by the withdrawal of the estrogenic substances. In Naborro's (48) series of cases some of the children complained of spasmodic pains in the abdomen, radiating from the umbilicus. Reading (49) and Lewis (17) likewise report abdominal pains, associated with slight fever and generalized tenderness of the abdomen, to palpation, following the administration of theelin. This seems to be due to a peritoneal irritation and quickly disappears if the injections are stopped.

Brown (50), has treated several patients afflicted with this disease using theelin. He injected fifty rat units of theelin,daily, intramuscularly in the gluteal or deltoid regions. Vaginal smears were taken every second day. If the smears are negative at the end of ten days, the fifty rat unit dose is continued for one or two weeks more. If the smears are still positive at the end of this time, this dosage is doubled (100 R.U.), and continued daily injections of this new dosage are maintained until five or six consecutive slides have shown no gonococci. In his series of cases, employing this technique, four of the nine cases had negative smears within ten days, eight had negative smears within twenty days and all had negative smears at the end of thirty days. There were no relapses in this group.

Hubermann and Israeloff (51), report their six cases under amniotin therapy. Five of their series received one hundred R.U. hypodermically, three times a week, the sixth received, daily, one hundred and twenty to two hundred R.U. orally. In these cases there were an equal number of acute and chronic cases. The infections of long duration were, clinically and by vaginal smears, cured after receiving a total average of twenty-one injections

or about 2,100 R.U. of amniotin. The three acute cases required longer and more intensive treatment. In these latter the vaginal smears were negative after eight weeks of treatment during which time they received a total average of twenty-seven injections, equivalent to 2,700 R.U. These investigators did not observe any breast or labial hypertrophy nor any uterine hemorrhage.

Nabarro (48), reports a series of twenty cases, ten of whom were subjected to the injection of estrin hypodermically, the others receiving the preparation orally. In the first series the patients received intramuscular injections of menformon, beginning with one hundred R.U. He found no vaginal response under seven hundred and fifty R.U. daily. Three of this series responded to one thousand R.U. daily given over a period of six weeks. Two children in this first group received one massive dose of fifty thousand units of dimenformon. They responded well and became gonococcic negative inone week.
In the second group treated with oral estrin, the results were more uniform. Two cases received one thousand units daily for ninety-three days. Negative vaginal smears were abtained after seventy-seven days of treatment. Both had recurrences of positive smears after the administration was discontinued. Five cases received two thousand units daily for fifty days. All had negative smears in twenty-

seven days but all had recurrence of symptoms and positive smear findings as soon as the treatment was stopped. Three other patients were given daily four thousand units orally, for twenty-eight days. At the end of this time they were all negative andthere was no recurrence in this group. From these results they concluded that one thousand to two thousand rat units of estrin daily is adequate if administered hypodermically, while the effective oral dose was four thousand rat units daily.

Lewis [illegible], in his series of eight patients in whom no other therapy was employed, during the administration of theelin reports favorably on this type of therapeutic control. His cases were likewise equally distributed between acute and chronic infections. All of his patients received, daily either one, two, or three hypodermic injections of theelin of fifty R.U. each, in the arm or leg. In four instances, theelin was also given, in small quantities, by vaginal suppositories but this latter method of administration was soon abandoned as an unnecessary adjuvant. In the four chronic cases the amount of theelin given varied between eight hundred and fifty and one thousand R.U. The child who was given the one thousand R.U. hypodermically received also approximately two hundred and fifty

rat units by the vaginal suppositories. The four acute cases received larger quantities of theelin over a longer period of time. They received a total of 2,800 R.U. hypodermically and four hundred and fifty R.U. by suppositories, over a period of nineteen days. The leucorrhea stopped soon after the treatment was begun and smears became negative after twenty days. There were no recurrences in this series.

Phillips (35), in thirteen cases, administered approximately, 700 to 900 R.U. in three divided doses weekly. The smallest amount of theelin received by any patient was 2,100 R.U. andthe largest was 4,460 R.U. The smears became negative in every instance within four to six weeks of treatment. Six weeks following the cessation of treatment, 70%, or nine of this series relapsed. Two of the remaining four continued to have a slight discharge, which was smear negative, and which cleared up after several more weeks of treatment. The average total dosage administered to this group was 3,160 R.U.

Numerous other articles with results equally as gratifying as these, could be cited, ad infinitum, but these illustrate the typical effects of this type of therapy. In all the literature on this subject to date, there is only one unfavorable report, recorded. This from

Witherspoon (52), who attemped this therapy on ten cases ofthis disease. He administered daily doses of from fifty to one hundred rat units, over a period of from forty to ninety-two days. The amount of discharge lessened with the prolongation of treatment. Weekly vaginal smears were made by him, using gram's staining technique, and in only one patient did these smears become negative, and this after sixty-six days of treatment. Lewis (38) ascribes Witherspoon's failure to the low daily doses of this particular preparation, administered.

TeLinde and Brawner (53), using vaginal suppositories, containing seventy-five rat units of amniotin, treated seventeen cases of gonorrheal vulvovaginitis. Of this number twelve exhibited negative vaginal smears, after an average of 17.8 days treatment. The remaining five cases were clinically cured but recurred. The second course of treatment in these yeilded negative smears.

Lewis and Adler (54) also report successful treatment of twenty cases employing only vaginal suppositories. Fifteen of their patients responded favorably with negative smears in from ten to thirty-seven days. The remaining five cases were free from vaginal discharge, but still exhibited gram-negative diplococci.

From the above cases it should be quite clear that

this methodof therapy is not only sound from a physiological point of view but also from a practical one. The test of clinical application has been made and the therapy has proven effective, in the majority of cases, if properly administered. Indeed today we are capable of effecting cures for this dread disease where we, but a short time ago, could only hope that by some means we might halt the progress of this infection. Improvements in the technique of administration are needed and the problem of total dosage is not yet definitely fixed, but new hope has been given the profession in the guise of hormone therapy, for the therapeutic control and possible eradication of those gonorrheal infections in children.

Complications.

Perhaps the failure to appreciate the prevalence of gonorrheal vulvovaginitis, accounts for the fact that so little has been done in the study of its after effects. Fortunately, serious complications are rarely seen in the acute stages of the disease and only occassionally are seen in those cases of long standing. Nevertheless, the disease is capable of producing sequellae, which may prove as serious as the primary disease. Only a few of the more common complications will be treated in this paper and for further study of this subject the reader is

directed to the literature on the subject.

Stein (55) believes that endometritis, gynatresia, sterility and dysmenorrhea may be late sequellae of the diseas but he does not support his statement with examples from his own experience or by reference to the work of others. Vogt (56), said that ovulation and the passage of the ovum through the Fallopian tubes may be so disturbed, through changes resulting from gonorrhea of childhood, that sterility and extrauterine pregnancy may be a result. This seems hardly likely because the pathology of this disease is limited to the lower genital canal and involvement of the tubes is rarely, if ever, seen. The relative immunity of the upper genital tract in children is probably due to the absence of menstruation and the fact that the external os is usually closed. This has been stated by Titus and Notes (57), as an explanation of infrequent involvement of any structure outside the vaginal canal. These investigators report only one instance of tubo-ovarian involvement, in their series of 260 cases.

Northrup (58), saw two cases of peritonitis following gonorrheal vulvovaginitis. These cases did not terminate fataly though one case simulated appendicitis and was subjected to surgery.

Miller (59), found a number of complications in his series of sixty-eight cases. There were two cases of

ophthalmia, one of proctitis, six of urethritis and three of salpingitis.

In all cases resistant to what is now considered adequate therapy one must keep in mind the fact that in the great majority of these infections there is an associated proctitis, which serves as a wonderful source of reinfection. It is considered good therapy to wash the rectum with a solution of potassium permanganate, which in most instances, will take care of the infection in this location. The urethra likewise may be a foci of reinfection which would explain the many recurrences seen. This latter structure, in the opinion of many, is not as frequently involved as was at one time thought.

Bernstein (60) and Williams (1) hold that otherwise unexplained, acquired vaginal atresia, may be due to adhesions produced by the previous inflammation in the vagina.

In a check up of thirty-two women who had a gonorrheal infection in childhood, Dooley (61), found seventeen of them had later married. Of this number, ten had borne children; two were at the time, pregnant and two had habitually practiced contraception. Only one woman in this series had any menstrual difficulty.

Sheffield (62), in a series of one hundred and forty-eight cases, found, as complications, proctitis in

three cases, arthritis in four, local peritonitis in four, adenitis in twelve andpurulent ophthalmia in seven of these patients.

Spaulding (63) had six cases of proctitis, five of cystitis, four of arthritis and one of pelvic peritonitis in one series and one case of inguinal adenitis with suppuration, one of ischiorectal abscess and one of salpingitis in another series.

Gleich (64) had a fatal case of peritonitis following vulvovaginitis.

Stein (32) found thirteen percent of his one hundred and eighty-eight cases, complicated. He reports tubal infection, ophthalmia, arthritis, generalized peritonitis, and pelvic peritonitis in the order named, as most frequently seen sequellae. Stein also believes that involvement of the cervix is the rule and cites Rubin and Leopold as being of the same opinion. This is in distinction to the belief of most authors who think that in rare instances the cervix might be involved as a complicating factor. They suggest careful linear, cauterization of the cervix, if it is involved.

These few examples are given to illustrate the fact that while complications are not usually seen following this disease, they do occur and should be carefully watch-

ed for and avoided, if possible. Early, adequate, persistent therapy is the only means of preventing these undesireable after effects.

Summary and Conclusions.

1. Gonorrheal vulvovaginitis, an inflammatory disease of the lower genital tract, is characteristically limited to children who have as yet not reached puberty.

2. The disease is transmitted by direct or indirect contact with an infected adult.

3. Fomites are capable of transmitting the disease, and of these, the common lavatory seat is perhaps the greatest offender.

4. Because of the peculiarities in the histological structure of the vaginal canal in children, the pathology is confined to this region.

5. The diagnosis is made on vaginal smear examination with the finding of the typical bacteria.

6. Estrogenic therapy now offers a reasonably accurate method of control of this disease.

7. These estrus producing substances can be administered by hypodermic injection, by mouth and directly into the vagina in the form of suppositories.

8. These hormones produce an increase in the thickness of the vaginal epithelial lining as well as a shift in the acid-base balance of vaginal secretions, and through

these mechanisms, effect a-cure.

9. There are apparrently no harmful effects induced by the administration of these estrogenic substances.

10. Complications are rarely seen following this disease but though they do occassionally occur, they can be prevented by early, strenuous treatment.

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