NON-BACTERIAL INFECTION OF THE URINARY TRACT*

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Infection of the urinary tract of males and females by non-bacterial agents has been known to bacteriologists, venereologists, and urologists for many years. Notwithstanding this fact, and especially during and after the world war 1939-45, numerous cases of so-called abacterial, aseptic, or non-specific infections of the urinary tract have been published in current medical journals regardless of a few papers pointing out new routes for a possible explanation as to the true nature of many such undefinable infections. In most instances, probably because of difficulties arising from war conditions, no proper search appears to have been made for non-bacterial living agents.

Review of the Literature

Among others, Collins (1946) during a period of six months observed 120 cases of non-specific prostatitis at the urological clinic of the Royal Canadian Naval Hospital in St. John, Newfoundland. Phillips (1946) pointed out the great frequency of non-specific infections—pyelitis, cystitis, epididymitis, prostatitis, etc. Vassallo (1946) during a period of eighteen months observed twenty cases of hæmaturias and pyurias following, in most instances, non-bacterial urethritis; Cooper and McLean (1946), in a group of one hundred cases of chronic prostatitis, found that 50 per cent. had a previous history of non-specific urethritis, and 14 per cent. no previous history of urethritis. Of these last, 28 per cent. presented pyuria without symptoms. Baines (1947) described several cases of cystitis and epididymitis of non-specific type. Weyrauch (1947) observed fifteen cases of acute abacterial posterior urethritis and cystitis. Parkhurst and others (1947) referred to 226 cases of non-specific urethritis studied by them. Bourgault du Coudray (1947) observed a high incidence of abacterial post-gonorrheal residual prostatitis.

Another large group of authors observed cases of

abacterial pyurias of the Wildbolz type. Wildbolz himself in 1933, presented at the Thirty-third Congress of French Urologists several cases of chronic abacterial pyuria, unsuccessfully treated by different methods, which were cured dramatically after a few injections of "novarsenobenzol" (NAB). Among those authors who have treated cases with this drug and registered satisfactory results may be mentioned Briggs (1935), Cook (1936), Wildbolz (1937), Schaffhauser (1937), Houtappel (1939), Moore (1940, 1945), Ewert and Hoffmann (1943), Cook (1944), Bodner (1945), Donovan (1945), Lydon (1945), Peters (1946), Vassallo (1946), McGinn (1946), Wallman (1946), Lawson (1946), Fieldsend (1946), Baines (1947), and Lanceley (1947).

According to Wildbolz (1933) the examination of urine for spirochaetes by dark-ground illumination was always negative. Cook (1936) believed that the pyuria was due to the excretion of toxins absorbed from a septic focus in some other part of the organism. Moore (1940) and Donovan (1945) believed in a viral origin; Peters (1946) believed that the agents belonged to the spirochaete group but that the spirochaete had not been identified possibly because of some morphologic peculiarity. Wheatley (1946) and Fieldsend (1946) favoured the action of trichomonads; McGinn (1946) upheld the view that abacterial pyuria may be produced by fungi, viruses, or protozoa; Vassallo (1946) felt almost sure that infection was connected with sexual intercourse and that some inhabitant of the vagina, of perhaps low-grade toxicity, might find its way into the urethra and set up symptoms. Baines (1947) analysed the problem from a new angle and considered the urinary syndrome as part of a disease that might attack any portion of the genito-urinary tract. Although he recognized that owing to restricted laboratory facilities difficult bacteriological investigations were not carried out, he declared that the old theories of staphylococcal, spirochaetal, or virus infection remained without much evidence in favour of any of them.

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It is of interest to mention that many of the authors who published cases of abacterial pyuria recorded, in a number of cases, that the process had been preceded by an abacterial urethritis and in many instances was concomitant with a similar type of prostatitis, a complication not observed by Fieldsend (1947) in any of his four published cases.

At present it is accepted that the urinary tract may be infected by fungi, viruses, spirochaetes, and proto- and metazoa. Infection by such groups of agents may be of the hæmatogenous type, may reach the system by way of lymphatic channels, may be of an ascending urethrogenous type, or may originate directly from neighbouring foci or structures.

Candida infection involving heart and meninges has been described, but it is rare. Manousakis (1928) demonstrated that the spinal fluid in cases of dengue fever contained the virus and was infective to volunteers; Wollstein (1918) found the virus of mumps in the blood of a severe case of mumps meningitis; Beeson and others (1946) isolated the virus of lymphogranuloma venereum from the circulating blood and spinal fluid of a patient with secondary bubo-complex; Bruyneghe and Ronse (1946) obtained a positive hæmo-culture for spirochaetes in a patient suffering from a febrile condition of undetermined nature; Pentimalli (1925) found *Trichomonas vaginalis* in the circulating blood of humans; Wagner and Hees in 1935 cultured *Tr. vaginalis* from the blood of a woman, and in 1937 in seventy-five cases of vaginal trichomoniasis obtained in fifty-three (75.3 per cent.) positive hæmo-cultures for *Tr. vaginalis*.

Winsbury White (1933) and Parker (1936a, b), among others, demonstrated the close relationship of the lymphatics of the prostate, seminal vesicles, and cervix uteri with those of the urethra, trigone, and bladder. Nesselrod (1936) described the intimate connexions of rectal and perirectal lymphatics with those of the uterine cervix, posterior urethra, prostate, bladder, etc. Powell (1944) recently found a vast network of minute unvalvulated lymphatics completely surrounding the bladder neck and intimately connected with the lymphatics of the posterior bladder wall and cervix uteri. In his experimental work on dogs he found that in unvalvulated lymphatics the lymph may flow backwards if the main channels are obstructed. These facts support the opinion of many who sustain that cervicitis is frequently the cause of urological infections.

Various Aetiological Factors

Abnormal sexual intercourse—coitus buccalis, coitus analis, etc.—is more commonly practised

than we are ready to think and may be a direct or indirect means of infection, especially during relations with prostitutes, who usually accept both normal and abnormal intercourse and may therefore be infected during abnormal intercourse and may transmit infection during normal coitus. As regards this aspect, it is well known that both oral and rectal cavities harbour numerous non-bacterial micro-organisms such as fungi, viruses, spirochaetes, and proto- and metazoa. The presence of some of such organisms may occasionally be evidenced by simple microscopic observation of fresh material.

In pathological material existence of fungi is best shown by culture of specimens in appropriate media. When mycelium is present a diagnosis under the microscope is not difficult, but the presence of spores in secretion or sediment containing large numbers of pus cells usually escapes detection.

Viruses can only be demonstrated by special staining methods; inoculation into developing chick-embryos is in certain types of infection occasionally successful. Stained smears of suspected material—secretion or urinary sediment—with Mann's method as adapted by us to such types of preparations or with a 2 per cent. aqueous solution of nigrosin, a 3 per cent. Victoria blue or a 2 per cent. brilliant-green solution—may show the presence of inclusion bodies or clumps of elementary bodies in the interior of epithelial cells or lying freely outside the cells. It is much easier to stain and recognize virus life-cycle forms in tissue fragments obtained from surgically removed specimens, by biopsy, or from autopsy material. Sections are best stained using Mann's or Machiavello's methods.

Spirochaetes and proto- and metazoa should be searched for under dark-field illumination. Secretions, if containing many pus cells, should be diluted in normal saline. Urinary sediment should be obtained by decantation of urine in a culture-stove or by slow centrifugation in order not to destroy fragile bodies of micro-organisms.

'Slides' of secretions or sediment can be mixed with a solution of methyl-cellulose in order to slacken the movements of micro-organisms and render observation easier.

Characteristics of Non-bacterial Genito-urinary Infections

After this brief survey of the problem we will analyse in particular the different types of non-bacterial genito-urinary infections already mentioned and their outstanding characteristics.

Fungus Infections.—Fungi have been found living saprophytically in different body cavities. According to Skinner (1947), Todd isolated *Candida albicans* from 10 per cent. of a thousand young adults'

mouths in the absence of disease of mouth or pharynx. Knightdon isolated *Candida*, *Saccharomyces*, etc. from the oral cavity of 32.5 per cent. of 125 toothless people. Fisher in 24.5 per cent. of samples of human saliva isolated *Candida albicans*. Frank found the same fungus in 17 per cent. of normal lip commissures, etc. Castellani (1929) found *Monilia*, *Saccharomyces*, *Cryptococcus*, *Aspergillum*, *Penicillium*, etc. in vaginal discharges but rarely in normal vaginas; Negroni (1935) studied the vaginal flora of a hundred non-pregnant women without vulvo-vaginal inflammation and in eight found *Mycotorula* (*Monilia*) *albicans* and in one *Saccharomyces cerevisiae*. Recent investigations suggest that fungus infection of the genito-urinary tract is far more prevalent than was formerly supposed and that probably certain obscure conditions will eventually be proved due to them. According to Castellani (1929) when fungi are present in small amounts in the uro-genitalia they probably act only as saprophytes, but when present in large numbers they produce inflammation. The exact reason why some of these saprophytic fungi acquire virulence and produce disease has so far not been satisfactorily explained. Many times a fungal origin is assumed on insufficient evidence. In order not to overrate their importance we must therefore carefully interpret the significance and true value of fungi in smears and sediment, especially when they appear associated with other micro-organisms.

Mycotic urethritis appears rarely in the medical literature; cases mostly in males have been published, among others, by Klausner (1924), Girard (1924), Frei (1925), Pierangeli (1925), Falchi (1927), Karl and Forro (1928), Spicca (1929). In 1929 Castellani called attention to the existence of such an origin and recognized five types of mycotic urethritis—due to yeasts, *Nocardaceae*, *Oidium*, *Aspergillum*, and *Hemosporidia*. Latterly Pisacane and Coppolino (1938) described five new cases; in three cultures of *Cryptococcus ruber*, in one *Penicillium caudatum*, and in one *Monilia tropicalis* (Castellani) were obtained. In all cases they observed a long period of incubation, the minimum being fifteen to thirty days, the maximum several months.

We have studied two cases of urethritis in males in which *Candida albicans* was the cause. In one of them there existed a concomitant infection of the prostate by the fungus; both were married men and the infection was proved to be of the conjugal type (Coutts, in the press). Twice we have found yeast-like organisms in sections of epididymis removed from cases of chronic non-specific epididymitis. It will therefore be of interest in the future

to culture material obtained by aspiration from epididymis in adequate media.

In relation to *Candida* infections it is of interest to point out that according to most mycologists the morphology of these yeasts is very variable, especially in cultures, and that frequently variants of the same species have been classified in a different species or genera.

According to the nature of the fungus the urethral discharge may be whitish or yellowish in colour (*Candida*, *Nocardia*), reddish (red pigment producing *Cryptococcus*) or black (*Aspergillum*, *Penicillium*).

In 1928 Müller described a case of urethrocystitis due to *Saccharomycetes*; Moulder (1946) described a case of *Candida albicans* infection of the bladder; Ferrada (1946) isolated *Candida tropicalis* from a case of cystitis observed at our clinic. Direct propagation of actinomycotic processes from neighbouring structures to bladder and prostate have been described. We also find in the medical literature the description of cases of genito-urinary blastomycosis. Both actino- and blastomycosis are extremely rare.

Genital ulcers produced by *Histoplasma capsulatum* have been described lately in the medical literature, among others by Palmer and others (1942) and Curtis and Cowley (1947). This type of infection is commonly present.

Virus Infections.—The term virus has come to be used as a general designation for a group of pathogenic agents presenting many similarities to the pathogenic micro-organisms. The animate nature of viruses is confirmed by the result of serial transmission of virus diseases in animals.

Viruses propagate and multiply in the animal body; outside living cells they have never been grown on artificial culture media. The demonstration of elementary bodies in a number of viruses establishes their particular nature. In the majority of virus diseases, organized structures appear in the cytoplasm or nucleus of infected tissue cells. These inclusion bodies are of varying sizes, round or ovoid, and are Feulgen- and McCallum-negative as well as resistant to the action of acids. They are considered, by most authors, as forms of the developmental cycle of the virus.

Bang (1947) has demonstrated that under certain conditions the virus of Newcastle encephalitis is converted from a spherical to a filamentous form, the viral forms appearing under the electron microscope like spermatozoa.

As with bacterial infections, healthy persons may harbour specific viruses (carriers). Viruses may also establish themselves in the human body and

remain latent or inactive for considerable periods. Owing to the action of additional factors, such viruses can be activated.

Kidney and Bladder Infection by Viruses.—These are little known to most urologists. Hæmorrhagic nephritis and renal degeneration have been described in measles (Bender, 1931), in mumps (Sabrazès, 1927; Dutta, 1935; etc.), in psittacosis (Wilson, 1930). Hæmaturia has been observed in severe cases of dengue fever, but at post-mortem Photakis found no renal lesions to account for this condition. Gutman (1939) referred to a case of nephritis in which he attributed axial importance to the virus of lymphogranuloma venereum; functional changes in kidneys during secondary and tertiary periods of this disease have been reported by Lobo-Onell and Leyton (1941), Midana (1940), etc. Reichle and Connor (1935), in a case of secondary bubo-complex that ended fatally two months after initiation of symptoms, found at necropsy small circumscribed zones of necrosis disseminated in the renal cortex; Ahumada (1943) describes kidney amyloidosis in a fatal case of esthiomene. Experimentally Gomes and Magaldi Jordao (1942) and Coutts and others (1943) have found and produced nephropathies respectively in monkeys and guinea-pigs infected with lymphogranuloma-venereum virus from human buboes.

Acute inflammation of the bladder by viruses has occasionally been reported in the medical literature. In 1916 Dubois observed herpetiform vesicles in urethra and bladder in a case of herpes zoster of the buttock; hæmorrhages of the bladder have been recorded in severe cases of dengue fever. May, in Uruguay, describes a case that started with cystalgia before the appearance of inguinal adenopathy, and interprets this phenomenon as an invasion of the bladder by the virus of lymphogranuloma venereum. Personally we have seen and described several cases of slight pollakiuria with a few pus cells in the urine in cases of lymphogranuloma venereum with intense deep iliac lymph-node reaction. In such cases cystoscopy showed congestion of the bladder wall next to the lymph-node process. Cystography showed displacement and deformity of the bladder contour in relation to the neighbouring lymph-node mass (Coutts, 1938a; Coutts and others, 1938).

Rectal and genital tertiarisms are frequently accompanied by changes in the posterior urethra, neck, trigone, and bladder walls. Lesions may be of ulcerative, proliferative, or infiltrative types. Weissenbach and others (1934), Touraine and Vialatte (1936), Banciu and others (1936) described lesions of such types in women suffering from

esthiomene or Jersild's genito-ano-rectal syndrome. In men with peno-scrotal elephantiasis, rectal stricture, or perineo-urethro-genital syndrome, as well as in women suffering from esthiomene or Jersild's syndrome, we have observed similar lesions to those observed by the above-mentioned authors, as well as others of diverse nature to which we will refer later. In most of the cases studied by us, bladder findings were intensely marked; in most cases symptoms were nevertheless of the subclinical type (Coutts, 1938a).

Proliferative and infiltrative lesions are most common and are usually found in the posterior urethra, bladder neck, and trigone. Pseudopolypoid growths, pale infiltrated bladder necks, and infiltrated non-distensible zones in trigone and bladder walls, sometimes leucoplakic in appearance, at others with saline deposits, are commonly found. In some cases we have observed such lesions in the absence of genital or rectal tertiarisms; in a large proportion of such cases the Frei test was positive.

Vesical-neck fibrosis and chronic interstitial cystitis (Hunner's ulcer) may also be of lymphogranuloma venereum nature. Since our work on this subject (Coutts, 1938a, 1939) Rodriguez Diaz (1942) and Vargas-Zalazar (1944) have published cases of such a nature. In 1945 with Vargas-Zalazar we published a number of cases in which we had demonstrated the existence of lymphogranuloma venereum virus forms in specimens of bladder neck removed transurethrally (Coutts and Vargas-Zalazar, 1945c).

In 1943, D'Erizans referred to the case of a woman with extensive vulvo-urethral lesions who also presented chronic pancystitis. Clinical, laboratory, and histopathological findings pointed to the virus of lymphogranuloma venereum as the only possible cause for such lesions. In 1945 with Vargas-Zalazar we published four cases of chronic interstitial cystitis in males with positive Frei tests; in two of them we found lymphogranuloma venereum virus forms in fragments, surgically removed, of infiltrated bladder wall (Coutts and Vargas-Zalazar, 1945a).

Lymphogranuloma venereum lesions of the bladder similar to those described in preceding paragraphs have also been registered by Gonzales Valles (1944), Lauria (1946), etc. Their frequency is much larger than would be expected, and Marshall and Endicott (1943), impressed by this fact, insisted that a skin Frei should be made in all urological cases of doubtful or obscure aetiology.

In relation to bladder infections by viruses and the frequency of viral cervicitis, Saez (1947), following up our earlier studies of virus infections

of the cervix uteri (Coutts, 1942b; Coutts and others, 1944), examined the cervical secretion of 423 women—153 prostitutes and 120 pregnant and 150 non-pregnant women—and established that in 25 per cent. of positive cases inclusions could be considered as of lymphogranuloma venereum nature. In the remaining positive cases it was not possible to define their true nature, although in many instances they closely resembled buccopharyngeal inclusions as described by Broadhurst and others (1940) or those found by Thygeson and Stone (1942) in the cervix uteri.

Viral Infection of the Urethra.—This may present itself as an isolated entity, associated with other venereopathies, or as an integrating element of a defined syndrome (Reiter's disease). When present in the pure form, symptoms are commonly those of a mild urethritis with watery, mucoid, discharge containing a few pus cells and numerous epithelial cells, some of which contain varying numbers of inclusion bodies whose possible nature and significance were well studied in 1944 by Dosa.

Mumps urethritis has been recorded by several authors (Satler, 1919). During an epidemic in 1924 we also observed several cases. Satler sustained that in most cases the virus was carried to the urethra by infected hands, a conclusion to which we also arrived. It is of interest to point out that twice we have observed aseptic urethritis in fathers in whose homes several of the children were suffering from mumps. In one case it was complicated by epididymitis. The carrier was saliva.

Active urological processes may persist in the genito-urinary tract for months after acute phases of dengue fever have subsided. Weyrauch and Gass (1946) in 5.7 per cent. of 141 cases that had recovered from this disease found evidence of involvement of its parts. Orchitis and spermato-cystitis with hæmospermia were recorded in ten of these patients.

Urethritis due to the virus of herpes simplex have been described by several authors. We have seen two cases accompanying an outbreak of herpes progenitalis; vesicles were present on the lips of the meatus, which appeared congested and oedematous. Anterior urethroscopy showed intense congestion of the mucosa and numerous punctate hæmorrhages. As the virus has been isolated from healthy saliva (Levaditi, 1922) "suctio penis" may constitute a means of transmission of the virus to the urethra.

Lymphogranuloma Venereum and Urethritis.—Lymphogranuloma venereum virus is known to produce urethritis. As happens with most viral in-

fections of the urethra, symptoms are mild and usually escape detection. Hellerström (1929), Kleeberg and Löwenstein (1930), Pollak (1933), Coutts and Banderas-Bianchi (1934), and others have described several cases. Many have probably been recorded in the medical literature under different names, especially as urethritis of the Waelch type. In the cases studied by us we practically always found præputial oedema and dorsal penial lymphangitic symptoms that have been considered by May (May, 1938; May and Castiglione, 1938) as pathognomonic of lymphogranuloma venereum infection. Along with these signs we have always noticed a varying degree of deep iliac lymph-node inflammation, a symptom of value in cases of mixed simultaneous lymphogranuloma venereum-gonococcal infections (Coutts, 1943a). Chevallier and Bernard (1932) described chronic perimeatic oedema as the only manifestation of lymphogranuloma venereum infection; we have also found such a type of lesion in women, either as an isolated manifestation or accompanying other genital lesions of the disease. In four cases in men we have observed inflammation of the balano-præputial sulcus lymphatics with slight involvement of the lymphatics of the penial dorsum and of the deep iliac lymph nodes. Sulcus lymphatics stand out clearly as transparent, crystalline, chords under the mucosa. In all cases the Frei skin test was intensely positive.

Lymphogranuloma venereum urethritis may extend to all the urethra, and infection may reach the prostate, seminal vesicles, and epididymi, as we demonstrated years ago (Coutts and Vargas-Zalazar, 1936) and as was afterwards proved by Sato Akira (1936), Bizzozero and Franchi (1937), and Huard and Joyeux (1939). Bastos de Sequiera (1942), Midana (1942), Grosser (1947), and others have described cases of lymphogranuloma venereum orchitis. Stricture of the urethra may be a sequel to lymphogranuloma venereum urethritis. In 1919 Leinert mentioned lymphogranuloma venereum strictures of the urethra; in 1931 Kleeberg (1928) refers to such a condition, and in 1935, on the basis of a larger number of cases, he confirmed his former observations. Considering such a possibility we revised the clinical records of all patients with urethral strictures that had attended our clinic during the past thirty years, and found that a large proportion had suffered from inguinal buboes of lymphogranuloma venereum type. A very high proportion of cases attending in the latter part of this time, and tested with Frei's antigen, gave positive skin tests. These observations have made us consider the possibility that the gonococcus is not the responsible agent in the production of the

stricture, which would be induced by the action of lymphogranuloma venereum virus.

In a recent communication S. Williams (1946) refers to nineteen cases of urethritis in soldiers infected by Chinese and Indonesian women. In smears of urethral discharge he found inclusion bodies, and he believed that they might constitute an intracellular phase of micro-organisms belonging to the pleuropneumonia group. No Frei test was made in any of these cases. We have also observed in the last years, especially after the use of penicillin and sulphadiazine, many cases of a similar type of urethritis in which the Frei test was negative and there was absence of deep iliac lymph-node reaction. We classified them under the denomination of "inclusion urethritis" and compared their nature with that of inclusion cervicitis, already mentioned above (Coutts, 1942a; Coutts and others, 1944; Saez, 1947). In some cases urethroscopy showed the existence of vesicular lesions as described by Ross in cases of millet seed or "sago grain" urethritis. Such lesions may correspond to early phases of so-called "urethritis cystica erythematosa" (Glingar) or "urethritis indurativa cystica" (Oberländer).

In Reiter's disease Harkness (1945) found inclusion bodies in epithelial cells of urethral discharge and conjunctival secretion. In seven cases of this syndrome, some of a *forme fruste* type, seen by us during a period of several years we found in three (42 per cent.) a positive Frei skin test. Harkness did not find this test positive in his cases. In two of our Frei-positive cases eye fundus changes as described in lymphogranuloma venereum by Funakawa (1934), Kitagawa (1934), and Espildora and Coutts (1934) were found. Inclusion bodies were found in epithelial cells in the urethral discharge, and an antigen prepared from the urethral secretion of such cases gave positive reactions in lymphogranuloma venereum patients (Coutts, 1947a).

Behcet's syndrome, so called after the Turkish dermatologist who in 1937 published his first paper on the subject integrating its several manifestations, is characterized by aphthous-like ulcers appearing in the oral mucosa and genitalia and a variety of ocular disturbances—uveitis, hypopyon, etc. In some of his cases published in 1939 the eye fundus changes described were similar to those found by Funakawa (1934), Kitagawa (1934), Espildora and Coutts (1934) in a certain proportion of lymphogranuloma venereum cases. *Formes frustes* of this syndrome have been studied by us. The Frei test was positive in some, and there were fundus changes in the eyes. Ear, nose, and throat specialists as well as oculists should keep this syndrome in mind

when consulted for aphthous lesions of the mouth or uveitis of doubtful origin, and they should search for other integrating symptoms. Probably when interest is aroused a larger number of cases of the syndrome will be discovered. Although we do not possess any further evidence, we believe it is a viral disease.

In relation to lymphogranuloma venereum infections, whose distribution and frequency are little known to many physicians, it is of interest to point out that investigation of large masses of the asymptomatic population have revealed some very important facts. In 1933 (Coutts and others) in 250 non-venereal women patients a positive Frei skin test was found in nine (3.6 per cent.); Morales and Carrera (1943-4), in 650 individuals belonging to the poorer classes of Puerto Rico, found a positive Frei test in 81 (12.9 per cent.); Beeson and Miller (1944) investigated the blood complement-fixation with lymphogranuloma venereum antigen (Lygranum) in non-venereal clinic and policlinic patients, and in 671 over fifteen years found 29 per cent. to be positive; Wright and others (1947), in 1,512 routine non-venereal hospital admissions, found no biological evidence of lymphogranuloma venereum infection in 130 children tested. Among the 1,382 adults tested, 26 per cent. had positive reactions. In all countries the proportion of positive results in venereal disease patients has always been higher than those just mentioned.

Before ending this survey of viral infections it is worth mentioning that parasitization of an individual host cell is not limited to infection by a single virus; Syverton and Berry (1947) have reported experiments in which two or more viruses can simultaneously manifest their characteristic activities within a single host cell. This fact must be kept in mind when evaluating the evolution of viral infections of the genito-urinary tract.

Spirochæte Infections.—Study of spirochætes, with the exception of *S. pallida*, has unfortunately been neglected both by bacteriologists and protozoologists; it is therefore not surprising that our knowledge about them is still very incomplete. They appear to be more closely related to the true bacteria than to the protozoa, and they may perhaps constitute a connecting link between the two. Very large numbers of spirochætes have been found in different parts of the human body. If present in small numbers, they are very easily overlooked or the chances of finding them are reduced or remote. According to Prowazek they may disappear owing to attenuation, or, as has been shown by many investigators—Dutton, Leishman, Balfour, Nicolle, Coutts, Marchoux, and others—this disappearance

is due to the fact that spirochætes divide up into granules or coccoid forms, probably expressions of attenuation or of a life cycle. Recent investigations by Simon and Mollinedo (1941) have shown the existence of granules (granules spirochætogènes) in syphilitic gummata. The breaking up of spirochætes impedes their recognition, a fact that must be kept in mind when they are not found in fresh material or in sections. Until proved to be absent in different samples taken at different intervals or from different parts, a negative answer must not be too promptly given.

Under the electron-microscope Mudd and others (1943) observed the cell wall (periplast) to be very delicate and to extend beyond the cell protoplasm as a terminal filament. Dense granules appear within the cell protoplasm; flagella are frequently present, either along the sides or near the ends (present in *S. macrodentium* but absent in *S. microdentium*). Dense spheroid bodies are found closely applied or attached by short stalks to the cell body, usually near the end of cells or free in the medium. They are definite and characteristic bodies originating from the spirochætal wall and recall conidia and clamydospores of higher fungi. Apart from the type of movement, length, curvature, and number of the spirals, diameter, etc., most spirochætes have no other distinguishing morphological characteristics under the ordinary microscope or dark field; they are also difficult to culture on artificial media, and very little is known of their physiological and physico-chemical properties. Therefore nomenclature and classification are still in an uncertain stage, and up to the present there is no general agreement as to the separation of some of the genera.

Le Play and others (1912) found spirochætes in kidneys with inflammatory processes; Kon and Watabiki (1918) also found such micro-organisms in human kidneys with acute, subacute, or chronic inflammatory lesions. Spirochætes with or without renal involvement have been described in so-called "trench fever" (Nankivell and Sundell), in war nephritis (Salomon and Neveu), and in Weil's disease, etc. Stoddard 1917, Patterson, 1917, and Symonds 1917 studied the origin and nature of spirochætes found in the urine of soldiers suffering from a febrile process of general infectious type.

In 1937, at one of the internal meetings of the Urological Clinic of the Medical College of Chile University, Vargas-Zalazar presented a case of abacterial pyuria. During the discussion Coutts recommended dark-field study of the urinary sediment in order to search for spirochætes, keeping in mind the possible existence of granular or coccoid forms as evidenced by several authors and by himself in 1929 and 1934. He attributed the origin

of the syndrome to oral cavity spirochætes. Prof. Luis Bisquertt added a case from his private practice of bilateral aseptic renal pyuria that was cured spontaneously after extraction of a damaged molar. Vargas-Zalazar (1937) investigated spirochætes in the urinary sediment of his patient. He found numerous spirillæ and treated him with endogenous arsenicals, obtaining a rapid cure.

In 1938 (b) both Coutts and Bisquertt-Torres described new cases of spirillar pyuria. In 1945 (b) and 1946 Coutts and Vargas-Zalazar increased the Chilean literature on this spirochætal syndrome and Caro (1946) added some new cases. In 1947 Fieldsend described a case of spirillar abacterial pyuria, the first-published case not observed in Chile.

From textbooks consulted we have gathered that years ago Castellani described under the name of *S. urethrale* a very fine spirochæte, with many regular spirals, occurring in a purulent urethral discharge; Macfie (1931) described a spirochæte larger than relapsing-fever spirochæte from the male urethra which he called *S. urethra* and which he supposed to be of pathogenic significance, etc. In 1937 we (Coutts and others, 1937) wrote that, examining non-gonococcal urethral discharge under dark-field illumination, we had observed in men the presence of a very fine and active spirillum to which we attributed a buccal origin. Next year Bustamante published a case of spirillar urethritis in a male. In the same year, with Monetta, we referred to three cases of spirillar urethritis in males following "suctio penis."

In cases of subacute or residual abacterial prostatitis we have frequently found spirochætes in the prostatic fluid. In a group of fifty such patients we found spirochætes in six (Coutts and others, 1947). Edna Silva (1948) brought the series up to ninety-six patients, with a total of twelve in whose prostatic fluid, examined under dark-field illumination, spirochætes were found. In six cases of chronic abacterial residual prostatitis in our private practice spirochætes were also present in the prostatic fluid; in another patient in our private practice (seen with Prof. Bisquertt), who presented an intense abacterial cystitis, spirils and trichomonas were found both in bladder urine and prostatic fluid. Sepulveda Jara (1936), under our guidance and at the Social Hygiene Department Laboratory, investigated under dark-field illumination the urethral and perimeatic secretion of a hundred prostitutes and found non-syphilitic spirochætes in the urethral secretion in eight, and in the perimeatic region in forty-four.

An ascending type of infection, preceded by urethritis, may be caused by oral-cavity spirochætes.

Normal or abnormal sexual intercourse may be the determining cause, as we suggested in 1933.

Spirochaetes have been found by numerous authors in the vagina: Noguchi and Kaliski (1918) found in the smegma of women *S. balanitidis*, *S. refringens*, and certain forms of *S. genitalis* whose morphology was similar to that of *S. microdentium*. Kranz (1922) found *S. celerrima*. Scherber (1927) described spirochaetes whose morphology was similar to that of *S. balanitidis*, *S. refringens*, *S. pseudopallida*, or *Treponema minutum*. In the cervix uteri of prostitutes suffering from chronic cervicitis Scherber occasionally found a large number of very fine spirochaetes with very close and regular spirals. Macfie (1931) described the case of a woman who suffered from vaginitis produced by spirochaetes morphologically similar to those of recurrent fever and which he called *S. vaginalis*; Coutts and others (1935) found in the cervix uteri of sixteen prostitutes spirochaetes morphologically resembling *S. buccalis crassa* and *tenuis*. Sepulveda (1936) examined the cervix-uteri secretion of a hundred prostitutes and found spirochaetes in twelve.

The human intestine also harbours numerous spirochaetes; *S. eurygirata*, *S. stenogirata*, *S. sangeorgis*, etc. In the rectum of pederasts examined at the Social Hygiene Department we have found in several cases spirochaetes of diverse morphology.

The descending type of infection may also, in some cases, be due to oral spirochaetes which, according to our observations, reach the kidneys through the blood stream. In a number of patients with intense inflammatory dental processes we have searched for spirochaetes in the urinary sediment before and after several simultaneous extractions, and we found spirilluria in two immediately after removal of damaged teeth. In one case studied by us of abacterial cystitis which appeared shortly after removal of an incisor complicated by an abscess we found large numbers of spirillae in the bladder urine (1946).

The relation of dental sepsis to urinary-tract inflammation has been recorded by several authors. In 1933 Phélip, of Lyon, at the Thirty-third Congress of French Urologists, insisted on the role of infected teeth as a cause of certain urinary infections and said he believed the infection to be of hæmatogenous or digestive types; Saez de la Calzada (1934) presented a case of pollakiuria of dental origin and analysed the mouth as an ætiological factor in certain urinary diseases. In relation to the aspect we are considering, it is of interest to point out that Cavalié and Mandoul (1921) described a spirochaete, *S. perforans*, found constantly in the lesions of expulsive alveolo-dental polyarthritis. In a few

cases of severe entero-colitis we have searched for the presence of spirochaetes in urine but found no such micro-organisms.

Protozoan Infections.—The protozoal, the lowest group of the animal kingdom, is formed by numerous heterogeneous, unicellular organisms, frequently of great structural simplicity, and ranging in size from organisms scarcely larger than bacteria to some several centimetres in length. Their life cycle is complete, and involves the alternation of hosts and sometimes sexual and asexual phases. Many species are parasitic upon man.

Amæbas.—In man we find *Endamæba histolytica*, *E. coli*, and *E. gingivalis*. The first two are considered pathogenic for man.

The existence of amæbic infection of the urinary tract has been for long disputed although several authors have considered it a definite pathologic and clinical condition. The diagnosis has been based on the presence of *E. histolytica* in secretions or urine and the disappearance of symptoms under emetine treatment. According to Watson (1947), sufficient proof of their identity—positive inoculation in kittens—is lacking in most published cases. When examining material it is convenient to remember that *E. histolytica* can be mistaken for large hæmatophagous leucocytes—sometimes containing red blood corpuscles—or certain types of leucocytes which occasionally look like cysts of the parasite.

Cabot (1936) declares that there is no part of the genito-urinary tract that can escape infection by amæbas. Renal abscess, epididymitis, orchitis, etc., have been described. Cystitis has also been observed. We had the opportunity of studying a case of cystitis from *E. histolytica* (Coutts and Herrera, 1942). Caro (1946) found *E. coli* in the bladder urine of two (0.6 per cent.) among three hundred prostitutes examined; no bladder symptoms were present.

Amæbiasis of the vagina and cervix uteri has been described by Nisioka (1940), Morse and Seaton (1943), of skin and vagina by Bacigaluppo and others (1942), of the vulva by May (1943), and of the male urethra by Coutts (1945). Amæbic ulcers of the penis have been described among others by Shih (1935), and Herman and Berman (1942).

Trichomonas.—*Trichomonas vaginalis* was discovered by Donné in 1836 in the vaginal secretion of certain women suffering from leucorrhea. Investigations carried out by other authors soon showed that the infection of women by this parasite was widespread. The early observations have been latterly confirmed all over the world. Baatz (1902)

described the presence of *T. vaginalis* in the female bladder. Arnold (1914) found the parasite in the bladder urine of a gravid woman. Dastrdar (1925), in India, reported the presence of trichomonas in four cases during routine examination of some thousand specimens of urine from both sexes. Three of the cases were males; the urine was acid and contained a few pus cells. Caro (1946) examined urine obtained directly from the bladder of 321 women, 300 prostitutes, and twenty-one patients of a gynaecological clinic. In thirty-five prostitutes who had vaginal trichomonas the parasite was found in the urine of seven (20 per cent.); in the group of twenty-one, all suffered from vaginal trichomoniasis; the parasite was found in four (19 per cent.). Three (27 per cent.) of the women of this series with trichomonas in the urine had bladder symptoms (cystitis). Allen and others (1935) found trichomonas in fresh films of prostatic fluid of husbands whose wives suffered from trichomonas vaginitis; Drummond (1936) made a similar investigation and found the parasite in the prostatic fluid of four out of five husbands none of whom presented any symptoms; Karnaky (1938) states that he found thirty-eight (26 per cent.) infected among 150 husbands whose respective wives suffered from trichomonas vaginitis and that most of the positive cases had no symptoms.

The first case of trichomonas infestation of the urinary tract of a male was published by Kunstler in 1883, who found the parasite in the urine of a patient with pyelitis following suprapubic cystotomy. Marchand (1894) and Miura (1895), in Japan, published cases of infestation by the parasite in males; Dock (1896) published a case of difficult and painful micturition followed by hæmaturia in a man aged twenty-seven years; Escomel (1926) published a new case; Capek (1927) observed two cases of trichomonas urethritis. Riba and Perry (1929) reported two cases with urethral discharge and trichomonas in the prostatic secretion. Grimm studied several cases of urethritis. Rosenthal (1931) reported a case containing trichomonas in the urine following an attack of pyelitis; Stuhler (1933) found trichomonas sixteen times in 32,000 examinations of prostatic secretion; Cornell and Riba (1936) said that during a period of seven years they came across thirty cases of *T. vaginalis* infection in males, twenty-five of whom were married; Nitschke (1936) found five cases of trichomonas infestation among forty cases of non-specific urethritis examined by him; Liston and Lees (1940) described eight cases of anterior and three of posterior urethritis in which the parasite infected prostate, seminal vesicles, or bladder.

During the past few years and in relation to the evident increase in the number of cases of so-called abacterial infections of the genito-urinary tract we have observed a large number of trichomonas infections in our private practice. In the course of three years we have observed twenty-nine cases of trichomonas urethritis (acute form) and seven presenting as post-gonococcal residual urethritis. Many of our colleagues have registered similar cases. Trichomonas have also been found by us in the prostatic fluid of cases of chronic post-gonococcal residual prostatitis.

It is still not generally accepted that trichomonas may infect the urinary tract of females, and only a few cases have been registered in the medical literature. Lewis and Carroll (1928) described a case of *T. vaginalis* infection of the kidney pelvis in a young married woman. Visser (1929) described bladder symptoms in a woman suffering from trichomonas vaginitis. Coutts and Vargas-Zalazar (1945b) published a case of pyelitis with recurrent hæmaturia in which trichomonas were found in the urine obtained from kidneys. B. Williams (1946), in fourteen cases of trichomonas infection in women, noted that in most of them symptoms were those of urgency and frequency. In five (thirty-five per cent.) there was evidence of spread to the upper urinary tract.

Trichomonas urethritis in males has no particular characteristics; in some cases discharge is profuse. Bladder symptoms are usually of subclinical type, but we have seen cases of intense cystitis. Cystoscopy shows a congested mucosa, and in severer cases bullous œdema. Cases of pyelitis may be attributed a hæmatogenous origin if we consider the surprising findings of Wagner and Hees (1937).

Lambliæ.—We have found *Lambliæ intestinalis* (*Giardia lamblia*) in the vulva of prostitutes and in the præputium of pederasts but cannot give a definite opinion as to its pathogenic significance.

Gabrielle and others (1938) described a case of urethritis probably due to *G. lamblia*. We (1945) found this parasite in the urethral discharge of a young man who had practised anal coitus with a girl friend who did not accept normal coitus. Coitus analis is not infrequently practised by young couples; women accept it as a means of preserving their hymen or of preventing pregnancy. In localities where the incidence of intestinal lamblia is high, these facts must be kept in mind. The possibility of infestation by this parasite must not be overlooked in prisoner-of-war camps and among other segregated groups of men, among whom pederasty is frequently observed as a transient phenomenon.

Balantidium coli.—Brumpt says that in 1920 Maliwa and Von Hans found *Balantidium coli* in the urine of a woman suffering from urethritis, cystitis, and pyelonephritis. Remlinger, quoted by Craig and Faust (1943), described a case of mixed bladder infection by *Bilharzia* and *Balantidium coli*.

Metazoan Infections.—Infections of the urinary system by multicellular organisms, especially those occurring in tropical or subtropical countries, are well known. In this paper we will refer only to certain epidemiological aspects of schistosomiasis which are of special interest at present after the return of troops or volunteers from different battle fronts. After studying with Bisquertt (1938) a case of urinary bilharziosis, we considered the possibility that Chilean *Bullinus* might act as intermediary, as Porter had informed us of the existence of such animals in our waters. Stunkard (1946), similarly preoccupied in North America, infected North American *Bullinus* with *Schistosoma*. This fact we consider of the utmost importance as it opens up the possibilities of foci of the disease appearing in territories where this parasite did not exist.

Conclusions

If we thoroughly investigate each case of abacterial infection of the genito-urinary system we will soon be able to abandon such terms as non-specific, aseptic, and probably allergic which, up to the present, have merely described our ignorance. But we wish to emphasize that the fact of finding in secretion or sediment any one of the agents described in this paper must not make us overrate their importance. We must be guided by the clinical evolution of the disease after adequate treatment has been installed. If the agent disappears from the secretion or sediment and the symptoms partly subside but pus cells still remain, we must search for an associated infection—fungi, virus, etc.—or, in cases of abacterial pyuria, continue our search for Koch's bacilli.

In our articles of 1937 and 1943 we tried to draw the attention of venereologists, urologists, and bacteriologists to the pathogenicity of non-bacterial micro-organisms in infections of the genito-urinary tract. Once again today, on the evidence gathered from many papers dealing with non-bacterial infections of this system, we emphasize the necessity of keeping in mind all details mentioned in this paper.

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DISCUSSION ON NON-BACTERIAL INFECTION OF THE URINARY TRACT

MR. A. J. KING said that the Society was indebted to Dr. Coutts for his interesting address and also for drawing attention to this greatly neglected subject, not only at this meeting but in many medical journals for years past. He was glad that Dr. Coutts insisted so strongly upon the importance of the clinician instituting the preliminary laboratory investigations himself, and examining fresh specimens of the secretions.

At the Whitechapel Clinic he and his colleagues were particularly interested in the problem of chronic prostatitis, which was such a difficult problem in their work—a condition resistant to treatment of all kinds. During the last few weeks Dr. Atlas had examined under the dark field of the microscope specimens from the prostatic fluid of a number of these cases, and had found spirilla in the prostatic secretion in a number of them. It still remained to be established whether these spirilla were the cause of the condition, and in fact, whether they were pathogenic at all. The findings confirmed Dr. Coutts's observation and opened a field for further investigation. Some of these patients had been treated with neoarsphenamine, but up to the present the results had been disappointing. Perhaps the drug was not being used as it should be, and if so he hoped that Dr. Coutts would put them right on points of technique. He felt that, in using a drug such as neoarsphenamine, or similar arsenicals, it was important to be very sure of the indications because it was a toxic drug, and already, in these cases, there had been some toxic manifestations.

DR. ATLAS said that he started to investigate a group of cases of chronic and residual prostatitis, all of which showed an abnormal number of polymorphonuclear leucocytes on microscopic test of a number of specimens of the prostatic fluid. Forty cases had been investigated so far, and fresh specimens of the prostatic fluid had been examined under dark-field illumination. Spirilla such as Dr. Coutts had described were found in sixteen cases out of forty (40 per cent.), and had been found again on repetition of the tests. In two cases there were very thin hair-like spirilla. In the other fourteen

cases there were spirilla of the coarser type similar to those described by Dr. Coutts. The organisms were inclined to sink into the fluid, and a good deal of patience was required in order to find them and examine them properly.

Those cases with positive findings were treated with neoarsphenamine or arsenoxide; 0.3 g. neoarsphenamine or 0.04 g. mapharside was given twice in the first week followed by 0.45 g. neoarsphenamine or 0.06 g. mapharside at weekly intervals, to a total of six injections. So far treatment had been completed in six cases, but the results were disappointing. Spirilla were still present and the number of polymorphonuclear leucocytes had not decreased.

DR. ROBERT LEES said that he also had found non-specific urethral infections extremely difficult and puzzling. There were vast numbers of such cases, and they appeared to have no relation to gonococcal or other pyogenic infections of the urethral tract, but he thought the majority were certainly infectious. The usual investigations carried out by bacteriologists were quite useless in such cases, and it was common experience to find that the bacteriologist was reluctant to pursue any other investigation than a search for gonococci.

During the last year he had made some investigations, but they had proved unsatisfactory. Firstly he had tested a considerable number of cases of non-gonococcal urethritis with Frei antigen, and practically no positive results were obtained. Also over a hundred cases of urethritis, in whom gonococcal infection had been excluded, were treated with small doses of neoarsphenamine. Three doses of 0.3 g. were given at intervals of three or four days. If a distinct response had not been obtained after three injections, the treatment was abandoned. The number of cases which responded in this way was extremely small, and he was convinced that this was not a promising line of non-specific treatment. In addition there was the fear of concealing incubating syphilis. The conclusion from this clinical investigation was that the type of urethritis with which we were dealing in this country was probably not due to the virus of