Papers and Originals

Bladder Dysfunction in Multiple Sclerosis

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Disturbances of micturition are important in multiple sclerosis, not only because of their high incidence, the amount of discomfort and embarrassment they cause, and their contribution to the mortality of the disease, but because control of the excretory functions is the most important single factor which determines the patient's admission to hospital. Under satisfactory home conditions many patients with this disease can remain with their families for many years, but the development of urinary retention demands urgent admission to hospital, while incontinence very often necessitates long-term institutional care.

Estimates of the prevalence of bladder symptoms in multiple sclerosis vary considerably, but disparities have arisen chiefly because figures have been based on quite differently selected groups of patients. Bladder dysfunction as a presenting symptom was described in 5% of Müller's (1949) cases, in 2.8% of those of Adams, Sutherland, and Fletcher (1950), in 4.9% of those of McAlpine, Compston, and Lumsden (1955), but in only 1% of the series of Ivers and Goldstein (1963). Carter, Sciarra, and Merritt (1950) reported "sphincter disturbance" as a first symptom in 11% of their patients. But these last were cases confirmed by necropsy, while those of Ivers and Goldstein were mild, and 97% of the patients were still able to walk unaided. Indeed, the overall incidence of bladder disturbance in their patients was no more than 6%, by contrast with 78% in those of Carter and his colleagues, 44.5% among patients presenting for treatment in the series of Adams *et al.* (1950), 62% of Müller's (1949) patients who had had the disease for 20 years, and 69% of Thygesen's (1953) patients.

The purpose of the present study was to define the problem of bladder dysfunction in multiple sclerosis in terms of the pathophysiological considerations involved, to present a careful analysis of the prevalence and symptomatology of bladder and related disturbances in an unselected group of patients with the disease, to give a short account of current methods of management, and finally to indicate the possibilities of further research in this field.

Normal Bladder Function

Even a superficial consideration of the problems of bladder disturbance in multiple sclerosis emphasizes at once the current lack of clear conceptions of abnormal bladder function. The newer techniques of accurate investigation of normal and disturbed function have only recently become available, and have as yet been incompletely exploited. In the meanwhile, many of our ideas about both normal function and its disturbances cannot be more than tentative.

Bladder contraction can be regarded as a type of stretch reflex involving arcs within the central nervous system. All effector impulses reach the bladder through the second, third, and fourth sacral roots, being excited by afferent impulses reaching these segments of the spinal cord. Like any such reflex this is profoundly influenced by descending impulses from higher levels, which may be excitatory or inhibitory, voluntary or involuntary. But the excitatory state of the reflex arcs concerned is also continuously influenced by the afferent input in the sacral segments themselves: bladder excitability and contraction are, for example, strikingly affected by the powerful afferent stimulation which results from infection of the bladder mucosa.

Micturition is, of course, a much more complex activity than bladder contraction, demanding co-ordinated relaxation of the muscles of the pelvic floor. Normal bladder function demands the ability to initiate or to postpone micturition as required. Continence must be preserved in all postures and during all activities, yet the act itself should be easily started and rapidly completed.

The normal bladder accommodates an increasing volume of urine with only a slight rise in intravesical pressure until it is completely filled, and during this filling phase continence is achieved by the maintenance of a urethral resistance which is higher than the pressure within the bladder. In the recumbent posture this resistance is furnished by the tone of the elastic tissue and plain muscle of the posterior urethra, but in the standing position this involuntary tone must be supplemented by a reflex increase in that of the voluntary muscles of the pelvic floor and especially of the levator ani. In man the external sphincter is said to be constantly in tone (Denny-Brown and Robertson, 1933; Nathan, 1964), yet in "approximately one-third" of 25 male and in 3 out of 12 female cases spinal anaesthesia effected no decrease in urethral resistance in the supine position (Lapides, Ajemian, Stewart, Breakey, and Lichtwardt, 1960). Stimulation of the pudendal nerves causes contraction of the bladder-neck (Bors, 1952), and of the external sphincter and perineal muscles; these actions are probably primarily concerned with ejaculation, when closure of the bladder-neck prevents reflux of semen into the bladder, and when the final ejaculatory movements call for repeated closure of the membranous urethra during compression of the urethral bulb by the bulbo-spongiosus.

The mechanisms concerned in the desire to micturate are incompletely understood, but are clearly if indirectly related to tension in the bladder and possibly also in the posterior urethral wall. The erect posture provides much greater afferent stimulation from the distended bladder than does recumbency, probably because the weight of the abdominal contents compresses the vault and stretches the bladder muscle by distortion.

Contraction of the bladder until it is empty requires continuous afferent stimulation and motor responses. The stimuli arise largely in the contracting bladder-wall itself, the same nerve-endings being stimulated both by stretch and by bladder

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contraction (Iggo, 1955). The arrangement of its fibres (Woodburne, 1960) ensures that the bladder outlet is opened by the contracting detrusor. The raised intravesical pressure then overcomes the elastic resistance of the posterior urethra, and with relaxation of the pelvic floor the bladder empties smoothly. Contraction of the abdominal wall is of little or no importance during normal micturition, though it may possibly assist initiation by depressing the pelvic floor.

Bladder contraction is mediated through reflex arcs traversing the sacral segments of the spinal cord, but in normal co-ordinated micturition the pathways concerned extend to hypothalamic levels, and at such levels they are subject to inhibition and excitation by stimuli from the diencephalon and the cerebral cortex.

Nature of Bladder Dysfunction in Multiple Sclerosis

There are important differences between the kinds of bladder disturbance encountered in multiple sclerosis and those produced by trauma and by most other organic nervous diseases. The first of these is the preponderance of female sufferers from the disease: this accentuates the problem of the management of incontinence, which is so much easier to deal with in male patients. The second concerns the striking but unpredictable tendency to remission which always obtains in multiple sclerosis. Furthermore, the complexity of the bladder disturbance in this disease is increased by the strong probability that in any particular instance this disturbance is likely to originate not in a single neurological lesion but in multiple lesions occurring at various levels of the nervous system. Yet another unusual feature is the frequent persistence of normal bladder sensation even where there is a gross disturbance in the motor functions of micturition. Finally, the position is further complicated by the high incidence of early and progressive weakness of the abdominal wall.

Both the understanding and the management of these disturbances depend on analysing the components involved. These can be described in various ways, but can be classified initially as (1) deficiencies of inhibition, and (2) retention syndromes, and the latter can be further differentiated into (*a*) partial or complete neurogenic bladder failure, and (*b*) subvesical obstruction.

Deficiencies of Inhibition

In its pure form deficient inhibition results in a hyperexcitable bladder, with uninhibited contractions which are manifest as frequency and urgency so intense that they lead to complete involuntary emptying of the bladder. Typically there is no hesitancy of micturition nor any residual urine. The dysfunction is aggravated by the upright posture or by a sudden increase of intra-abdominal pressure. This is the condition traditionally familiar as "cerebral incontinence": the lesion is due to a failure of inhibitory impulses which arise at levels above the hypothalamus. A superficially similar clinical disturbance may also be encountered where an automatic bladder with retained sensation has followed spinal shock, but in these instances the disorder arises at a lower level, and is also usually associated with a retention syndrome.

Retention Syndromes

Retention syndromes are usually characterized by the presence of residual urine. *Complete neurogenic bladder failure* is seen in spinal shock, or where there have been extensive lesions of the sacral segments of the cord. In some instances of spinal-cord damage above the sacral segments a "spinal shock" type of bladder failure persists, with complete failure of the reflex arcs; for reasons which remain obscure their function has not been restored during recovery. No bladder contraction can be elicited in theses cases, even by the instillation of iced water, which is normally a powerful stimulus to the reflexes governing bladder contraction (Bors and Blinn, 1957). In the absence of bladder contractions the bladder-neck remains closed, and this results in complete retention of urine with subsequent overflow.

Partial neurogenic bladder failure is seen during the stage of recovery from spinal shock, and it may also occur *ab initio* from lesions which interrupt the reflex arcs concerned in bladder contraction. Contraction is diminished in power or is not maintained, with the result that a varying amount of urine is retained. In these patients residual urine is probably due to inadequate contraction of the bladder-wall rather than to subvesical obstruction. It is notable, for example, that dilatation of the upper urinary tract is rarely encountered in patients with uninfected residual urine due to multiple sclerosis. In conditions with lesions restricted to sacral segments or roots, abdominal straining can largely compensate for inadequate bladder contraction, but in multiple sclerosis such compensation is rarely possible because of severe and often early weakness of the abdominal wall.

These disturbances, due respectively to overactivity and underactivity of the bladder, can be demonstrated in many cases by cystometry. However, there are many normal individuals in whom spontaneous bladder contraction does not occur during cystometry in the supine position, so that its absence is not necessarily pathological. For this reason the injection of iced water after emptying the bladder at the end of cystometric examination is a valuable confirmatory test of bladder contractility. Cystometry also demonstrates the contraction of the abdominal wall on straining, and is used in its quantitative measurement.

The classical causes of *subvesical obstruction* are, of course, mechanical, and include fibrosis and hypertrophy of the prostate gland. In multiple sclerosis a very similar disturbance of function may be caused by spasm of striated muscle as a result of lesions in the lateral columns of the spinal cord. The bladder-neck contains striated muscle fibres, both anteriorly and laterally, which contract on stimulation of the pudendal nerve. These fibres may themselves cause obstruction of the bladder-neck, but it is likely that they also stimulate contraction of the plain muscle of the bladder-neck (Bors, 1952). Although it is probable that all the relevant striated muscles take part in increasing the urethral resistance, spasm of the bladder-neck, of the external urethral sphincter, or of the pelvic floor may be dominant in a particular case. The bladder muscle hypertrophies in response to obstruction. This increases the bladder-power but also increases bladder irritability. At a later stage residual urine may accumulate to a point where the patient can void only a fraction of his bladder contents.

Urethral Resistance

Lapides *et al.* (1960) investigated the resistance presented by various segments of the urethra to fluid injected towards the bladder in normal subjects. In subvesical obstruction the increased urethral resistance can be detected in various ways. In retrograde urethrometry the mucosa of the anterior urethra is anaesthetized to diminish reflex spasm, and warm normal saline is introduced into the urethra. The lowest pressure required to produce continuous flow via an intravenous drip chamber into the bladder—"minimal flow pressure"—is determined by slowly raising the reservoir. The "maximum static urethral pressure" can be demonstrated during this test or simply by injecting about 20 ml. of saline along the urethra into the bladder and noting the pressure of the volume remaining in the distal urethra after the posterior urethra has again closed (W. K. Y.). Urethral resistance during micturition can be calculated by measuring urine-flow rates concomitantly with

the recording of bladder and intra-abdominal pressures (von Garrelts, 1956 ; Cardus, Quesada, and Scott, 1963).

Micturating cysto-urethrography, preferably using an image intensifier and cine-recording, may reveal spasm either of the bladder-neck or of the external sphincter or both. Spasm of the external sphincter may cause dilatation of the prostatic urethra, especially in its posterior segment beneath the bladder-neck, where it is least supported. The appearances produced may simulate those of a median bar, and the site of obstruction so be misinterpreted. Changes in the urethral resistance and contours following caudal- or pudendal-nerve blocks may indicate the muscle groups concerned in the urethral obstruction and their degree of spasm.

Trabeculation of the bladder-wall and the state of the bladder-neck can be seen by cysto-urethroscopy, but the degree of spasm of the external sphincter cannot be assessed by endoscopy alone. Electromyography of the superficial external sphincter ani is not difficult, and may demonstrate hyperactivity indicative of that affecting the striated muscles of the pelvic floor (Cardus *et al.*, 1963).

Disturbances of micturition in most multiple-sclerotic patients are due to combinations of bladder dysfunction and increased urethral resistance: careful assessment of the contribution of the various factors mentioned above is essential if treatment is to be rational. In any irritable bladder, infection is the most important additional factor concerned in the provocation or aggravation of symptoms. This is difficult to control in many cases, and virtually impossible to eradicate where there is persistent residual urine.

Symptomatology and Clinical Correlations

The purpose of the present investigation was to clarify the clinical syndromes of bladder disturbance in multiple sclerosis, to establish the relation of these symptoms to the natural history of the disease in general, and to find out how far they correlated with other clinical evidence of spinal-cord involvement. Two hundred and ninety-seven patients with probable multiple sclerosis were re-examined specifically from this point of view. All these patients lived on Tyneside, and were drawn from the clinical records of the Royal Victoria Infirmary, and of a survey of multiple sclerosis in Northumberland and Durham carried out by Poskanzer, Schapira, and Miller (1963). With regard to age and sex distribution and duration of the disease, these 297 cases were virtually identical with the larger series reported in the survey mentioned above, and can be regarded as fairly representative of multiple sclerosis as it presents in the general population in this part of Great Britain.

These patients were grouped into three simple categories according to the grade of functional disability present. The first group were either symptom-free or had symptoms which in no way restricted their activities, the second consisted of intermediate cases, and the third consisted of patients who were confined to their home and able to take only a few steps or were confined to bed or a wheelchair. Close inquiry was made about specific bladder symptoms, their duration, and whether they were persistent or intermittent. The severity of bladder symptoms was graded as none, temporary (one transient episode), intermittent, persistent (but without incontinence or retention), and finally repeated episodes of acute retention or "unconscious" incontinence. This phrase is used where the patient is unaware of the passage of urine, in contrast with urge incontinence, where the patient is clearly conscious of the uncontrolled passage of urine. Bowel and sexual function were also assessed.

Bladder symptoms had occurred at some time in 140 female and 91 male patients (78%). Urinary symptoms which had persisted for more than six months were present in 52% of patients at the time of examination. In 2% of all cases a disturbance of micturition had been the sole initial symptom, and in 12% it had constituted one feature of the initial episode. The mean duration of multiple sclerosis in these patients was 12 years, and that of the bladder symptoms six years.

Statistical comparison of the grades of severity of functional disability and bladder disturbance showed that the severity of bladder symptoms at the time of examination was unrelated to their duration, to the age of the patient, or to the duration of the neurological illness as a whole. The severity of bladder disturbance was, however, clearly related to the severity of the disease, and this was particularly evident in relation to spastic weakness resulting from lesions of the corticospinal tracts. Bladder symptoms were significantly more frequent in patients with bilateral spasticity than in those whose spastic weakness was unilateral, and correlation between bladder disturbance and bilateral impairment of vibration sense was even more striking. However, it is of interest that 21% of the patients who were entirely free of bladder symptoms had severe bilateral spasticity, 13% had extensive loss of vibration sense in the lower limbs, and 8% had both.

There was no single abnormal neurological finding with which bladder disturbance was invariably associated, nor was there any finding which was invariably present in patients with bladder disturbance, but all patients with "unconscious" incontinence or repeated retention had spasticity of both lower limbs, and this was severe in 70%.

It is clear that neither extensive disease of the lateral columns involving the descending corticospinal tracts nor of the ascending tracts which convey vibration sense necessarily impairs bladder control. On present evidence we can correlate the severity of bladder symptoms only with the general severity and extent of neurological damage within the spinal cord.

Specific Bladder Symptoms

Solitary transient episodes of bladder disturbance were ignored in the analysis of specific bladder symptoms, the commonest of which was urgency: this was followed by frequency, urge incontinence, hesitancy, "unconscious" incontinence, and retention, in that order. Combinations of symptoms were present in 64%.

Urgency of micturition occurred in 60%, and was often combined with frequency, urge incontinence, and hesitancy. Frequency was found in 50%, and was always associated with urgency. Urge incontinence occurred in 36%, and was commoner in women than in men. The term "urge incontinence" is a broad one covering at one extreme urgency with potential leakage and at the other urgency with precipitancy—that is, with more or less complete bladder-emptying. Most of these patients had mild symptoms, such as urgency with slight leakage, and it is probable that many with urge incontinence would not be wet if they could hasten to the lavatory, but this is prevented by their restricted mobility. A crude though useful clinical assessment of the severity of urge incontinence is to inquire whether the patient is "damp," "wet," "soaked," or "flooded." Thirty-three per cent. of the patients had hesitancy, and the proportion of males with this symptom was excessive, presumably owing to the ability of the male to develop a stronger contraction of the external sphincter and levator ani than the female (Lapides *et al.*, 1960).

"Unconscious" incontinence was present in 10% of patients, and in these the causal disease was more severe and long-standing than in those with other symptoms. Curiously, there was a preponderance of men with "unconscious" incontinence. It is possible that many such patients may have had retention with overflow from a small contracted bladder, but cystometry would have been required to confirm this. Only six patients (2%) suffered repeated episodes of urinary retention, but this occurred once in five others, and all 11 were severely disabled by their multiple sclerosis. When retention occurs it seems to affect younger patients, and it certainly tends to arise earlier

in the disease than other urinary symptoms. No patient required permanent drainage, though a few needed indwelling catheters for as long as two months, and the only patient able to leave hospital with retention was a doctor's wife. Surprisingly, painful micturition was present in only three patients with florid infection of the urinary tract, but many others had infection manifest in other symptoms, such as urgency.

The prevalence of bowel disturbance due to multiple sclerosis is difficult to determine, since there is so much constipation in the community. However, there was no bowel disturbance in 45% of the patients. Constipation was the commonest symptom (39%), but nearly half of these cases had always been constipated. Urgency of defaecation occurred in 10% of patients. In 2% it was a feature of the initial attack, in 3% it coincided with the onset of bladder symptoms, and it was associated with urgency of micturition in all except two patients who had no urinary symptoms whatever.

Inquiry about sexual difficulties encountered some resistance in the female, and in both sexes the situation is complicated by purely psychological factors. In women loss of libido or of the capacity to achieve orgasm was an occasional concomitant of bladder disturbances. Sixty-two per cent. of the male patients were impotent: in 18% this was possibly due to evident psychological disturbance, but in the remaining 44% it could be attributed only to the physical effects of the disease. Such failure to achieve erection was always associated with and had most often followed the onset of bladder symptoms.

Management

Not only has acute retention of urine a special predilection for the young patient with early multiple sclerosis but it nearly always clears, and treatment is therefore conservative. Immediate catheterization using a Gibbon catheter (10 F.G.) is followed by continuous urethral drainage for 24 hours. If function does not return on removal of the catheter it is replaced by a Gibbon balloon catheter (12 F.G.), and drainage continued. Two 2-mg. tablets of carbachol are given six-hourly, as well as a sulphonamide. Bladder function should be reassessed by cystometry every three days initially, and then weekly as in post-traumatic spinal shock.

The primary aims of treatment of chronic bladder dysfunction in multiple sclerosis are to preserve renal function by the elimination of residual urine if it is infected or associated with dilatation of the upper urinary tract; to reduce bladder irritability whether from diminished inhibition, bladder hypertrophy, reduction of bladder capacity by the presence of residual urine, or from infection; and to palliate irremediable incontinence by collection, drainage, or diversion of the urine.

Drug Therapy

Anticholinergic agents such as Belladenal and propantheline bromide (Pro-banthine) may be of considerable benefit for the uninhibited bladder where there is little or no residual urine. Cholinergic agents such as carbachol may be of value in partial neurogenic bladder failure, especially since such bladders tend to be hypersensitive to acetylcholine. The drug is also worth a trial when this syndrome is combined with obstinate subvesical obstruction. Infection of the paralysed bladder usually demands treatment with a succession or combination of antibacterial drugs determined by the results of repeated cultures of the urine.

Reduction of Urethral Resistance

Pudendal neurectomy is theoretically the ideal procedure for bladder-neck and perineal muscle spasm, but has the disadvantage of producing impotence. It is indicated especially where pudendal nerve blocks temporarily remove the obstruction, and where potency is no longer at issue. In most cases transurethral resection of the bladder-neck and the upper part of the elastic ring at the apex of the prostatic urethra produces effective reduction of resistance, but in some it is necessary to carry out transurethral resection or lateral incisions lower down in the region of the external sphincter.

The removal of obstruction may restore a fairly satisfactory degree of function with continence, but, as Ross, Gibbon, and Damanski (1964) have demonstrated, the results in multiple sclerosis are more disappointing than in other neurogenic bladder disorders. Many cases continue to have dysfunction referable to the bladder itself. Some have residual urine from neurogenic bladder failure because the abdominal wall is too weak to provide compensatory expulsive power. In others deficient inhibition causes persistent urge incontinence. Either may benefit to some extent from appropriate drug treatment.

Appliances, Drainage, and Diversion

Many patients are eventually incontinent because of bladder irritability or weakness of the urethra as a result of necessary surgical reduction of resistance. In men this incontinence can be controlled fairly satisfactorily by wearing a portable urinal, but no effective appliance has yet been devised for female patients.

Long-term urethral drainage with a Foley catheter is indicated in occasional patients of both sexes with retention of long duration, and in women with uncontrollable incontinence. Suprapubic drainage may be required in the few men intolerant of urethral drainage.

Although catheter drainage may be fairly satisfactory for years in some cases, urinary diversion may be indicated in women with persistent incontinence or retention who have a life expectancy of more than about a year, and is certainly indicated in those with leakage round a large Foley catheter. In thin women anterior urethral transposition (Griffiths, 1960, 1964) is especially suitable. In others an ileal conduit is indicated, as it is in men with persistent retention where urethral and suprapubic drainage have become unsatisfactory on account of bladder pain, infection, or repeated calculus formation. This operation is also of value in cases of male incontinence where a portable urinal is for some reason unsuitable.

Replacement of a hyperactive detrusor by a segment of ileum (Shuttleworth, 1964) may restore continence, but even after transurethral resection of the bladder-neck weakness of the abdominal wall may prevent micturition by straining, and manual expression by others may be necessary. Less abdominal straining may be needed after colocystoplasty than ileocystoplasty, but the colon itself might be affected by deficiencies of inhibition.

Electrical Stimulation

Electrical stimulation of the bladder muscle is an attractive suggestion for primary bladder failure, but has so far not proved a practicable proposition. However, where adequate removal of subvesical resistance has resulted in incontinence it might be possible to use a technique (Caldwell, 1963, 1964) for restoring continence by constant stimulation of the pelvic floor. Electrical stimulation might also conceivably be used for stimulating the muscles of the abdominal wall to aid expulsion.

Further Research

There are many gaps in our understanding of both normal and disordered bladder function, and the views on these subjects set out above are nothing more than tentative. Continued

exploitation of the newer methods of investigation already mentioned should increase our understanding both of normal function and of the complex disorders encountered in multiple sclerosis. Rational treatment must be based on further research in this direction. Experience must also be gained in the value of the several ingenious operations which have been devised to deviate the incontinent urinary stream to more convenient outlets: these operations have not yet been widely applied. To the patient the greatest boon would be the development of a safe, leak-proof, comfortable female urinal. From the academic viewpoint the most interesting possibilities are those raised by recent developments in the field of electrical stimulation of the bladder and sphincters, which may ultimately furnish useful therapeutic methods.

Summary

Estimates of the prevalence of bladder dysfunction in multiple sclerosis vary considerably because of differing case selection.

Current views on normal bladder function are described, and the nature of its disturbance in multiple sclerosis is discussed. Bladder dysfunction in this disease differs from that in other conditions because of the preponderance of females, the tendency to remission, the presence of multiple neurological lesions, and the frequent weakness of the abdominal wall. Bladder sensation is often retained to a late stage.

A study is described in which bladder dysfunction was evaluated in a representative sample of patients with multiple sclerosis in Northumberland and Durham. Bladder disturbance had occurred at some time in 78%, and was persistent in 52% ; it was the sole initial symptom in 2%, and one feature of the initial attack of multiple sclerosis in 12%. The severity of bladder symptoms was more clearly related to the severity of clinical disablement than to any other factor, though patients with severe spasticity as well as profound impairment of vibration sense are sometimes entirely free of bladder symptoms. Sixty-four per cent. of patients had combinations of different symptoms, 60% had urgency, 50% frequency, 36% urge incontinence, 33% hesitancy, and 10% "unconscious" incontinence. Only 2% suffered from repeated episodes of urinary retention. Constipation occurred in 39%, and urgency of defaecation in 10%. Impotence was present in 44% of males.

The management of bladder disturbances in multiple sclerosis is discussed in terms of drug therapy, surgical reduction of urethral resistance, bladder reconstruction, and diversion of urine. Electrical stimulation of the bladder and sphincters may afford therapeutic possibilities for the future.

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Mosquito-borne Haemorrhagic Fever in Malaya*

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Although mosquito-borne haemorrhagic fever with circulatory collapse had been observed in the Philippines and Thailand (Hammon, Rudnick, and Sather, 1960), and in Singapore (Lim, Rudnick and Chan, 1961), it had not been reported in Malaya[1] when this study was initiated in 1962. This is the first report of the disease in Malaya. This disease syndrome has been aetiologically associated with several types of dengue virus in the Philippines, Thailand (Hammon *et al.*, 1960), and Singapore (Lim *et al.*, 1961), and with chikungunya virus in Thailand (Hammon *et al.*, 1960). The disease has also recently appeared in Calcutta, involving both dengue and chikungunya viruses (Chaudhuri, Chatterjea, Saha, and Chaudhuri, 1964). In all of these areas it appears that *Aëdes aegypti* has been the primary vector of the viruses incriminated (Chaudhuri *et al.*, 1964 ; Rudnick and Hammon, 1960, 1961).

Some observers in the field felt that the disease had been recently introduced to the Philippines, Thailand, and Singapore, but we believed that the viruses involved were probably endemic

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[1] Singapore, Sarawak, and Sabah joined the Federation of Malaya in 1963 to form the new Federation of Malaysia.