Altered clinical and histological features of male MM mouse pyelonephritis associated with a change in its microbiology

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Summary

Radical changes in the clinical, microbiological and histological features of spontaneous pyelonephritis in MM male mice occurred when they were transferred to a new environment after Caesarian derivation. Although the incidence of pyelonephritis remained the same, the survival age was increased. The renal histology indicated a shift to a more chronic form of pyelonephritis with renal amyloidosis as a common feature. At autopsy much more renal scarring was seen, resulting in the 'shrunken' kidney typical of chronic pyelonephritis. Renal lymphocytic accumulations were commonly found in MM mice, but they were also seen frequently in C57BL mice and in germfree stocks of both strains: no association was found between these lesions and pyelonephritis.

Keywords: Amyloid; Environment; Lymphocytic accumulations; MM mice; Pyelonephritis; Renal histology

Male MM mice have a high incidence of spontaneous pyelonephritis (Taylor & Fraser, 1975) which is precipitated by diabetes mellitus (Taylor, Neal & McBride, 1987). Originally, the urinary tract infections (UTIs) were caused predominantly by *Proteus mirabilis* (Taylor & Fraser, 1975). When the MM stock was transferred to a new environment 6 months after Caesarian derivation and cross-fostering, although the incidence of pyelonephritis remained unchanged, *Proteus* played a minor role and other bacteria, mainly *Pasteurella pneumotropica* and *Streptococcus faecalis*, became the dominant renal pathogens (Taylor, 1988). The disease also became more chronic, and affected animals survived to a greater age. At the same time it was found that all isolates of *Proteus mirabilis* from the new environment were atypical strains; it was demonstrated that they were still potentially pathogenic and it is not known why they were outranked by the other organisms causing UTI in this environment (Taylor, 1988). It is assumed that cross-fostering following Caesarian derivation permitted the establishment of a non-representative gut microflora which became fixed in the new environment. Concomitant changes which occurred in the clinical, pathological and histological features of male MM pyelonephritis are described in this paper.

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Materials and methods

Mice, husbandry and environment

These studies were carried out at the Animal Breeding Research Organisation, Edinburgh, where our animals were housed before the establishment of our present specified-pathogen-free colony. Details of the many mouse strains maintained and the husbandry regimes for the conventional (Taylor & Fraser, 1973) and germfree (Taylor, 1975; 1978) mice have been published previously. The differences between the original environment (environment A (EA)) and the second environment (environment B (EB)) have been described elsewhere (Taylor, 1988); the periods of study in each environment were approximately 30 months and 40 months respectively.

Histology

The routine histological procedures used have

been outlined before (Taylor & Fraser, 1973). The severity of renal periarteriolar lymphoid accumulations in coded sections was scored on the following scale: 0, unaffected; 1, mild; 2, moderate; 3, severe.

Results

Clinical observations

In EA there was generally a period of a few weeks prior to death during which affected male MM mice showed a deterioration in condition, marked by a staring coat and general lassitude. Staining of the abdominal fur was common as a consequence of 'dribbling' rather than a clean voiding of urine, and crystalline material was frequently seen protruding from the meatus. During the EA study an excessive odour of ammonia was associated with MM male cages, which necessitated doubling the normal cage-cleaning frequency.

Within EB, progressive deterioration of MM males still occurred, but over a period of months rather than weeks, and the average life-span was extended. Other notable changes were that protrusion of crystalline material from the meatus was rare and cage odour was sufficiently reduced to allow a return to the normal weekly frequency of cleaning. Large groups of MM mice from both environments were subjected to detailed autopsy; the mortality and microbiological data from these and control C57BL mice are presented elsewhere (Taylor, 1988). The average age at death of female MMs in EB compared with EA was significantly increased from 388 to 504 days ($P < 0.001$); this was due to the absence of mammary tumours which were eliminated towards the end of the EA study by Caesarian derivation and cross fostering. MM male longevity was also significantly greater, increasing on average from 356 days in EA to 412 days in EB ($P < 0.001$). Within both environments the survival of both sexes of MM mice was significantly less than for C57BL. In EA the life-span of C57BL mice was similar to that of the majority of the other 12 stocks bred there. The contrast in longevity between MM and C57BL males is illustrated by the survival curves in Fig. 1; an end-point to 600 days was selected and this was quite adequate to show the marked divergence ($P < 0.001$). The possibility that the difference is simply due to intrinsic genetic traits for longevity between mouse strains is excluded by our observation that under germfree conditions C57BL mice and MM mice survive to comparable ages well in excess of 800 days (Taylor, unpublished observations).

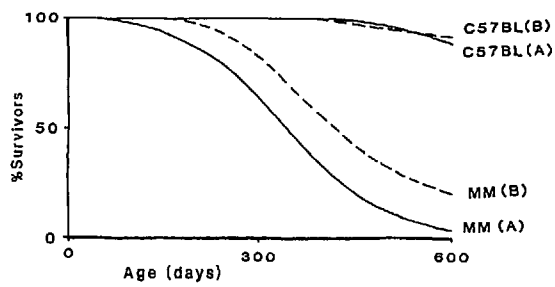

Fig. 1. Comparison of survival to 600 days of C57BL and MM mice in EA and EB.

Autopsy observations

In EA, MM males often became terminally ill so rapidly that inspection was necessary twice daily to ensure that fresh carcasses were available for postmortem study. All mice in the study were subjected to a full autopsy except for examination of the brain. Autopsy findings for the 188 C57BL mice have not been tabulated as they were unspectacular. One C57BL female and one male had mesenteric tumours. The only other observation was that all the males had plugs of 'waxy' material lodged in the urethra, frequently extending into the bladder, but this is a normal finding in our mature male mice (Taylor, 1985). By far the most common abnormalities of the 172 MM females in EA were mammary tumours (102 cases) usually accompanied by splenomegaly and occasionally by mesenteric tumours. One female had a lymphoma of the left kidney and three had a thickening of the bladder wall. In

contrast, MM males had a considerable range of abnormalities (Table 1).

Because of the complexity of the data in Table 1, detailed analysis of combinations of abnormalities has not been attempted; the most frequent combination in EA was splenomegaly, renal abnormality, bladder abnormality and urethral abnormality. In EB urethral and bladder stones were less frequent, renal abscesses were rare and renal scarring was considerably increased. The mesenteric and thymic tumours seen in MM males from both environments were incidental findings and were not uncommon in all strains in the colony examined by routine autopsy. Renal abscesses varied from large single lesions to multiple pinhead lesions on the surface of the kidney. Renal scarring ranged from small discrete fibrotic areas on otherwise normal kidneys to shrunken kidneys with irregular surfaces showing much fibrosis. Abscesses and fibrosis were not detected in the same kidneys. Bladder stones showed considerable variation in size and consistency, the largest being a greyish-white nodular crystalline mass with a diameter of 1 cm, but more frequently they consisted of multiple greyish-white stones with an average diameter of approximately 1 mm forming a gravel. Bladder thickening was detected as a loss of its usual semi-transparency and ranged from mild changes to gross thickening accompanied by dilation of the mural blood vessels. The cases of renal abscess were associated with cystitis, but cystitis also occurred in the absence of macroscopic renal lesions. Turbid bladder urine ranged from pale watery mildly opalescent fluid to thick muco-purulent material.

Histological findings (environment A)

The histological findings from the EA animals are presented in Table 2. The small number of C57BL mice in EA is a reflection of the shorter period of that part of the study and the good health and longevity of this strain. Examination of the kidneys of the 408 dead or dying MM males revealed the presence of pyelonephritis, usually massive, in 188 cases. There was a low or zero incidence in other groups. Necrosis and abscess formation (Fig. 2 and 3), showing a polar or segmental distribution (Fig. 4), were frequent features. Fibrosis, with complete narrowing of the whole thickness of the medulla and cortical parenchyma, sometimes occurred (Fig. 5). Lymphoid, plasma and other inflammatory cells were present in the

Table 1. Summary of autopsy abnormalities detected in male MM mice

Abnormality	*No. affected*		
	Environment A (408 mice)	*Environment B (317 mice)*	*P* (χ^2)
Mesenteric tumour	13	20	< 0.05
Thymic tumour	7	8	NS*
Splenomegaly	151	169	< 0.001
Left renal abscess	1	0	NS*
Right renal abscess	1	1	NS*
Bilateral renal abscess	3	0	NS*
Left renal scarring	2	71	< 0.05
Right renal scarring	6	83	< 0.001
Bilateral renal scarring	90	105	< 0.001
Cystitis	140	169	< 0.001
Severe bladder distension	35	93	< 0.001
Bladder stones	28	17	NS*
Turbid bladder urine	77	141	< 0.001
Urethral inflammation	13	6	NS*
Urethral stones	17	2	< 0.01
Urethral 'waxy' plugs	408	317	NS*

*Not significant ($P > 0.1$).

Table 2. Renal histological findings in the environment A mice

Mouse strain	*Sex*	*No.*	*Pyelo-nephritis (%)*	*Lymphocytic accumulations (%)*	*Other lesions*[a] (%)	Negative (%)
MM	M	408	46[b]	41	9	4
MM	F	172	5	58	22	15
C57BL	M	10	10	40	30	20
C57BL	F	9	0	12	33	55

[a]Findings in this column represent a variety of lesions, principally tumour metastases.
[b]Those with pyelonephritis had a mean age at death of 328 days compared with 380 days for the others.

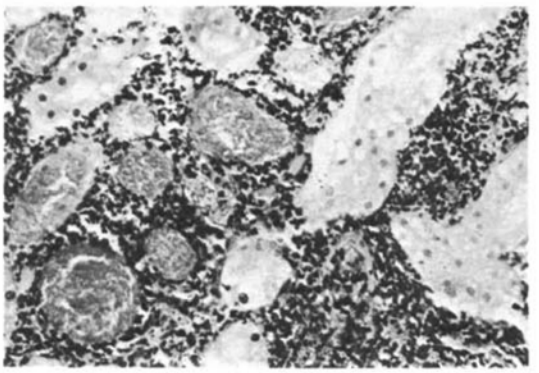

Fig. 2. Severe pyelonephritis with necrosis of renal tubules. (H&E; 800×.)

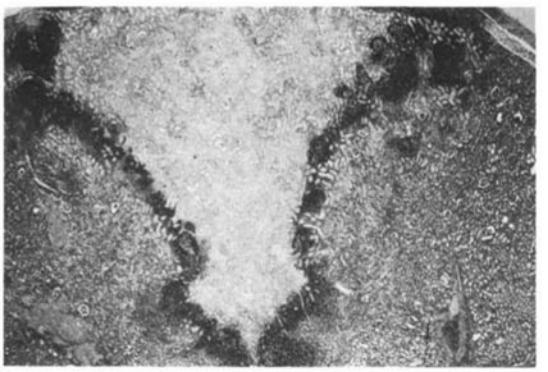

Fig. 4. Segmental necrosis and severe suppurative inflammation. (H&E; 40×.)

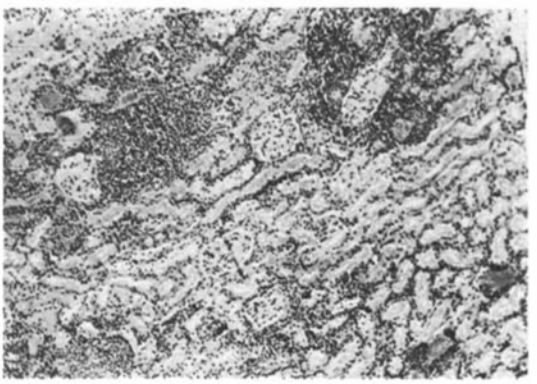

Fig. 3. Severe polymorphonuclear infiltration in the renal cortex. (H&E; 200×.)

peri-ureteric and renal fat (Figs 5 and 6). These inflammatory processes also involved the lumen of the ureter (Fig. 7). Papillary necrosis (Fig. 8) was a less common but striking feature accompanying pyelonephritis. Renal lymphocytic accumulations were frequently seen, usually around small arterioles (Fig. 9). More severe manifestations of this lesion were accompanied by plasma cells within the cortex and the outer zone of the medulla and in the vicinity of the hilus (Fig. 10). Periarteriolar lymphocytic accumulations were also seen in C57BL mice, but the overall incidence and severity were greater in MM mice.

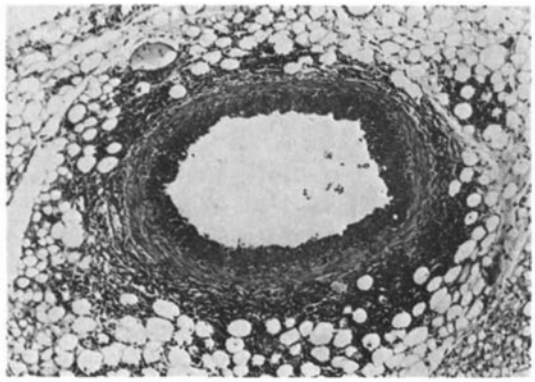

Fig. 5. Narrowing of medulla and cortex, and infiltration of surrounding renal fat with plasma and lymphoid cells. (H&E; 200×.)

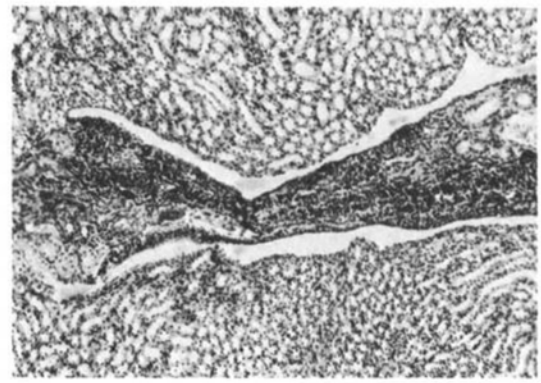

Fig. 8. Papillary necrosis accompanying pyelonephritis. (H&E; 40×.)

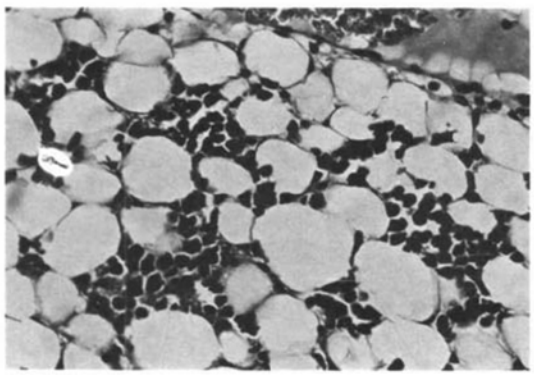

Fig. 6. Plasma cells and lymphocytes infiltrating the renal fat. (H&E; 800×.)

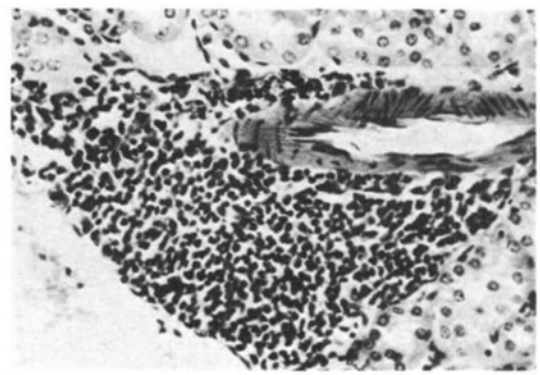

Fig. 9. Periarteriolar accumulation of lymphocytes (score 3). (H&E; 800×.)

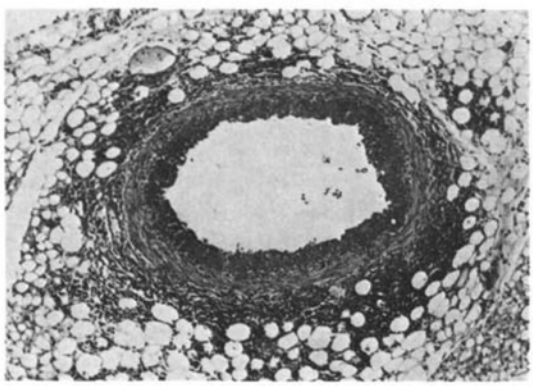

Fig. 7. Severe inflammatory involvement of ureter and associated renal fat. (H&E; 200×.)

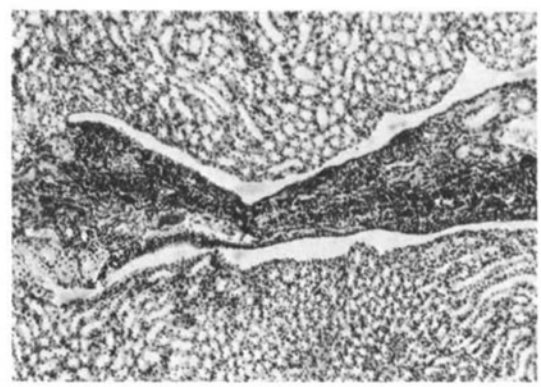

Fig. 10. Lymphocytes accumulating at the renal hilus. (H&E; 200×.)

Examination of the bladders from pyelonephritic MM males always revealed a suppurative cystitis, sometimes with mural necrosis and sloughing of the epithelium.

The general experience gained from the routine examination of large numbers of animals in unrelated experiments indicates that the '10% incidence' (one case) of pyelonephritis in the dead or dying C57BL males is an overestimate. This conclusion is supported by the EB data and by another study in which 2481 mice of all the strains in this colony were examined for the presence of hydronephrosis but none had macroscopic evidence of pyelonephritis (Taylor & Fraser, 1973).

Groups of culled healthy controls were examined for renal histological changes (Table 3). Comparison of Tables 2 and 3 shows that pyelonephritis is much less common in younger clinically healthy MM males, and that the incidence of lymphocytic accumulations is higher in older mice including C57BL. The single apparent contradiction to this is the MM male group, but severe pyelonephritis would supplant the underlyng lymphosis.

Histological findings (environment B)

The incidence of pyelonephritis and lymphocytic accumulations detected in the EB MM males is shown in Table 4. There are no dramatic differences between Table 2 (EA) and Table 4 (EB), but the greater average age of the EB pyelonephritics is consistent with the overall later average age at death of EB MM males.

The increased longevity of the EB pyelonephritics was associated with changes in the histological picture, and the concomitant microbiological changes between EA and EB are described elsewhere (Taylor, 1988). Although the various renal changes associated with the acute phase were still present, a new more chronic form of the disease was regularly seen. The most common and prominent features were tubular swelling, interstitial nephritis, fibrosis, cystic changes and amyloidosis (Fig. 11). The renal amyloid was found to be only part of a more generalized amyloidosis and was sufficiently frequent to require further analysis. For clarity, renal amyloid was not listed as a specific histological characteristic in

Table 3. Renal histological findings in culled healthy MM and C57BL mice

Mouse strain	*Sex*	*No.*	*Mean age (range)* (days)	*Pyelo-nephritis* (%)	*Lymphocytic accumulations* (%)	*Other lesions* (%)	*Negative* (%)
MM	M	191	168 (51–922)	4	52	2	42
MM	F	139	179 (51–573)	1	51	1	47
C57BL	M	197	270 (54–867)	0	15	5	80
C57BL	F	167	298 (50–762)	0	14	9	77

Table 4. Renal histological findings in the EB mice

Mouse strain	*Sex*	*No.*	*Pyelo-nephritis* (%)	*Lymphocytic accumulations* (%)	*Other lesions* (%)	*Negative* (%)
MM	M	317	44[a]	46	5	5
MM	F	192	1	66	3	30
C57BL	M	97	0	47	35	18
C57BL	F	82	0	29	19	52

[a]Mice with pyelonephritis had a mean age at death of 392 days compared with 428 days for the others.

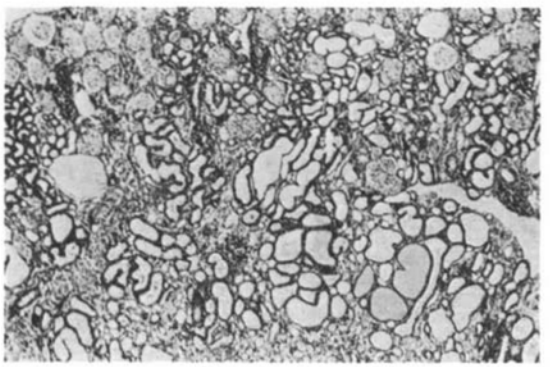

Fig. 11. Chronic nephropathy showing cystic tubular change and casts, interstitial fibrosis and amyloidosis. (H&E; 200×.)

Tables 2 and 4. Table 5 shows the incidence of renal amyloid in these animals.

There was a considerably increased incidence of MM male renal amyloid in EB (Table 5), presumably reflecting the more chronic nature of the EB disease; secondary amyloidosis is a common consequence of prolonged stimulation of the immune mechanisms through chronic infection (Dunn, 1967). However, the occurrence of renal amyloid in 11% of EB MM females was surprising considering that the incidence of pyelonephritis was only 5%. However, we subsequently discovered that 33% of MM females can have very mild cystitis which does not often lead to pyelonephritis (not tested for in EA), which could explain their relatively high incidence of renal amyloid. The fact that amyloidosis was not present in C57BL mice at any stage of the study

Table 5. Incidence of renal amyloidosis in the animals from Tables 2 and 4

Environment	*Mouse strain*	*Sex*	*No.*	*No. with renal amyloid*
A	MM	M	408	8 (2%)
	MM	F	172	0
	C57BL	M	10	0
	C57BL	F	9	0
B	MM	M	317	78 (25%)
	MM	F	192	20 (11%)
	C57BL	M	97	0
	C57BL	F	82	0

supports the concept that it is precipitated by infection. Furthermore, none of the germfree mice studied had amyloidosis at any age.

Histological findings (germfree mice)

Renal periarteriolar lymphocytic accumulations occurred as the only renal lesion in germfree MM mice, but the incidence and severity were considerably lower, with a later age of onset, than in conventional MM mice (Table 6).

Discussion

As the role of *Proteus* diminished in EB, the male MM pyelonephritis became more chronic (Taylor, 1988). Renal scarring, for example, which was more common in EB, is recognized as a common consequence of chronic pyelonephritis resulting in the typical 'shrunken' kidney; the reduced role of *Proteus* was consistent with the knowledge that *Proteus* causes particularly acute pyelonephritis (Braude, Siemienski & Shapiro, 1960). The increased longevity and the changes in the autopsy findings for MM males in EB were consistent with the more chronic nature of the renal histology and were accompanied by a changed microbiological picture (Taylor, 1988).

It is widely agreed that most cases of pyelonephritis in humans are a result of ascending infection; the haematogenous route of spread is much less common. In MM mice also the fact that renal abscesses were much less common than cystitis but were always accompanied by cystitis suggests that the infection is ascending.

Because of the association between pyelonephritis and diabetes mellitus in MM mice (Taylor, Neal & McBride, 1987), the detection of papillary necrosis is interesting. Among the causes of papillary necrosis in humans are diabetes (Robbins & Angrist, 1949), pyelonephritis (Simon, Bennett & Emmett, 1957) and diabetic pyelonephritis (MacGregor, 1970).

Despite the qualitative differences between the histological changes seen in pyelonephritis in the two environments, the incidence re-

Table 6. Comparison of the incidence and severity of renal lymphocytic accumulations in conventional and germfree MM mice

	Sex	*Group*	*No.*	*Age range (average age)* (days)	*No. with accumulations*	*Average score of severity of accumulations*	*Age range of those with accumulations (average age)* (days)
Environment B conventional MM mice	F	Culled	127	51–573 (175)	69 (54%)	1.4	95–573 (212)
		Killed because of illness (or dead)	21	36–756 (335)	11 (52%)	2.1	235–756 (442)
	M	Culled	139	22–548 (167)	84 (60%)	1.4	78–548 (194)
		Killed because of illness (or dead)	24	218–722 (411)	14 (58%)	2.1	310–619 (474)
Contemporary germfree MM mice	F	Culled	127	21–645 (152)	14 (11%)	1.3	188–645 (329)
		killed because of illness (or dead)[a]	21	190–681 (340)	5 (24%)	1.4	494–681 (567)
	M	Culled	139	21–791 (157)	25 (18%)	1.2	167–645 (350)
		Killed because of illness (or dead)[a]	24	65–652 (307)	7 (29%)	1.1	161–652 (443)

[a]Caecal volvulus, pregnancy complications or haemorrhagic syndrome.

mained the same but the microbiological picture changed (Taylor, 1988). This, together with the fact that UTI is rarely present in the other mouse strains in our colony (the experience of many thousands of autopsies), reflects an underlying susceptibility of MM males owing to their diabetic status (Taylor, Neal & McBride, 1987); the occurrence of some cystitis in the females which are non-diabetic suggests that other genetic factors might also be involved.

Table 6 shows that MM mice are susceptible to renal lymphoid accumulations which are aggravated by factors in the conventional environment, but these have not been implicated in the aetiology of MM pyelonephritis. Furthermore, these lesions also commonly occur in our conventional and gnotobiotic C57BL mice and in our other strains of mice. The possibility that these lesions are an immunopathological process which might give rise, for example, to a generalized low-avidity antibody responsiveness (Soothill & Steward, 1971) was not confirmed by studies carried out for us by Dr M. Williams, Institute for Research on Animal Diseases, Compton. Irradiation and transplantation studies (Taylor, 1983) excluded the possibility that they might represent an early manifestation of lymphosarcoma. The pathogenesis of the renal lymphosis therefore remains unsolved.

In view of the relatively high incidence of UTI in humans and some domesticated animal species, it is surprising that useful natural models for such infections had not been found in inbred laboratory animals until the model in MM mice was reported (Taylor & Fraser, 1975). Severe interventional techniques had usually been used to render the urinary tract of experimental animals susceptible to infection, but the relevance of such investigations to natural disease is open to question (Gorill, 1960; Guze, 1960), particularly since the acute disease is the most often studied but the chronic disease is the greater medical problem. Furthermore, many experimental techniques induce haematogenous pyelonephritis, whereas most natural infections are ascending in nature.

The interventional techniques have included administration of renal toxins (Yamauchi *et al.*, 1961), potassium depletion (Woods *et al.*, 1960), electrocautery (Rocha *et al.*, 1958), renal massage (Braude, Shapiro & Siemienski, 1955), ureteric occlusion (Lepper, 1921), occlusion of renal arteries (Goldblatt *et al.*, 1934), challenge with highly virulent bacteria (Cotran *et al.*, 1963) and foreign-body implantation (Miller *et al.*, 1956). The routes of bacterial challenge have included intravenous (Helmholz, 1934), intracardiac (Pitsch, Hebert & Carey, 1962) and intra-urethral (Hepinstall, 1965) injection, and the introduction of infection directly into the bladder (Brooks, Lyons & Braude, 1974) or kidney (Alderman & Freedman, 1963). Another approach has been to induce experimental infection in laboratory animals with pre-existing urinary tract anomalies (Guze, Hubert & Kalmanson, 1965). However, with artificially induced infections there is a risk that the subject will develop secondary anatomical, physiological or biochemical abnormalities which are not found in natural infections (Guze, 1960; Vaughn, Sorenson & Gillenwater, 1970; Arendshort, Finn & Gottschalk, 1974; Hodson *et al.*, 1975; Morrison, Nishikawa & Needleman, 1977). Furthermore, the relevance of the use of bacterial strains cultured in the laboratory is doubtful. This is because the pathogenicity of bacteria for the urinary tract is often facilitated by their adhesion to urinary tract epithelium by means of their sticky surface pili (Costerton, Geesey & Cheng, 1978) which can be rapidly lost under laboratory culture conditions (Swanson, Kraus & Gotschlich, 1971). For these reasons it is considered that the spontaneous pyelonephritis which occurs at high incidence in male MM mice represents an important and unique laboratory animal model. There is also a clear association of the MM mouse pyelonephritis with diabetes mellitus (Taylor, Neal & McBride, 1987), and this is important in its own right. MM mice are available on request.

References

Alderman, M. H. & Freedman, L. R. (1963). Experimental pyelonephritis: X. The direct injection of *E. coli* protoplasts into the medulla of the rabbit kidney. *Yale Journal of Biology and Medicine* **36**, 157–164.

Arendshort, W. J., Finn, W. P. & Gottschalk, C. W. (1974). Nephron stop-flow pressure response to obstruction for 24 hours in the rat kidney. *Journal of Clinical Investigation* **53**, 1497–1500.

Braude, A. I., Shapiro, A. P. & Siemienski, J. (1955). Haematogenous pyelonephritis in rats I. Its pathogenesis when produced by a simple new method. *Journal of Clinical Investigation* **34**, 1489–1497.

Braude, A. I., Siemienski, J. & Shapiro, A. P. (1960). The role of bacterial urease in the pathogenesis of pyelonephritis. In *Biology of Pyelonephritis* (eds E. L. Quinn & E. H. Kass), pp. 69–88. London: Churchill Livingstone.

Brooks, S. J. D., Lyons, J. M. & Braude, A. I. (1974). Immunisation against retrograde pyelonephritis I. Production of an experimental model of severe ascending *Escherichia coli* pyelonephritis without bacteremia in rats. *American Journal of Pathology* **74**, 345–364.

Costerton, J. W., Geesey, G. G. & Cheng, K.-J. (1978). How bacteria stick. *Scientific American* **238**, 86–95.

Cotran, R. S., Vivaldi, E., Zangwill, D. P. & Kass, E. H. (1963). Retrograde *Proteus* pyelonephritis in rats. Bacteriologic, pathologic and fluorescent-antibody studies. *American Journal of Pathology* **43**, 1–31.

Dunn, T. B. (1967). Amyloidosis in mice. In *Pathology of Laboratory Rats and Mice* (eds. E. Cotchin and F. J. C. Roe), pp. 181–212. Oxford: Blackwells.

Goldblatt, H., Lynch, J., Hanzal, R. F. & Summerville, W. W. (1934). Studies on experimenal hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischaemia. *Journal of Experimental Medicine* **59**, 347–380.

Gorrill, R. H. (1960). Bacteriology and pathogenesis of experimental pyelonephritis. In *Biology of Pyelonephritis* (eds E. L. Quinn and E. H. Kass), pp. 3–10. London: J & A Churchill.

Guze, L. B. (1960). Experimental pyelonephritis: observations on the course of enterococcal infection in the kidney of the rat. In *Biology of Pyelonephritis* (eds E. L. Quinn and E. H. Kass), pp. 11–26. London: J & A Churchill.

Guze, L. B., Hubert, E. & Kalmanson, G. M. (1965). Pyelonephritis. VI. Observations of the effect of congenital partial ureteral obstruction on susceptibility of the rat kidney to infection. *Journal of Infectious Diseases* **115**, 500–505.

Helmholz, H. (1934). Experimental studies in urinary infections of the bacillary type. *Journal of Urology* **31**, 173–191.

Heptinstall, R. H. (1965). Experimental pyelonephritis: a comparison of blood-borne and ascending patterns of infection. *Journal of Pathology and Bacteriology* **89**, 71–80.

Hodson, C. J., Maling, T. M. J., McNamanon, P. J. & Lewis, M. G. (1975). The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). *British Journal of Radiology, Suppl. 13* **48**, 1–26.

Lepper, E. H. (1921). The production of coliform infection in the urinary tract of rabbits. *Journal of Pathology and Bacteriology* **24**, 192–204.

MacGregor, M. (1970). Consideration of childhood urinary infection as the forerunner of renal insufficiency in later life. *Archives of Diseases of Childhood* **45**, 159–172.

Miller, G. H., Chapman, W. H., Seibutis, L. & Vermeulen, C. W. (1956). Furadantin treatment of experimental urinary tract infections and its influence on stone growth. *Journal of Urology* **76**, 42–46.

Morrison, A. R., Nishikawa, K. & Needleman, P. (1977). Unmasking of thromboxane A^2 synthesis by ureteral obstruction in the rabbit kidney. *Nature, London* **267**, 259–260.

Pitsch, B., Herbert, T. & Carey, W. P. (1962). Establishment and treatment of experimental *Escherichia coli* pyelonephritis. In *Antimicrobial Agents and Chemotherapy* (eds M. Finland and G. Savage), pp. 54–60. Ann Arbor, MI: Braun-Brumfield.

Robbins, E. D. & Angrist, A. (1949). Necrosis of renal papillae. *Annals of Internal Medicine* **31**, 773–793.

Rocha, H., Guze, L. B., Freedman, L. R. & Beeson, P. B. (1958). Experimental pyelonephritis III. The influence of localised injury in different parts of the kidney on susceptibility to bacillary infection. *Yale Journal of Biology and Medicine* **30**, 341–354.

Simon, H., Bennett, W. & Emmett, J. (1957). Renal papillary necrosis: a clinicopathologic study of 42 cases. *Journal of Urology* **77**, 557–567.

Soothill, J. F. & Steward, M. W. (1971). The immunopathological significance of the heterogeneity of antibody affinity. *Clinical and Experimental Immunology* **9**, 193–199.

Swanson, J., Kraus, S. J. & Gotschlich, E. C. (1971). Studies on gonococcus infection. I. Pili and zones of adhesion: their relation to gonococcal growth patterns. *Journal of Experimental Medicine* **134**, 886–906.

Taylor, D. M. (1975). The use of laminar flow for obtaining germfree mice. *Laboratory Animals* **9**, 337–343.

Taylor, D. M. (1978). Rationalisation and modification of a germfree isolator design. *Laboratory Animals* **12**, 21–22.

Taylor, D. M. (1983). Male-specific, spontaneous pyelonephritis associated with diabetes mellitus in MM mice. *Ph.D. Thesis*, Open Univerisity.

Taylor, D. M. (1985). Urethral plugs and urine retention in male mice. *Laboratory Animals* **19**, 189–191.

Taylor, D. M. (1988). A shift from acute to chronic spontaneous pyelonephritis in male MM mice associated with a change in the causal micro-organisms. *Laboratory Animals* **22**, 27–34.

Taylor, D. M. & Fraser, H. (1973). Hydronephrosis in inbred strains of mice with particular reference to the BRVR strain. *Laboratory Animals* **7**, 229–236.

Taylor, D. M. & Fraser, H. (1975). The association of *Proteus mirabilis* with pyelonephritis in male MM mice. *Proceedings of the Society for General Microbiology* **111**, 15 (abstract).

Taylor, D. M., Neal, D. L. & McBride, P. A. (1987). The association between spontaneous pyelonephritis and maturity-onset diabetes mellitus in male MM mice.

Laboratory Animals **21**.
Vaughn, F. D., Sorenson, E. J. & Gillenwater, J. Y. (1970). The renal haemodynamic response to chronic unilateral complete ureteral occlusion. *Investigative Urology* **8**, 78–90.
Woods, J. W., Welt, L. G., Hollander, W. & Newton, M. (1960). Susceptibility of rats to experimental pyelonephritis following recovery from potassium depletion. *Journal of Clinical Investigation* **39**, 28–33.
Yamauchi, H., Rosenau, W., Brainerd, E. & Hopper, J. (1961). Experimental pyelonephritis in rats with aminonucleoside (AMN) nephrosis. *Clinical Research* **9**, 107.