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Acquiescent renal infection

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Acquiescent renal infection. The relationship between bacterial infection of the renal parenchyma with *Escherichia coli* and the establishment of pathologic lesions has been investigated experimentally. Infection was established in one kidney and the bacteriologic, pathologic and immunologic features of infection were compared in the pyelonephritic and contralateral unmanipulated kidney. Whereas active bacterial infection was associated with pathologic changes in the pyelonephritic kidney, a poor correlation was found between bacterial growth and the gross pathology and histopathologic changes in the contralateral kidney. The conclusion from these studies is that infection of the kidney is not always associated with pathologic changes. The term "acquiescent infection" has been used to describe this host–parasite relationship in which active, persistent, bacterial infection is not associated with pathologic lesions. Evidence is presented that bacteria in the contralateral unmanipulated kidney are present in the renal parenchyma and that bacterial proliferation can be induced following renal trauma. Activation of infection and bacterial proliferation did not always result in histopathologic damage to the kidney and was not associated with an increase in serum antibody.

Infection rénale consentante. La relation entre l'infection bactérienne du parenchyme rénal par *Escherichia coli* et l'établissement de lésions pathologiques a été étudiée expérimentalement. L'infection a été établie dans un rein et ses manifestations bactériologique, histologique et immunologique ont été comparées dans le rein pyélonéphritique et le rein controlatéral non manipulé. Alors que l'infection bactérienne active est associée à des modifications histologiques dans le rein pyélonéphritique, la corrélation est pauvre entre la croissance bactérienne d'une part, et, d'autre part, la morphologie et les modifications histologiques dans le rein controlatéral. La conclusion de ces travaux est que l'infection du rein n'est pas toujours associée à des modifications histologiques. Le terme "d'infection consentante" (acquiescent infection) a été utilisé pour décrire cette relation hôte–parasite dans laquelle une infection bactérienne active et persistante n'est pas associée à des lésions histologiques. La preuve est apportée de la présence de bactéries dans le parenchyme rénal controlatéral non manipulé et de la possibilité de prolifération bactérienne induite par un traumatisme rénal. L'activation de l'infection et la prolifération bactérienne ne déterminent pas toujours une lésion histologique du rein et ne sont pas associées à une augmentation des anticorps sériques.

Persistence of active infection in the kidney remains a characteristic feature of pyelonephritis in both human disease and some experimentally induced renal infections. Despite early convictions that chronic renal infection led to chronic pyelonephritis, the association of continuing infection with progressive loss of renal function has been challenged [1–3]. Recent procedures that allow the localization of infection have been of value in determining the site of infection, but details of the relationship between the presence of an infectious organism and the development of pathologic lesions have been difficult to acquire. When the effect of infection on renal function has been followed, the results have shown that infection in an otherwise normal urinary tract does not result in a deterioration of renal function [4, 5].

The suggestion from previously published studies is that infection of the kidney is not synonymous with pathologic changes, although this has been difficult to prove in man because of the patchy distribution of the lesions and the inconclusiveness of a normal renal biopsy. In these experiments we have examined the relationship between the establishment of infection and the development of pathologic changes in the kidney using an animal model.

A host–parasite relationship has been disclosed where the organism established an active infection in the renal parenchyma, but infection alone did not usually lead to pathologic changes in the kidney. It is suggested that the term "acquiescent infection" be used to describe the host–parasite relationship in this situation where a balance is maintained between the host and the invading organism.

Methods

Animal strain. Female rats weighing 220 to 230 g were obtained from an inbred HS (hooded) strain of rat obtained from Dr. Barbara F. Heslop, University of Otago Medical School, New Zealand, and maintained in this Department by consecutive brother-sister mating.

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Bacterial strain. The strain of *Escherichia coli* 075 used in these experiments was the same as that used in previous studies of experimental pyelonephritis [6–8].

Production of renal infection. Pyelonephritis was induced by the direct inoculation of *E. coli* into the surgically exposed kidney using a glass microcapillary. Details of the method have been given previously [9].

Bacterial content of renal tissue. Nutrient agar pour plates of serial tenfold dilutions of homogenized kidney were made to obtain the bacterial count per gram of wet renal tissue.

Histological processing. Tissue for histologic examination was placed directly into a 0.1% solution of cetylpyridinium chloride in 10% formaldehyde. After routine processing and cutting, sections were stained with hematoxylin-eosin.

Collection of blood for antibody titers. Blood was collected from the tail of lightly anesthetised rats directly into microcentrifuge tubes. After centrifugation, the serum was removed and stored at −20°C until analyzed.

Determination of serum antibody in the autoanalyzer. Serum antibody concentrations were determined by an automated procedure using an autoanalyzer (Technicon) adapted to determine the level of antibacterial antibody [10]. The method is essentially a passive hemagglutination procedure using sheep red blood cells coated with endotoxin as a source of "O" antigen. With this procedure antibody titers are reported on a continuous scale and are not restricted to the limitations of serial dilution end points. The results recorded in Table 1 are the reciprocal of the highest dilution of serum showing detectable agglutination in the autoanalyzer.

Dissection of the kidney into cortex, medulla and papilla. The medulla with attached papilla was removed from each kidney with a hollow cylindrical blade of 7 mm internal diameter [11]. Cortical tissue on each side of the medullary cylinder was removed and the remaining tissue cut at the line of demarcation between medulla and papilla. The crescent of the cortex left after removal of the medullary cylinder was then trimmed to remove residual medullary tissue. Each piece of tissue was weighed and homogenized in physiologically normal saline. Agar pour plates of dilutions of the homogenate were made to obtain the bacterial count per gram of tissue.

Measurement of maximum urine concentrating capacity. All animals had food and water removed 24 hr before being placed in a metabolic cage specifically designed for urine collection. At the end of the 24-hr period animals were forced to micturate, using a whiff of ether in a nose cone, before being placed in the metabolic cage still without food or water.

All urine passed overnight was collected under

Table 1. Immune response of the host during the activation of acquiescent infection

	Animal No.	Antibody titer						
		Pre-thermal trauma, *weeks*				Post-thermal trauma, *days*		Assessment[a]
		4	3	2	1	3	7	
Control group (unilateral infection only)	1	579	678	499	701	472	543	NSI
	2	1316	371	244	877	279	512	NSI
	3	278	571	729	1122	1056	1562	NSI
	4	738	1270	785	570	888	1599	SI
	5	207	131	130	248	141	219	NSI
	6	130	98	155	200	448	444	NSI
	7	1382	581	799	162	795	1299	SI
	8	143	154	155	134	140	294	NSI
	9	652	1076	1225	947	1658	3654	SI
	10	541	562	459	367	499	787	NSI
Test group (unilateral infection and thermal injury to contralateral kidney)	1	241	361	348	171	292	600	SI
	2	2752	3283	3112	4185	4185	1349	NSI
	3	454	398	622	570	1320	4310	SI
	4	411	348	407	191	258	2499	SI
	5	652	278	669	224	267	675	NSI
	6	1981	1420	1434	883	1756	3014	SI
	7	5930	1098	825	463	1925	6497	SI
	8	584	537	516	371	324	694	NSI
	9	847	405	683	521	423	1003	NSI
	10	521	322	448	186	250	410	NSI

[a] NSI = no significant increase after thermal injury. SI = significant increase. An increase of 500 or more titer units between the final pre-thermal trama—post-thermal trama serum antibody concentration was considered to be a significant increase.

paraffin to prevent evaporation. At 9 AM the following morning, they again micturated and this urine was added to the overnight collection. Urinary osmolality was measured in an osmometer (Knauer) after preparing a 1:4 dilution of the urine in water.

Antimicrobial therapy. When necessary, infection in the kidney was eliminated by treatment with gentamicin for ten days at a dosage of 20 mg/kg/day. In some experiments intragastric nalidixic acid treatment was used at a dosage of 250 mg/kg/day for ten days. The *E. coli* 075 strain used in these experiments was sensitive to 1.0 μg/ml of gentamicin and 1.6 μg/ml of nalidixic acid.

Results

Experimental pyelonephritis. Unilateral pyelonephritis was induced in 34 rats by the direct inoculation of *E. coli* into one kidney and the animals were maintained under normal laboratory conditions for up to six months. Characteristic features of the experimental infection in the pyelonephritic kidney have been described in a previous report [9]. The natural history of the infection in the contralateral unmanipulated kidney was studied in two groups of animals which were killed two and six months after the induction of unilateral infection. At the time of death, the gross pathology (Fig. 1), histopathologic changes (Fig. 2) and bacteriologic features of infection in the contralateral and pyelonephritic kidney were compared.

The most notable feature was the lack of correlation between bacterial growth, the gross pathology and histopathologic changes in the kidney (Fig. 3). Although the method of inducing pyelonephritis involved minor local trauma, when killed bacteria were introduced instead of viable organisms both the gross and histopathologic changes were minimal and were confined to the microcapillary tract.

In the pyelonephritic kidney into which bacteria had been directly introduced, scarred and contracted kidneys were found showing the characteristic features of pyelonephritis. Similar numbers of bacteria were present in the contralateral kidney but in contrast the pathologic changes were minimal.

Determination of the distribution of bacteria in the pyelonephritic kidney and the contralateral kidney. Unilateral pyelonephritis was induced in a further group of six animals and the infection allowed to proceed for six months. At the time of sacrifice, both the pyelonephritic and the contralateral kidney were dissected into cortical, medullary and papillary tissue and the bacterial content of each region was determined. Macroscopic differences between cortical, medullary and papillary tissues were quite distinct so that the spongy medulla and papilla could be readily separated from cortical tissue.

In these experiments bacteria were found to be evenly distributed throughout the contralateral kidney and were not confined to the renal pelvis or medulla (Fig. 4). The presence of equivalent numbers of organ-

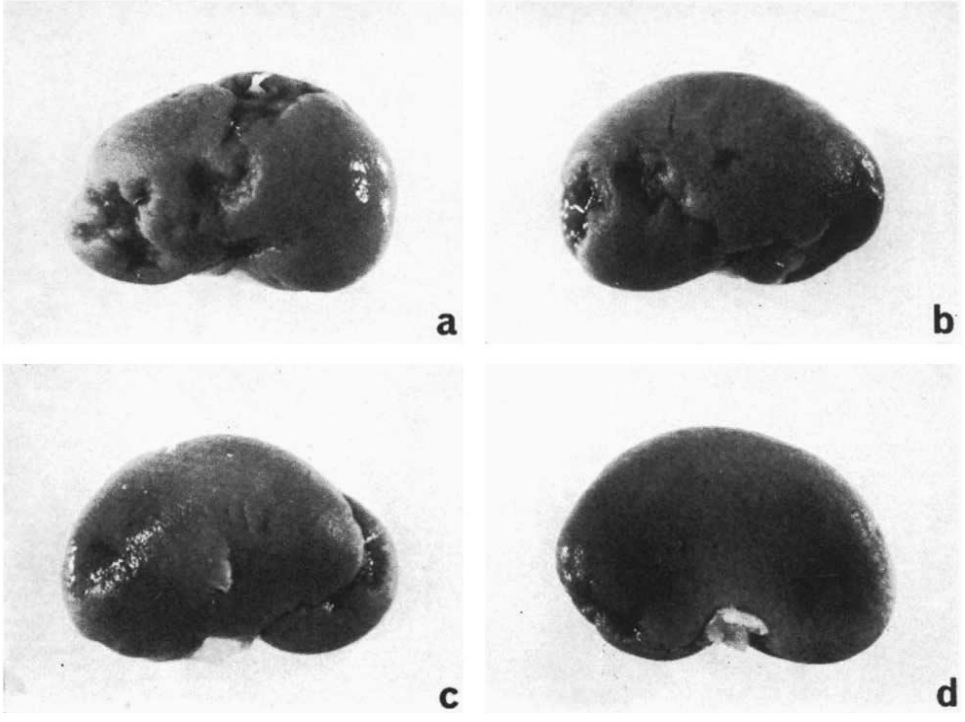

Fig. 1. *Quantitation of the degree of scar formation.* Assessment was made on a 0 to 10 scale with each *point* on the scale representing one tenth of the surface of the kidney. The kidney illustrated in (a) was scored as 6, (b) as 4, (c) as 2 and (d) as 1.

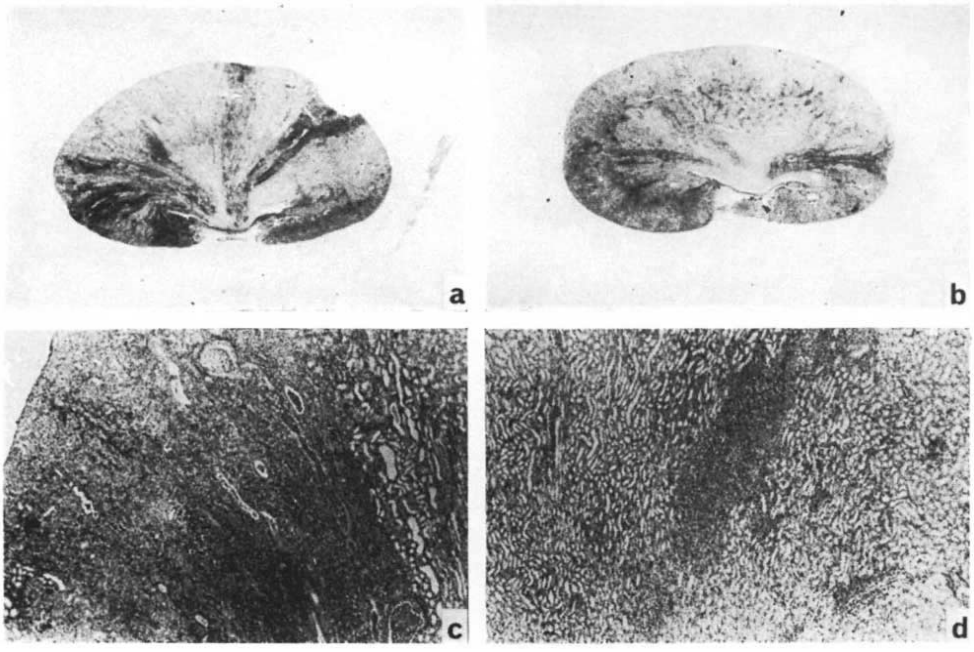

Fig. 2. *Histopathologic assessment of the degree of renal damage.* On the scale used, 10 represented lesions involving 25% or more of the area of the section. Lesser degrees of damage were scored on a 0 to 10 scale where each unit represented 2.5% of the area of the kidney. The section (×8) illustrated in (a) was scored as 10 and (b) as 2. (c) and (d) are photomicrographs taken under lower power magnification (×40).

isms in renal cortex, medulla and papilla of the contralateral kidney suggested that the invading organisms had penetrated into the interstitium of the kidney.

The effect of acquiescent infection on the renal concentrating capacity. Unilateral pyelonephritis was induced in a group of nine animals and the infection allowed to proceed for eight weeks. A further group of 12 matched animals was used as controls. The pyelonephritic kidney and an unmanipulated kidney in the control group were then removed and the urine concentrating capacity of the remaining kidney was determined two and three months later. The ability to form a concentrated urine was significantly impaired in the animals with acquiescent infection ($P < 0.001$) when this function was compared with control animals with a sterile kidney (Fig. 5).

When the animals were killed, two of the nine animals from the acquiescent infection group were found to be sterile. One of these had a concentrating capacity of 1988 mOsm/kg and the other a maximum of 1,600 mOsm/kg. The remaining animals in the group were all infected and an average bacterial count

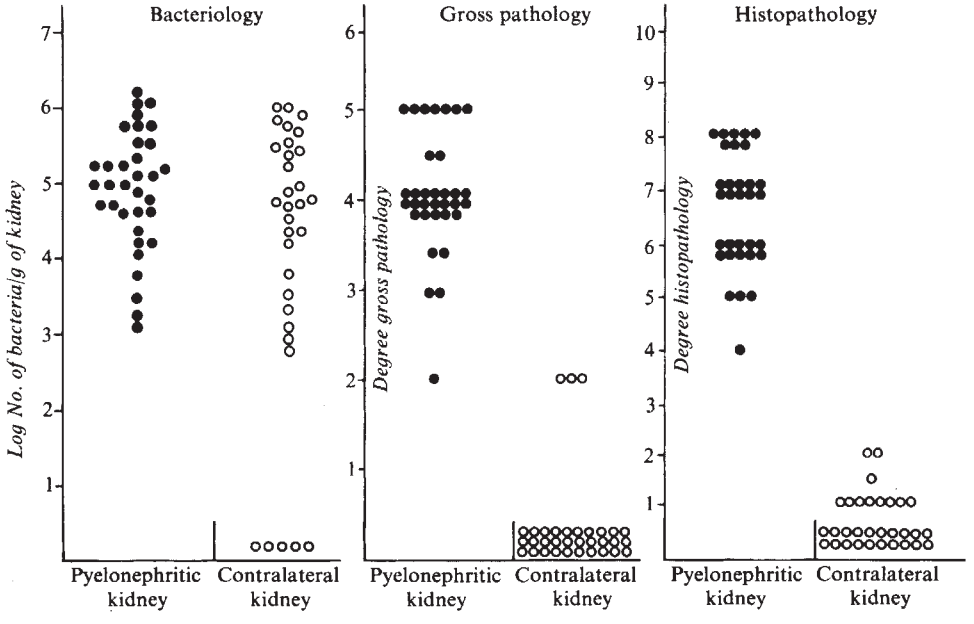

Fig. 3. *The gross pathology, histopathologic and bacteriologic features of infection in the pyelonephritic kidney* (closed circles) *and the contralateral unmanipulated kidney* (open circles) *two to six months after the induction of a unilateral infection in the pyelonephritic kidney only.*

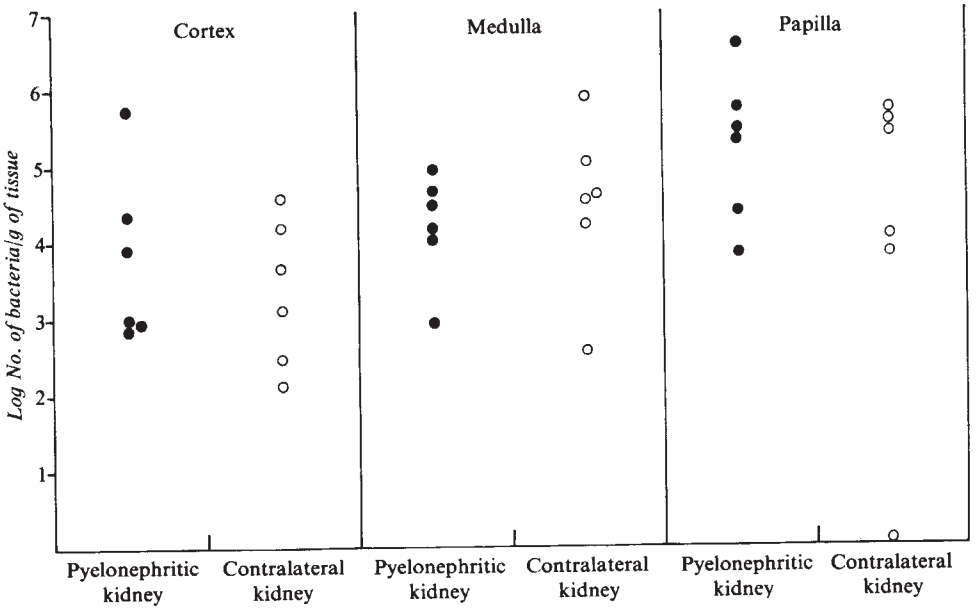

Fig. 4. *Distribution of bacteria within the pyelonephritic and contralateral kidney.*

of 2.3×10^5 organisms/g of kidney was found. All kidneys from the control group were sterile.

Effect of luminal sterilization on bacterial numbers in the pyelonephritic and contralateral kidney. To investigate the intrarenal location of bacteria in the contralateral kidney, unilateral pyelonephritis was induced in three groups of six animals and the infection allowed to proceed for three months. At the end of this period, one group was treated daily for ten days with the urinary antiseptic nalidixic acid, and the animals were killed seven days after the end of treatment. A further group of animals was treated with gentamicin, 20 mg/kg/day for ten days, a treatment schedule that was known to eliminate effectively infection from the renal parenchyma. The third group of animals was left untreated and served as a control group. The kidneys of all three groups of animals were examined for residual infection and the bacterial content of the pyelonephritic and contralateral kidneys was determined.

In these experiments, gentamicin was able to eradicate an established infection while nalidixic acid had no effect on the number of bacteria in either the pyelonephritic or the contralateral kidney although the infecting organism was sensitive to less than 2 μg/ml of nalidixic acid (Fig. 6).

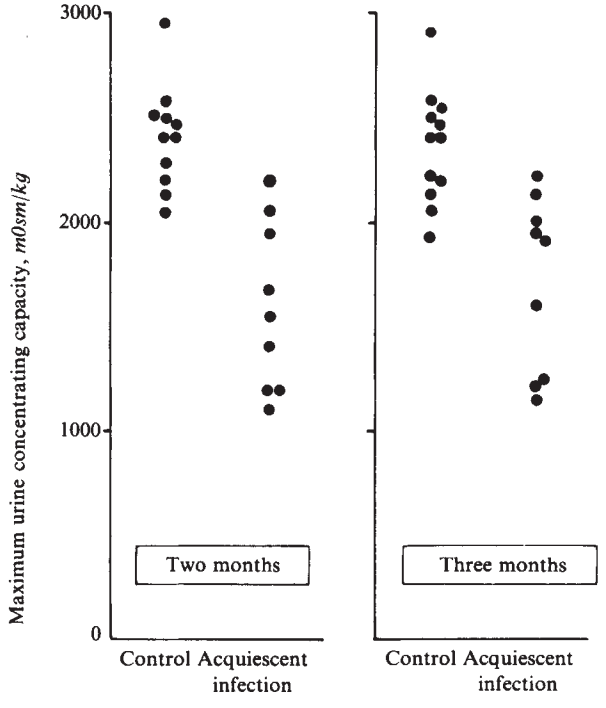

Fig. 5. *Maximum urine concentrating capacity in animals with acquiescent renal infection compared with control animals, two and three months after unilateral nephrectomy.*

Induction of bacterial proliferation in the contralateral kidney following renal injury. Data reported above have shown that large numbers of bacteria were present in the contralateral unmanipulated kidney although the pathologic changes were minimal. Further experiments were carried out to determine whether the host–parasite relationship could be altered by intrarenal obstruction. Unilateral pyelonephritis was induced in two groups of 18 rats and three months after the initiation of infection, the contralateral kidneys of one group were thermally injured in three sites using 23-gauge hot nichrome wire. When the effect of thermal injury on the bacteriologic status of the contralateral kidney was examined seven days after injury, a remarkable increase in bacterial numbers had occurred in the thermally injured kidney. Whereas the

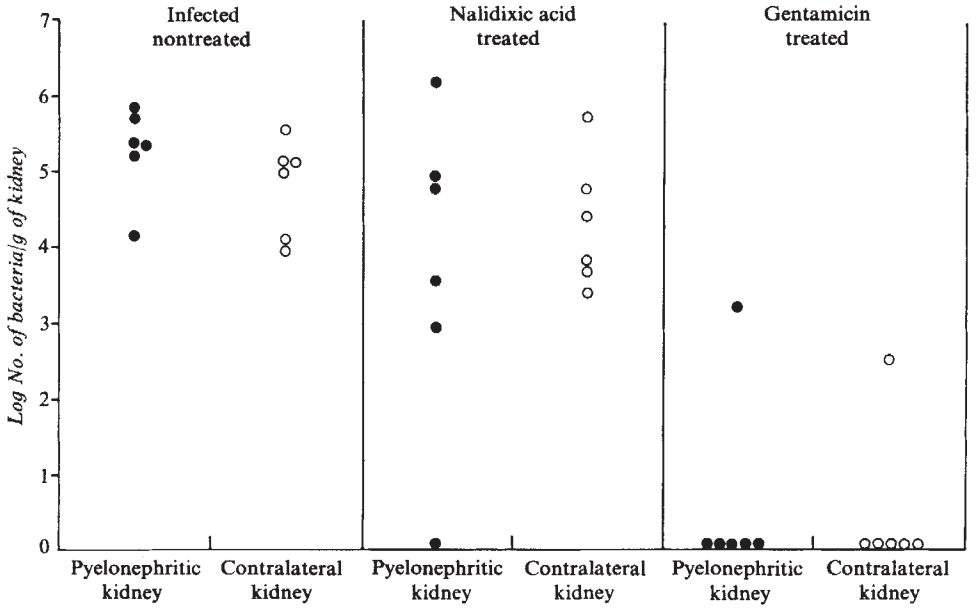

Fig. 6. *The effect of sterilization of the renal tubular lumen with nalidixic acid treatment on bacterial numbers in the pyelonephritic and contralateral kidney.*

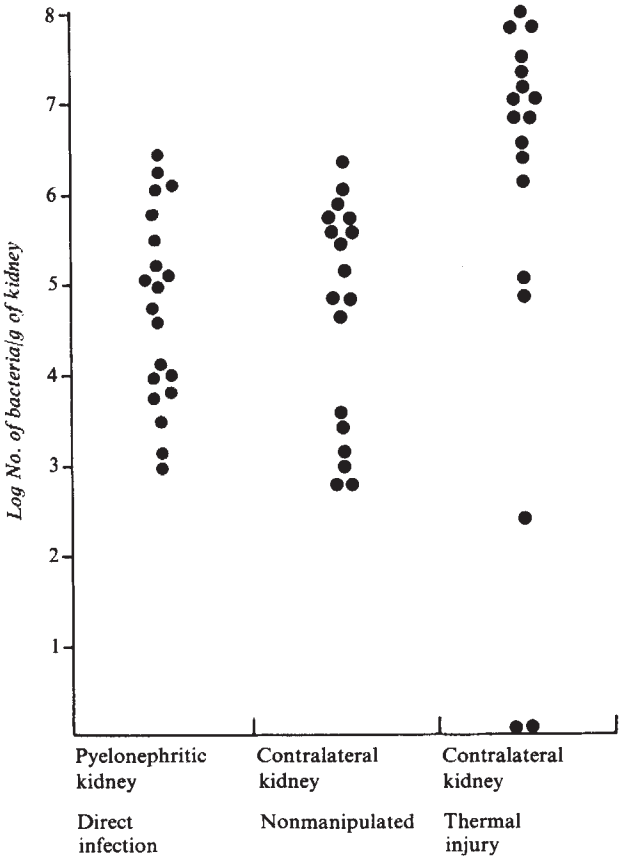

Fig. 7. *Induction of bacterial proliferation in the contralateral kidney by renal trauma.* Animals were killed seven days after thermal injury and the bacterial numbers determined in the thermally injured contralateral kidney, pyelonephritic kidney and a group of manipulated contralateral kidneys.

number of organisms in the pyelonephritic kidney and the unmanipulated contralateral kidney in the first group was again found to be similar, bacterial numbers in the thermally injured contralateral kidney of the second group were increased up to 100 times that of the nonmanipulated contralateral kidney (Fig. 7).

Histologic sections of the thermally injured kidney were also examined. Although most of the thermally injured kidneys had shown a marked increase in bacterial proliferation, there was histologic evidence of a pathologic lesion being established in only five of the 15 kidneys with bacterial proliferation. Kidneys from the remaining 13 animals with no inflammatory foci discernible histologically showed only a mild, nonspecific response to trauma similar to that seen following thermal injury to sterile control kidneys.

Immunologic status of the host during the activation of acquiescent infection. Serum antibody concentrations in rats with chronic renal infection remain at a raised level for prolonged periods after the initial infection has subsided [7] but the effect of activation of bacterial proliferation on the concentration of serum antibody is not known. To investigate this question, unilateral pyelonephritis was induced in two groups of ten animals and the source of the disease allowed to proceed for three months. Serial determinations of serum antibody concentrations were carried out, using the automated procedure, prior to the induction of bacterial replication in the contralateral kidney of one group by thermal injury. Serum samples were obtained from both groups three, seven and ten days after the activation of infection and serum antibody concentrations again determined in the autoanalyzer.

Although increased bacterial proliferation occurred in all animals with thermal injury to the contralateral kidney, there was no consistent increase in serum antibody concentrations. Five of ten individual animals showed an increase in serum antibody after thermal injury but similar increases were seen in three control animals so that the significance of the increase in the five test animals remains doubtful (Table 1).

Discussion

A cause and effect relationship between infection and the pathologic changes characteristic of chronic pyelonephritis was accepted for several decades. Early studies claiming that up to 16% of patients examined at postmortem had histological evidence of pyelonephritis [12] have been challenged [13] and the relationship of bacterial infection alone to chronic progressive pyelonephritis remains in doubt [14]. The frequency of bacterial invasion of the kidney [15, 16], and the relative infrequency of associated chronic pathologic lesions illustrate the outcome of a host–parasite relationship that has been difficult to investigate in man and has not been clearly defined in the experimental animal.

Our views of this host–parasite relationship in renal infection have been influenced by findings of the current experiments where unilateral pyelonephritis was induced by the direct inoculation of bacteria into one kidney only. Subsequent events leading to the establishment of infection in the contralateral unmanipulated kidney provided a unique model in that no manipulation of the contralateral kidney or the urinary tract was necessary. Under these circumstances the establishment of infection in the contralateral kidney, we believe, represents the natural history of renal infection in these animals and mimics many of the clinical and pathologic features of renal infection in man.

Using this model it has been possible to investigate the relationship of the invading organism to the host and the association between the presence of viable bacteria in the kidney and the development of pathologic lesions. The most striking feature was the poor correlation between bacterial infection and the degree of pathologic changes in the kidney. Although renal tissue must still be considered unusually susceptible to persistent infection, the association of renal infection with consistent pathologic lesions is not tenable.

The finding that a high level of infection was readily established in the contralateral unmanipulated kidney was at variance with the findings of our previous studies using a unilateral pyelonephritis where the contralateral kidney remained sterile [7]. The original experiments were carried out using a random-bred strain of Wistar rat and the capacity of the organism to establish an acquiescent infection was only disclosed when hooded rats were used in an attempt to establish the experimental model in an inbred strain of rat.

With this inbred strain, acquiescent infection has been found in 100 of 114 contralateral unmanipulated kidneys examined to date, which clearly demonstrates that this is a consistent feature of renal infection in these animals. The strain of hooded rat used in these experiments is widely used in transplantation studies but we are not aware of any specific characteristics relevant to the present experiments. The phenomenon is not unique, however, and although this is the first occasion where such a host–parasite relationship has been described in detail, there are a number of reports in the literature recording similar findings. Freedman [17] noted that it was remarkable that large numbers of *E. coli* could be recovered from experimentally infected kidneys without evidence of pathologic changes—and the results of studies by Prat, Hatala and Benesova [18]; Freedman and Beeson [19]; Carone, Kashgarian and Epstein [20]; and Woods et al [21] all contain evidence of acquiescent renal infection in animals challenged by the retrograde route. Continuing investigations in our own laboratory have also established that acquiescent infections can be found when strains of *E. coli* other than the one used in the present experiments are used to induce pyelonephritis.

From the evidence available, bacteria in the contralateral kidney appeared to have penetrated into the renal parenchyma and were not simply in the tubular lumen. Nalidixic acid was selected as a urinary antiseptic to sterilize the luminal contents on account of its protein binding (93%), negligible activity before excretion in the urine [22] and the sensitivity of the infecting organism to low concentrations of nalidixic acid (1.6 μg/ml). The failure of nalidixic acid therapy to affect bacterial numbers in the kidney strongly suggests that the bacterial cells are present in the renal interstitium in both the pyelonephritic and contralateral kidney and are consequently inaccessible to urinary antiseptics. Gentamicin, on the other hand, is rapidly and uniformly distributed in blood and tissue [23], and although the sensitivity of the *E. coli* strain to gentamicin was similar (1 μg/ml) to nalidixic acid, infection was readily eliminated from the kidney with gentamicin treatment.

Some of the differences between the experimental models where pathologic changes were usually found and our own studies probably relate to the manner

in which infection is initiated. Most experimental models involve distension of the bladder with a heavy suspension of bacteria which is then forced up the ureter into the kidney by pressure on the bladder. Vesico-ureteric reflux, however, occurs normally in the rat and the acquiescent infection established in the current experiments is more likely to have occurred as a result of constant but gentle reflux of infected urine.

Once a pyelonephritic lesion is established in the kidney, the host responds with a vigorous and well characterized immune response which appears neither to control the infection nor result in an extension of the pathologic process. The host seems to have become tolerant to a state of continuing infection in a normally sterile tissue and is incapable of eliminating the invading organism.

The term "tolerance" has a well established immunologic meaning and we suggest that the term "acquiescent infection" be used to describe the host–parasite relationship in this situation where the balance is maintained between the host and the invading organism, without local pathologic lesions.

Although a causal relationship between bacterial infection of the urinary tract and the development of radiological changes of chronic pyelonephritis as documented by Smellie and Normand [24] is generally recognized, there are many inconsistencies. Where patients with persistent renal infection have been followed, deterioration of renal function has not occurred, and even where upper urinary tract infection has resulted in a concentrating defect, this has been reversible both in man [25] and experimental animals [26].

A similar lack of correlation between bacterial invasion and renal pathology was found in a study of renal disease in patients with diabetes mellitus [27], and the normal renal function in most patients with ureterosigmoidostomy [28] and patients with indwelling catheters for up to 15 yr [29] supports the concept of an altered host–parasite relationship.

Acquiescent infection resulted in a substantial reduction in maximum urine concentrating capacity although we initially believed that the acquiescent state represented a relatively benign condition. The mechanism by which infection without any associated pathological changes causes a reduction in the concentrating capacity is not clear but is being investigated.

In attempting to explain the biological basis for an acquiescent state in renal infection, we have reexamined the role of the specific immune response. One possibility is that the invading organism may be utilizing the immune response to induce an acquiescent state and so escape host defence mechanisms. This pathogenic mechanism of immunologic enhancement has been well studied in tumor immunology [29] although it has not yet been applied to microbial persistence. Immunologic enhancement as a factor in acquiescent infection has been investigated in recent studies where the immune response of the host has been manipulated with cyclophosphamide therapy [31]. A remarkable inverse relationship between the immunocompetence of the host and the ability to clear bacteria from the infected kidney was found and the data suggested that the immune response led to the establishment of an acquiescent state that protected the organism from normally effective host defence mechanisms.

The effects of activation of acquiescent infection on the immune status of the host were of interest in view of the reliance that has been placed on serum antibody concentrations to indicate infection of the renal parenchyma in man [32]. In these experiments a consistent antibody titer was maintained for several weeks before the thermal injury and the activation of infection. Although increased bacterial proliferation was observed in all animals, there was no consistent increase in serum antibody concentrations. The results support earlier reports where circulating antibody concentrations did not reflect the course of the disease in chronic infection [7, 8] and provide a ready explanation for the poor correlation between clinical renal infection and serum antibody response [15].

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