At our mother's knee – an occasional review

Diabetes mellitus and infection

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Introduction

'Atishoo! Atishoo! All fall down'
(popular rhyme, anon)

Whether it be the plague or influenza, one thing we learn at the knee of our 'alma mater' is that diabetics are more likely to get it. The origins of this presumption are unclear. The decrease in mortality from sepsis and tuberculosis following the introduction of insulin has been well documented (Flynn, 1935) but in recent years there has been a tendency to presuppose an increased incidence of infection in diabetics and to search for an underlying cause. The complex problem of infection and diabetes mellitus requires critical re-examination and we have considered the following three questions:

- (1) Are diabetic patients more prone to infection?
- (2) Are infections more serious when they occur in diabetics?
- (3) Is there an explanation for positive answers to the first two questions?

Incidence of infection in diabetes

Discussion of the first question has given rise to dogmatic statements at both extremes of opinion. In a recent monograph (Galloway, 1980) the entire subject of infection was dismissed in one paragraph: 'The increased frequency of infection in the diabetic is well known, but its precise cause has not been discovered', while the opposing view that 'Infections are no commoner in well-controlled diabetics than in non-diabetics' has been claimed (Ireland *et al.*, 1980). Before reviewing the more common afflictions, mention must be made of a recognised group of rare infections where the incidence is definitely increased in

diabetics, and which may be confined almost entirely to patients with diabetes. The more important of these infections are listed in Table I showing the percentage number of affected patients who were diabetic.

Mucormycosis is caused by fungi of the family Mucoraceae. A renal case reported recently in this journal (Flood *et al.*, 1985) is unusual since the fungus more usually invades the nasal sinuses of the poorly controlled diabetic with ketoacidosis (Lehrer, 1980) and a fatal case was described recently in the UK in a newly-diagnosed diabetic returning from Spain (Larkin *et al.*, 1984). Facial pain and swelling are followed by neurological involvement, with the development of ophthalmoplegia or hemiparesis as the organism invades the brain via the blood vessels – the syndrome of rhinocerebral mucormycosis. Mortality from mucormycosis was 90% or higher (McBride *et al.*, 1960) until the introduction of amphotericin B and radical surgery which has reduced mortality to between 15% and 60% (Pillsbury & Fischer, 1977; Marchevskey *et al.*, 1980).

'Malignant otitis externa' was coined by Chandler in 1968 to describe a severe infection in 13 patients. This deep pseudomonas infection frequently causes facial nerve palsy and extensive necrosis of bone, often with a fatal outcome. Zaky *et al.* (1976) pointed out that early diagnosis and specific antibiotic therapy can improve the outlook and a recent editorial (*Lancet*,

Table I Rare diseases associated with diabetes mellitus, showing the percentage of affected patients who have diabetes.

Mucormycosis	42% (McBride <i>et al.</i> , 1960)
Malignant otitis externa	100% (Zaky <i>et al.</i> , 1976)
Emphysematous cholecystitis	38% (Casey, 1983a)
Necrotizing cellulitis	75% (Stone and Martin, 1972)

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1982) has suggested that dual therapy with an aminoglycoside and a penicillin of the carbenicillin group should accompany aggressive surgical management.

Emphysematous cholecystitis is caused by the clostridium species. The mortality is high, leading Wheat (1980) to advocate a high index of suspicion and the use of serial abdominal X-rays to aid an early diagnosis. Similar diseases can be caused by this organism in the kidney or urinary tract (Casey, 1983a).

Necrotising cellulitis (and fasciitis) can be caused by various organisms, some of which are gas-producing, and aerobic and anaerobic organisms often co-exist ('synergistic necrotising cellulitis'). Treatment requires a specific antibiotic for the identified organism (*Clostridia* and *Enterobacteriaceae* being common) and debridement of necrotic tissue. Despite these measures mortality remains high in diabetic patients (Stone & Martin, 1972).

There is little disagreement concerning the increased incidence of the above in diabetes, but recently the traditional acceptance of the association of common infections with diabetes has been disputed.

Urinary tract infection (UTI)

The increased incidence of UTI in diabetic patients was shown both in post-mortem studies (Robbins & Tucker, 1944) and in clinical studies reviewed by Wheat (1980). As Savin (1974), and other authors have suggested, this may be a manifestation of regular catheterisation and/or a poorly-emptying neurogenic bladder rather than the result of an underlying immune disturbance. Sjucs *et al.* (1960) found that diabetes *per se* did not predispose to clinically active UTI unless glycaemic control was poor which led some authors to surmise that UTI does not occur more frequently in well-controlled diabetic patients. It seems however to be generally accepted that poor diabetic control does increase the incidence of UTI. Even the well-controlled diabetics in Sjucs's study had an increased incidence of bacteriuria; so much depends on how 'infection' is defined. Fungal infections of the genito-urinary tract also appear to be more common in diabetics but factors such as the frequent or inappropriate use of antibiotics may play a role in promoting these more opportunistic infections.

Skin infections

Infections of the skin, particularly staphylococcal, are associated with poorly-controlled diabetes (Farrer & MacLeod, 1960). Conversely, an epidemiological study to screen patients for glucose intolerance found no increase in skin infections (Welborn *et al.*, 1968). One possible explanation is that the latter survey

identified a population with a less severe form of diabetes, and the estimated incidence of infection would therefore be closer to that of a non-diabetic population. There is a corollary with the increased incidence of asymptomatic bacteriuria in well-controlled diabetes since an increase in the nasal carriage of staphylococci has been found in diabetics by Smith *et al.* (1966). The concept that this leads to clinical infection only if glycaemic control is poor is an appealing one.

Periodontal disease

Despite previous disagreement a convincing study has confirmed the view that periodontal disease is more common in diabetes (Finestone & Boorujy, 1967), and appears to be worse when blood glucose is poorly controlled. Monilial infections in the mouth appear to be more common, and though this is not well documented, it is certainly a common presentation in a new diabetic patient.

Post-operative infection

The incidence of post-operative infections has variously been found to be either doubled (Cruse, 1970) or normal (Cohen *et al.*, 1964) in diabetic patients. The quality of glycaemic control in these patients was not described although Cohen's group mentioned that acidosis was not present. More specifically, 'septic shock' has been found in a much higher percentage in diabetics (7%) than in non-diabetics (1%) by Ariyan & Halasz (1967).

Pneumonia

Pneumococcal pneumonia is not more common in diabetic patients, but pneumonia caused by *Staphylococcus aureus* and *Klebsiella pneumoniae* may be more frequent (Casey, 1983a). The severity of pneumococcal pneumonia in diabetic patients has provoked debate as to whether vaccination should be instituted (Austman & Winegrad, 1980; Editorial, 1980).

Conclusion

While there are several negative studies, the evidence overall suggests that the rate of infection is increased in diabetes. Studies which have failed to show an increase have dealt mainly with well-controlled diabetics so that poor control would seem to predispose to infection. Recently Rayfield *et al.* (1982) supported this view by demonstrating a significant correlation between the overall prevalence of infection and mean plasma glucose levels (while uninfected) in 241 diabetic patients. The message seems clear. Good

control of diabetes is important for the prevention of infection.

Severity of infections in diabetes

Infections in diabetic subjects will obviously be more serious than in non-diabetic patients if the metabolic control of the diabetes is disrupted to a dangerous degree. Secretion of the anti-insulin hormones of stress (catecholamines, cortisol, growth hormone and glucagon) is an inevitable consequence of infection (Beisel, 1975), and whereas the non-diabetic with an intact pancreas will develop only mild glucose intolerance, glycaemic control is inevitably upset in the diabetic. This may vary from severe ketoacidosis in the insulin-dependent, to loss of control in the mild diabetic with a temporary need for insulin therapy. Moreover, loss of diabetic control and the consequent osmotic diuresis may easily precipitate a hyperosmotic state, especially in the elderly and typically where the drowsiness of infective toxæmia blunts the desire for fluid thus leading to accelerated dehydration through excess fluid loss and inadequate replacement. Thus in the non-diabetic many minor infections can be weathered without medical intervention, yet similar upsets in the diabetic may lead to hospital admission (Ireland *et al.*, 1980). This problem introduces an inevitable bias implying more infections, or more severe infection in diabetics when in fact the real problem for the diabetic is the unique risk of metabolic decompensation under stress.

Rayfield's demonstration in 1977 of an increase in insulin requirement when endotoxin was used as an infection model explains why infection is the most common precipitant of ketoacidosis (Soler *et al.*, 1973). Even without severe upset of control, diabetic patients would seem to fare worse with some infections. Cluff *et al.* in 1968 showed a mortality from staphylococcal septicaemia of 69% compared with 17% in non-diabetic subjects, while the incidence of ketoacidosis in the diabetic patients was fairly small (19%). Necrotizing cellulitis, which occurs more frequently in diabetes, also has a worse prognosis in patients with diabetes. Other specific infections such as pyelonephritis (Spagnola, 1978) and erythrasma (Montes *et al.*, 1969) have worse prognoses in diabetes, while on more common ground Forland *et al.* (1977) have shown that diabetics with urinary tract infections have a higher incidence of renal involvement than expected (79%).

These specific examples in association with the difficulty experienced by many physicians in treating apparently simple infections of the hands and feet, and moist fungal infections, suggest that infection is more serious in the diabetic patient, or is possibly more difficult to eradicate in the diabetic host.

Reasons for increased infection

If it is accepted that diabetic patients are indeed more prone to infection, are there any identifiable reasons for this? There are several potential causes but it is extremely difficult to assign relative importance. The development of diabetic complications such as autonomic and peripheral neuropathies will contribute. The abnormal function of a neurogenic bladder with a high residual volume of urine and frequent catheterization, predisposes to urinary tract infections. Peripheral neuropathy predisposes to trauma and foot ulceration with delayed recognition of symptoms of infection whilst poor peripheral circulation delays healing and encourages opportunistic infection. These factors have been proposed as an argument against an immunological deficiency in diabetes (Savin, 1974) but as all of these problems associated with diabetes constitute breaks in the defence mechanisms of the host, the result is essentially a defect at the 'first-line' level.

The search for a more intrinsic problem is quoted by Savin as starting with Lassar's postulation in 1904 that organisms thrive in a high sugar medium, and recent studies have demonstrated that some Gram positive cocci do prefer high concentrations of sugar (Robson & Heggors, 1969). The opposite effect was observed with Gram negative organisms. This still appears a rather simplistic approach.

Numerous reports are available on the function of leucocytes in the diabetic patient, which indicate that some deficiency exists. Perillie *et al.* (1962) showed decreased phagocytic migration in ketotic patients, and suggested that correction of the acidosis removed the abnormality. Similar results were found by Brayton *et al.* (1970) and were confirmed by Molenaar *et al.* (1976) who also suggested an inherited defect of leucocyte function amongst the relatives of diabetics. Phagocytosis is impaired in the poorly-controlled diabetic, this defect being variously shown as completely reversible (Bybee & Rogers, 1964) or only partly reversible (Bagdade *et al.*, 1974) by improved diabetic control. Bagdade suggested that the problem was more complex than an intrinsic defect of polymorphs since the serum from diabetics could reduce phagocytosis in normal granulocytes, while 'control' sera improved the function of the diabetic polymorphs. This did not occur in the earlier study by Bybee & Rogers (1964). Rayfield and his colleagues (1982) have shown that intracellular bactericidal activity against *Staphylococcus aureus* and *Escherichia coli* is inversely related to the quality of control in diabetic patients. Decreased production of antibodies to some organisms has been reported (Ludwig *et al.*, 1976) but the significance of this is unclear.

Studies of cell-mediated immunity provide similar conclusions as those examining phagocytosis. Mac-

Cuish *et al.* (1974) showed a decrease in lymphocyte transformation in response to phytohaemagglutinin (PHA) in poorly-controlled diabetics but not in well-controlled diabetics or in normal subjects. Sub-population lymphocyte studies showed no difference between any of the diabetics or the controls suggesting that the effect on the PHA transformation is caused by poor diabetic control rather than an inherent defect of the T-cells. Casey and her colleagues (1983b) however showed a poor response to staphylococcal antigen in lymphocytes of diabetic patients regardless of glycaemic control. Recent work in the diabetes-prone BB rat has shown 'T-lymphocyte immunoincompetence' in a good animal model of insulin-dependent diabetes (Elder & McLaren, 1983; Naji *et al.*, 1983).

Conclusions

Diabetic patients appear to be more prone to infections, and the accumulating evidence for an immun-

ological defect superimposed upon the metabolic abnormalities of diabetes is becoming increasingly convincing. Both clinical and *in vitro* studies of leucocyte function suggest that infection is more likely if glycaemic control is poor, so while arguments continue as to whether precise control of diabetes diminishes vascular complications, the prevention of infection is a self-sufficient justification to strive for better metabolic control in the diabetic population.

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