2. REVIEW

Since 1888, after Adolf Weil's description of rat disease, information are added everyday in leptospiral research and named the rat disease as Weil's disease. Adrian Stokes (1887-1957) identified the *Spirochetosis icterohaemorrhagiae* as the causative agent for Weil's disease. Stimson (1907) demonstrated leptospires in renal tubules from a human case of jaundice and febril illness by using silver staining technique and named it *Spirochaeta interrogans* due to the question mark like resemblance. More than 500 cases with Weil's disease cases had been identified (Faine, 1999). It was not until the second decade of the 20th century that leptospires were recognized by Inada and Ido (1916) in Japan and soon after, independently in Germany by Uhlenhuth and Fromme (1915) as the cause of the disease that had been originally described by Weil, nothing was known much about these organisms. Noguchi (1917) isolated the leptospires in his own medium and suggested the generic name leptospires. Ido (1917) identified *Leptospira hebdomadis* in field mouse that suffered with a non-icteric syndrome "7- day fever". After Alston *et al.* (1958) much information came to light regarding leptospirosis.

Leptospirosis in human and animals had been reviewed by several workers. The work on human leptospirosis had been well reviewed (Watt, 1992; Faine, 1994a, b, 1996; Farrar, 1995; Turner, 1967; Levett, 1999, 2001; Sehgal, *et al.*, 2003). Leptospirosis in animals like cattles, sheeps, goats, other ungulates, pigs, dogs, cats, horses, non-human primates, rodents, marsupials, birds had been studied well (Barkin *et al.*, 1974; Ellis *et al.*, 1985; Luzzi *et al.*, 1987; Ellis, 1990; Ellis, 1991; Perolat *et al.*, 1991; Gollop *et al.*, 1993; Poonacha *et al.*, 1993; Faine, 1994a; Torten...

As much review works are available in leptospiral research, a further review of literature on leptospirosis is not warranted in the present study. Hence in the present study, review on pathogenesis and epidemiology of leptospires, highlighting the lacunae in Indian scenario is given.

**Epidemiology**

Leptospirosis is a worldwide zoonosis; human sources are exceedingly rare. It is an axiom that the only people who get leptospirosis are those in direct or indirect contact with infected animals and a corollary that those with no contact will not be exposed to risk. Human infection may be acquired through occupational, recreational, or avocational exposures. Occupation is a significant risk factor for humans (Waitkins, 1986). Direct contact with infected animals accounts for most infections in farmers, veterinarians, abattoir workers (Chan et al., 1987; Terry et al., 2000), meat inspectors (Blackmore et al., 1979), rodent control workers (Demers et al., 1985) and other occupations which require contact with animals (Anderson et al., 1978; Looke, 1986). Indirect contact is important for sewer workers, miners, soldiers (Buckland et al., 1945; Mackenzie, et al., 1966; Johnston et al., 1983), septic tank cleaners, fish farmers (Robertson et al., 1981; Gill et al., 1985) gamekeepers, canal workers (Andre-Fontaine et al., 1992), rice field workers (Famatiga et al., 1972), farmers (Anderson et al., 1986; Natarajaseenivasan and Ratnam, 1997; Jeyakumar et al., 2004), banana farmers (Smythe et al., 2000) and sugar cane cutters
throughout the world (Levett, 2001). The highest risk is associated with dairy farming and is associated with serovar hardjo (Sakula et al., 1969; Waitkins, 1986) in particular with milking of dairy cattle (Skilbeck et al., 1986).

Human exposure is not limited by occupation but results more often from the widespread environmental contamination, particularly during rainy season (Harwood, et al., 1984; Levett, 2001; Jena et al., 2004; John et al., 2004; Czerwinski et al., 2004). Nedunchelliyan and Venugopalan (1998) reported leptospirosis transmission by blood transfusion and stressed the need to screen blood samples for leptospires before blood transfusion. There are also the areas where large outbreaks of leptospirosis occurred following floods, hurricanes or other disasters (Oliveria et al., 1977; Chen, 1985; de Souza, 1986; French et al., 1989; Park et al., 1989; Fuortes et al., 1994; Epstein et al., 1995; Pan American Health Organization, 1998; Vanasco et al., 2000; Ramakrishnan et al., 2003). The third pattern comprises rodent-borne infection in the urban environment while this is of lesser significance in developed countries (Derham, 1976), it is potentially more important in developing countries.

Leptospirosis is a rare disease in temperate countries. In Denmark an average of four laboratories confirmed cases were reported annually between 1970-1996. The average incidence in Denmark was 0.09 cases per 100,000 compared to a reported incidence in the United States of 0.05/100,000/year (Farr, 1995; Holk et al., 2000), in Great Britain of 0.1 - 0.2/100,000/year (Waitkins, 1986) tend in the Republic of Ireland of 0.45/100,000/year (Hogan et al., 1997) and 0.42/100,000/year in Bulgaia (Christova et al., 2003). In India several outbreaks of leptospirosis had
been reported (Sehgal et al., 1995; Muthusethupathi, et al., 1995; Kuriakose et al., 1997; WHO, 2000; Babu et al., 2001; Varaiya et al., 2002; John et al., 2004).

Pathogenesis

Leptospirosis is a disseminated disease worldwide, which causes extensive vasculitis of microvessels in multiple organs (Vachvanichsanong et al., 1999). Levett (1999) reported leptospirosis as an anthropozoonosis with wide geographical distribution and cause insensible illness and death as well as enormous economic damage. Watt (1992), Faine (1994a, b, 1996) and Farrar (1995) had reviewed the leptospirosis in humans. In mammals, marsupials and susceptible birds (Chick embryo) the primary lesion in leptospirosis is disruption of the integrity of the cell membrane of the endothelial cells lining small blood vessels in all parts of the body capillary leakage and haemorrhages results (Faine 1994a, b). These effects are due to the action of a Glyco-lipoprotein (GLP) toxins of leptospires, whose activity is mediated by its unusual long-chain fatty acids (Faine, 1996). GLP is different from leptospiral lipopolysaccharide (Alves et al., 1992). The widespread petechial haemorrhages are apparent in all organs and tissues, but are most prominent in those where there is movement that stretches blood vessels particularly the lungs, omentum and pericardium. Gross bleeding and large haematomata may be produced (Faine, 1996). Ischaemia from damage to blood vessels in the renal cortex leads to renal tubular necrosis, particularly of proximal convoluted tubules (Faine, 1996), leading to renal failure. Liver cell necrosis caused by ischaemia and destruction of hepatic architecture leads to characteristic jaundice of the severe type of leptospirosis and this aggravate haemorrhagic tendencies. There may also be thrombocytopenia (Faine,
1996). In the immunologically competent host, leptospiral LPS antigens are recognised and IgM antibodies are produced. The IgM opsonises the leptospires so that fixed and free phagocytes engulf them in both the reticuloendothelial organs (liver, spleen, lungs, lymph nodes) and areas of haemorrhage or tissue damage where they have invaded. However leptospires are able to persist in some anatomically localised and immunologically privileged sites like renal tubule for long time. Such animals had been reported to excrete leptospires intermittently or regularly for periods of months or years or for their lifetimes. However humans do not remain carrier for long (Faine, 1999). Leptospires also enter the brain and cause meningitis (Beeson et al., 1952; King et al., 1975). Leptospires also invade the anterior chamber of the eye and are localised in that site (Merien et al., 1993). It causes chronic eye infection (uveitis, inflammation, cataract) (Rathinam et al., 1996). In horses such ocular accumulation cause “moon blindness”. Similar sequestration can occur in the uterus and appendages in sheep and in the seminal tracts in rams and boars (Watt, 1992; Faine, 1994a).

In severe cases fever re-occurs rising quickly to 40°C or more, and the patient deteriorates rapidly as renal failure leads to uraemia and oliguria: jaundice may appear clinically or subclinically and haemorrhages may develop rapidly throughout the body (O’Neil et al., 1991; Vachvanichsanong et al., 1999; WHO 1999; Sehgal, et al., 2003). Adult respiratory distress syndrome and haemoptysis are common in infection with some serovars. Congenital leptospirosis may affect the foetus if the mother is infected in pregnancy (Faine, 1994a). Humans do not usually become chronic renal carriers or excretors, but chronic headaches, fatigue or
psychiatric disturbance may persist for months or years after leptospirosis (Faine, 1994a). Leptospirosis in animals has been reviewed (Ellis, 1990; Faine, 1994a; Torten and Marshall, 1994).

Early reports were limited to adults with occupational exposures (Lecour et al., 1989). Lately, it has been shown that children also can be infected with leptospirosis and can develop acute renal failure (Nimmannitya et al., 1984; Muthusethupathi et al., 1987; Seguro et al., 1990; Vachvanichsanong et al., 1999).

In spite of such alarming danger leptospirosis causes on children and adults and also an animals, its reporting is low because it is under-suspected and under-diagnosed. Further, leptospirosis mimics other illness such as acute gastroenteritis, viral hepatitis, influenza; dengue fever and other viral infections. Therefore, it is frequently misdiagnosed as another disease. As leptospirosis cannot be easily ignored due to its potential pathogenicity, the present study was conceived and designed to analyse in the area where livestock related activities predominate.