HISTOLOGICAL, HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL STUDIES ON THE EFFECTS OF INDOMETHACIN ON THE JEJUNAL MUCOSA OF ALBINO RATS

A Thesis Submitted For The Partial Fulfillment Of The Master Degree In Basic Sciences
(Histology)

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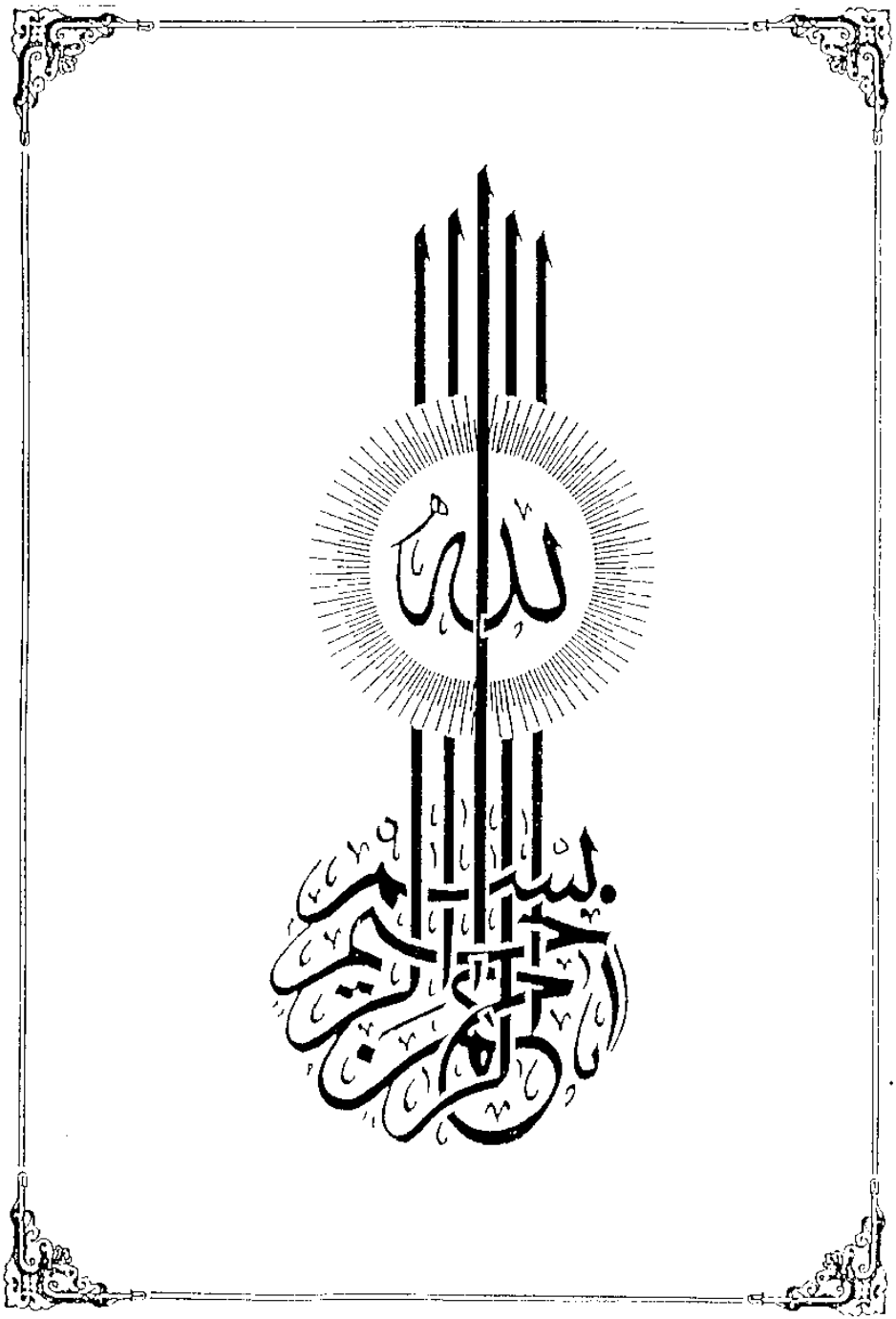

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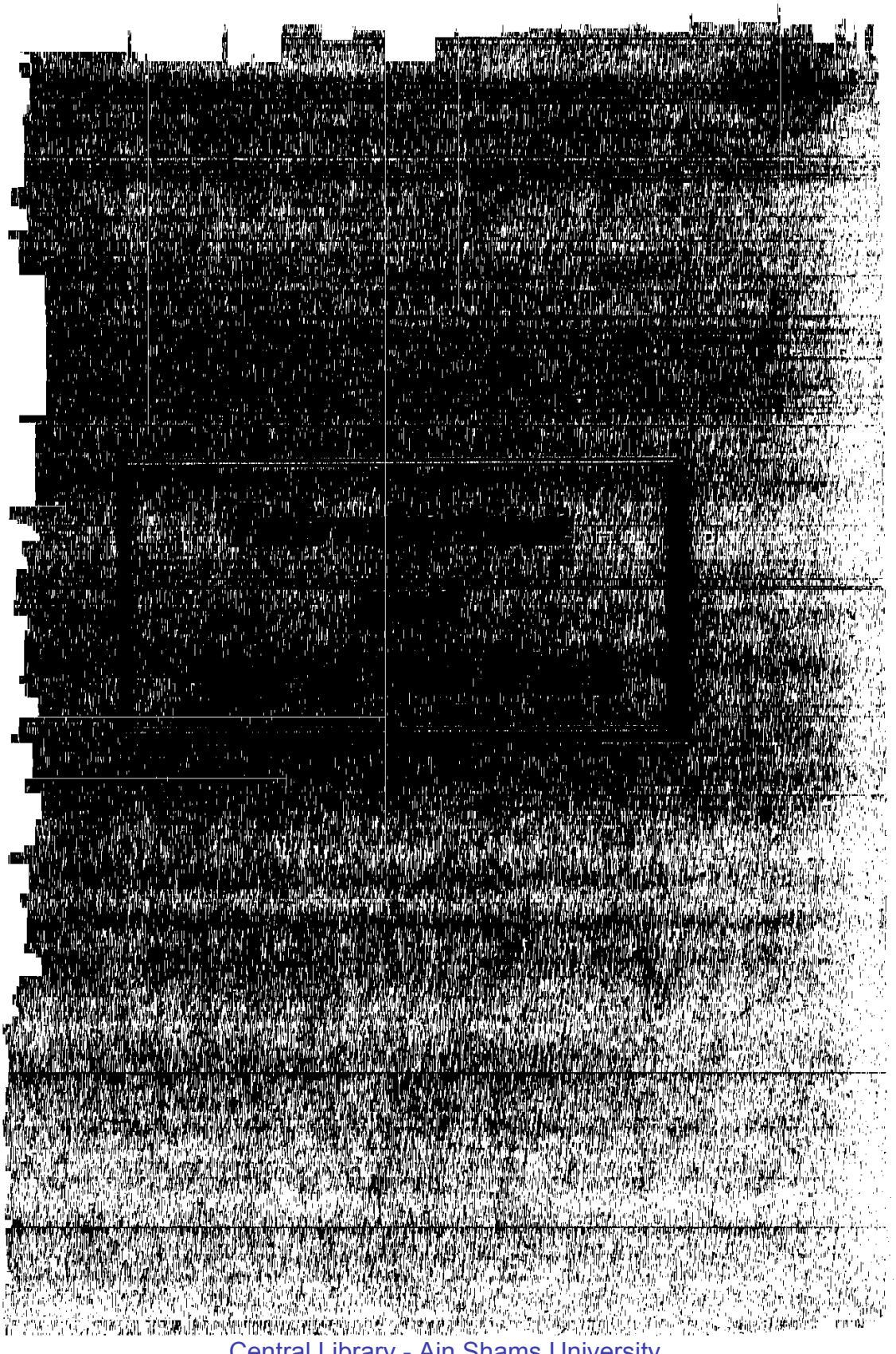
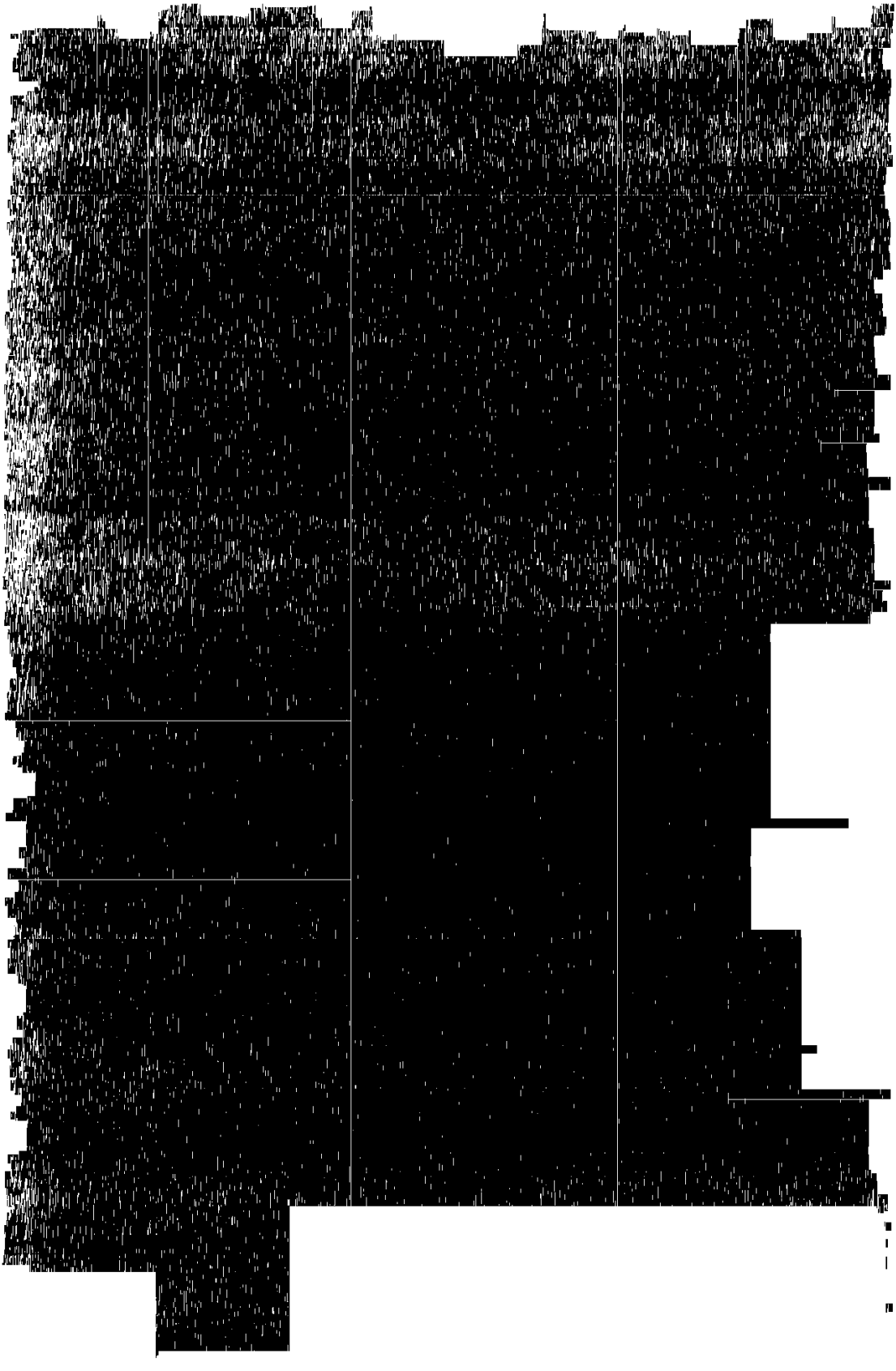




INTRODUCTION AND AIM OF THE WORK

Non steroidal anti-inflammatory drugs (NSAIDs) are known to be the most widely used antirheumatics. They lead to many complications specially gastrointestinal disturbances ***(Bjarnason, Hayllar, Macpherson and Russell, 1993).***

Indomethacin is an effective member of NSAIDs used for treatment of rheumatoid arthritis and related disorders. It should be used cautiously specially in patients with gastrointestinal bleeding ***(Flower, Moncada and Vane, 1980).***

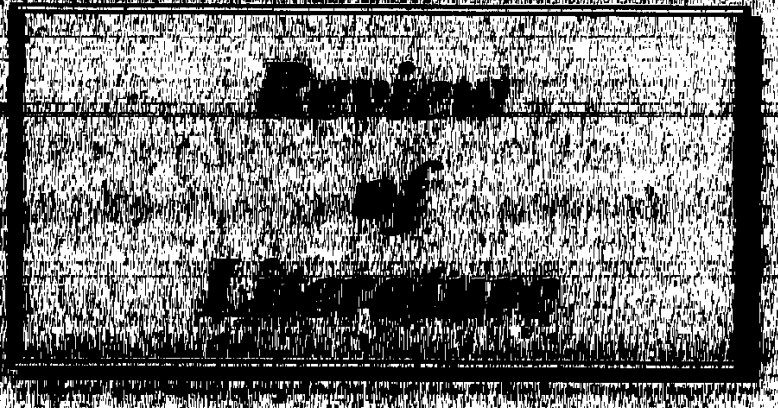
Patients on long term administration of indomethacin may develop asymptomatic small intestinal inflammation ***(Bjarnason, Smethurst, Fenn, Lee, Menzies and Levi, 1989, Scholz, Heiss, Roberts and Thomas, 1994).***

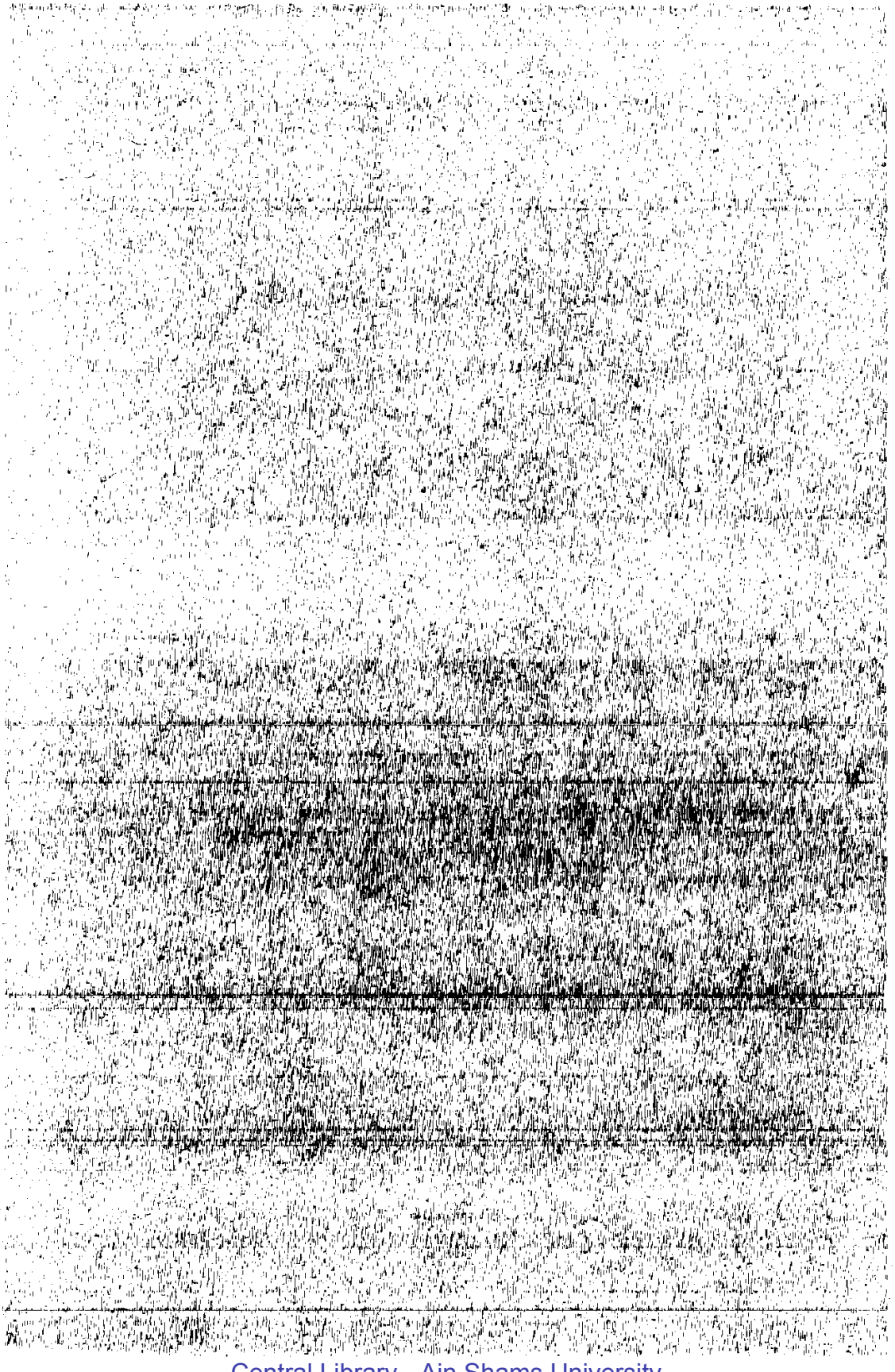
Indomethacin doesn't only lead to intestinal inflammation but also to occult gastrointestinal bleeding which leads to iron deficiency anaemia ***(Anthony, Dhullen, Nygard, Hudson, Piasecki, Strong, Trevethic, Cayton, Jordon Pounder and Wakefield, 1993).***

When indomethacin was used to decrease uterine contractions in preterm labour, it was found to be followed with neonatal complications. Neonates of preterm labour had an increased risk of developing necrotizing enterocolitis ***(Major, Lewis, Harding, Porto and Garite, 1994).***

Jejunal and ileal ulcerations were reported in chronic users of indomethacin. Although these ulcers were less common than those of the stomach, yet they could lead to life threatening conditions ***(Allison, Howatson, Torrange, Lee and Russell, 1992).***

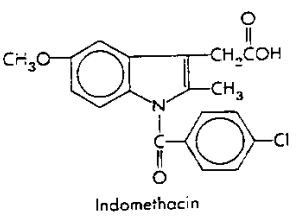
As most of the studies concentrated on the effect of indomethacin on the gastroduodenal region and ileum inspite of excretion of the drug by the liver ***(Reynalds and Prasad, 1982)***, it was important to look at the jejunum as well. The aim of the present work is to study the early effects that may occur in the jejunal mucosa after oral administration of indomethacin using histological, histochemical and immunohistochemical techniques.





Indomethacin

Hucker, Zacchei, Cox, Brodie and Cantwell (1966) mentioned that indomethacin is an antirheumatic drug and was first synthesized in 1963. They added that indomethacin has anti-inflammatory, antipyretic and mild analgesic actions.The structural formula of indomethacin is I-(4-chlorobenzoyl) -5methoxy-2-methyl indole -3-acetic acid.



Structural Formula of Indomethacin

Kent, Cardelli and Stomler (1969) studied the metabolism of indomethacin and found that the drug was absorbed rapidly by the small intestine after oral administration. They added that the drug reached its peak concentration in plasma after three hours in fasting state but the peak concentration was delayed if the drug was taken after meals.

Flower, Moncada and Vane (1980) found that indomethacin was conjugated in the liver with glucouronic acid by means of microsomal enzymes. These conjugated metabolites were eliminated in the urine, bile and feces.

Reynalds and Prasad (1982) mentioned that indomethacin was used for treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and acute gout. They added that indomethacin could also be used in delaying preterm labour and in closure of patent ductus arteriosus in preterm infants.

Moncada, Flower and Vane (1985) mentioned that the mechanism of action of indomethacin was mainly related to inhibition of cyclo-oxygenase enzyme. This enzyme acted upon arachidonic acid producing cyclic endoperoxides., prostaglandin G (PGG) and prostaglandin H (PGH) which were further isomerized into different products; PGE, PGF, PGD. Moreover, prostaglandins decrease due to inhibition of cyclo-oxygenase enzyme by indomethacin led to less oedema and less sensitization of nerve endings to inflammatory mediators and that favoured the anti- inflammatory and analgesic effects of the drug.