DISCUSSION
Struggle goes on unabated in laboratories and clinics in search of safer and potent drugs for the treatment of rheumatoid arthritis. The anti-inflammatory agents, being used clinically, possess remarkable pharmacological and biochemical activities. Non-steroidal anti-inflammatory agents with diverse chemical structure have been used in the last decade in clinical practice. However, these newer anti-arthritic drugs act as double-edged weapons because besides anti-inflammatory activity they are also prone to cause adverse effects of varying intensities. However, undesirable effects which accompany their use aroused interest in the development of more effective and safer non-steroidal anti-inflammatory drugs (NSAID). It remains debatable whether adverse effects of anti-arthritic drugs occur by the same mechanism which is responsible for their anti-inflammatory action.

Amongst the non-steroidal anti-inflammatory agents, anthranilic acid derivatives like mefenamic acid evoked interest in view of their anti-inflammatory activity. Though potent, these drugs are not devoid of undesirable effects on gastrointestinal and hematological systems. Recently, tromaril (N-B-phenylethylamine) reported by Sisodia et al. (1982) is a potent anti-arthritic drug. This drug was found to possess potent analgesic, antipyretic and anti-inflammatory activities with minimal side effects. It has been described to have
an edge over the existing drugs due to wider margin of safety. However, the effects of tromaril on various haematological and biochemical parameters have not been studied in detail. Therefore, the present study was undertaken to evaluate the effects of tromaril on various biochemical and haematological parameters usually influenced by anti-inflammatory agents. Besides, comparative study was also done between tromaril and other non-steroidal anti-inflammatory drugs like aspirin, indomethacin, brufen and tolmetin for assessment of their relative analgesic, antipyretic and anti-inflammatory activities in experimental animals while clinical study was undertaken for tromaril and aspirin on various parameters. An attempt was also made to determine their safety margin for various activities.

In the present study, tromaril, aspirin, indomethacin, tolmetin and brufen produced dose-related inhibition of carrageenin-induced oedema. Tromaril elicited highly significant dose-related anti-inflammatory activity. In this study tromaril (100 mg/kg) produced 36.36% inhibition of carrageenin-induced hind paw oedema whereas same dose caused 50% inhibition in the study of Sisodia et al. (1980). Indomethacin (5 mg/kg) and tolmetin (30 mg/kg) reduced carrageenin-induced oedema by 54.54% and 36.36%, respectively which was highly significant and confirms the earlier observations (Goodman and Gilman, 1980; Sangal, 1982). While tolmetin caused inhibition of
carrageenan-induced oedema by 36.36%, 50% and 57.2% in
doses of 30 mg, 50 mg, 100 mg/kg. This study suggests
that comparatively the effective anti-inflammatory dose
to tromaril was highest (ED$_{50}$ = 132 mg/kg) and of
indomethacin the lowest (ED$_{50}$ = 5 mg/kg). The relative
potency of anti-inflammatory agents in the present
study was found to be indomethacin ≥ brufen ≥ tolmetin ≥
aspirin ≥ tromaril. However, tromaril had the highest
LD$_{50}$ value (≥ 2000 mg/kg) thus it is comparatively safer
than the other anti-inflammatory agents (therapeutic
index ≥ 15.15). Bhargava et al. (1976) have also reported
the order of potency of anti-inflammatory agents on
carrageenan-induced oedema in following descending order:
indomethacin ≥ flufenamic acid ≥ hydrocortisone ≥ oxyph-
phenbutazone ≥ acetylsalicylic acid ≥ amidopyrin ≥ glycyr-
helic acid ≥ phenacetin ≥ sodium salicylate.

In the present study, all the anti-inflammatory
agents conferred protection in animals from acetic acid-
induced writhing (Table-3). While aspirin (50 mg/kg)
protected 100% animals, brufen (20 mg/kg) could protect 60%
animals. Tolmetin in dose of 50 mg/kg protected 40% of
animals and tromaril (150 mg/kg) could only protect 60%
animals. Thus it appears to be less effective analgesic
as compared to the other anti-inflammatory agents. The
present study showed the highest effective dose of
tromaril as compared to the other anti-inflammatory agents
under study (ED$_{50}$ = 141.3 mg/kg). As regards the analgesic
potency evaluated in this study - indomethacin > brufen > aspirin > tolmetin > tromaril. As tromaril shows highest LD_{50} value it appears comparatively safer than other anti-inflammatory agents used as angesics (therapeutic index 14.15). It has been reported that most of the anti-inflammatory drugs possess anti-pyretic activity (Winter et al., 1963). In our study too all the drugs studied significantly decreased the T.A.B. vaccine-induced pyrexia (Table-4). Comparatively tromaril was found to be equipotent to aspirin in antipyretic activity. It is in agreement with the observations of Sisodia et al. (1980) who reported tromaril along with aspirin, mefenamic acid and oxyphenbutazone to possess equal anti-pyretic activity in yeast-induced pyrexia in rats. Tromaril has also been observed to possess antipyretic activity in brewer’s yeast induced pyrexia in rabbits (Sisodia et al., 1980). Our findings confirm the postulation that aspirin and tolmetin reduce the magnitude and duration of antipyretic activity (Niemeggers, 1975; Sangal, 1982).

Anderson (1965) and Green et al. (1965) drew a parallelism between anti-inflammatory and ulcerogenic activities of anti-rheumatic drugs. One of the objects of synthesis of tromaril was to introduce a better tolerated drug. Dyspepsia (Muir, 1963; O’Brien, 1968), gastrointestinal haemorrhages and perforation (Alvarez and Summershill, 1958) of ulcers induced by the other non-steroidal anti-inflammatory agents is always
encountered in prolonged therapy. Our studies show that higher doses of tromaril (400 mg/kg) were less ulcerogenic than the lower dose of aspirin (200 mg/kg), indomethacin (4 mg/kg), tolmetin (200 mg/kg) and brufen (10 mg/kg). Aspirin, indomethacin and tolmetin showed marked increase in ulcer index in stress-induced and pyloric ligation-induced gastric ulcerations. However, tromaril and brufen slightly potentiated the ulcer index by Shay's technique and stress-induced ulcers. In view of the foregoing, tromaril appears to be less ulcerogenic and safer than the other antiinflammatory drugs.

In the present study, both aspirin and brufen produced a marked and highly significant hyperglycaemia. Aspirin has been found to elicit dual response on the carbohydrate metabolism. On one hand, it tends to lower the blood sugar level while on the other, it is known to cause hyperglycaemia, glycosuria and depletion of liver and muscle glycogen probably by releasing epinephrine consequent to activation of central sympathetic centres and partly by reducing aerobic metabolism of glucose (Goodman and Gilman, 1980). Sharma et al. (1981) reported the hyperglycaemic response of ibuprofen. It lends credence to our contention. We observed that indomethacin and tolmetin induced hypoglycaemia. Sangal (1982) has also reported the hypoglycaemic activity of indomethacin and tolmetin. This further supports our observation. Indomethacin has been reported to inhibit
the hyperglycaemia induced by angiotensin (Singh et al., 1978) and glucagon-induced hepatic glucose production (Ganguli et al., 1978). Tromaril did not affect the carbohydrate metabolism in usual doses but in higher doses it was found to cause persistent hypoglycaemia. Tromaril is known to be highly protein-bound and slowly released from binding sites (Sisodia et al., 1980) so it might be responsible for sustained hypoglycaemia for prolonged period in higher doses. On effective dose basis, tromaril as compared to the other anti-inflammatory agents in this study, does not appear to affect the carbohydrate metabolism.

Anti-inflammatory drugs have been reported to possess uricosuric action (Yu and Gutman, 1959), consequently lowering the uric acid level in serum. In our study, it was observed that tromaril possesses significant hypouricaemic activity. However, indomethacin (2 mg/kg) failed to show any change in the serum uric acid level (Mankeri et al., 1980). Tolmetin (10 mg/kg) showed a marked and highly significant hypouricaemic activity. These observations are in agreement with Sangal (1982) and brufen also produced hypouricaemia. Aspirin has been reported to lower plasma urate levels (Goodman and Gilman, 1980). Thus tromaril appears comparatively less potent in reducing hypouricaemia.

The haemopoietic system is also influenced by anti-inflammatory agents as aspirin and indomethacin are
reported to possess anti-platelet action and also reduce the release of platelet bound C-serotonin (Zucker and Peterson, 1970). In our study, indomethacin (5 mg/kg), tolmetin (50 mg/kg) and aspirin were found to cause significant thrombocytopenia. Brufen decreased platelet count after 24 hours but it was more significant after 7 days. However, tromaril failed to affect the platelet count during this period. This observation is in agreement of Manikeri et al. (1980). Indomethacin was more potent in inducing thrombocytopenia as compared to aspirin, tolmetin, brufen and tromaril.

Significant reduction in clotting time by aspirin, indomethacin, brufen and tolmetin was observed in the present study. However, tromaril failed to affect the coagulation time. Similar effect has been reported by Gupta et al. (1980).

Significant increase in plasma fibrinogen content was obtained with aspirin, tolmetin, indomethacin and brufen. However, tromaril produced a decrease in the plasma fibrinogen content but it was statistically not significant. Manikeri et al. (1980) also reported minor alternation plasma fibrinogen content by aspirin and tromaril. Tolmetin, indomethacin and aspirin significantly increased euglobulin clot lysis time while decrease in E.L.T. was observed with tromaril and brufen. However, Rishi et al. (1976) observed increased fibrinolytic activity by aspirin. Done (1960) reported an in vitro
inhibition of fibrinolysis with anti-inflammatory agents. Increased plasma fibrinogen content results due to inhibition of fibrinolysis (plasma). This lends support to our observations. In the present study, plasma E.L.T. was also increased after pre-treatment with aspirin, indomethacin and tolmethin. This observation further supports the presence of anti-fibrinolytic effect in anti-inflammatory agents. However, pretreatment with tromaril and brufen resulted in decreased plasma E.L.T. which needs further study to explore the mechanism involved there in.

In this study, tromaril had the highest LD_{50} value ( > 2000 mg/kg p.o.) as compared to other anti-inflammatory drug. Comparative safety (based on the therapeutic index) of the anti-inflammatory agents in this study was found to be as follows in descending order brufen > aspirin > tromaril > tolmethin > indomethacin (Table-9). Thus it is evident that tromaril is comparatively a safer anti-inflammatory agent.

In the clinical study, aspirin produced significant and a higher degree of improvement in grip-strength than tromaril. An increase in grip strength has also been earlier reported with aspirin (Ansell et al., 1978), and trolefut (Sattur et al., 1980; Mathur et al., 1980). Tromaril and aspirin were equi-effective on walking time which improved appreciably and gradually as is evident in our study by a decrease in walking time. This is in agreement with the observations of Sattur et al., (1980), who clinically
examined trolamiril. Significant decrease in digital joint (P.J.P.) circumference was observed with both trolamiril and aspirin in patients. However, Ansell et al. (1978) reported no change in proximal interphalangeal joint measurement throughout the period of treatment, but Sattur et al. (1980) obtained results similar to this study. In our study, aspirin was found to decrease the duration of morning stiffness significantly as compared to trolamiril. Sattur et al. (1980) also reported decrease in morning stiffness in trolamiril-treated group and its increase in aspirin-treated patients (Ansell et al., 1978). Both the drugs were found to provide significant relief from pain subjectively, although objective assessment of relief from pain has been reported by earlier observations (Lee et al., 1973; Huskisson, 1974). Aspirin was comparatively more effective in this respect than trolamiril as evidenced by our study. No significant change in level of pain was reported in aspirin-treated group by Ansell et al. (1978). However, several workers observed significant and marked relief from pain with trolamiril which lends support to our observation (Mathur et al., 1980; Nutshing Rao, 1980; Swamy et al., 1980; Sattur et al., 1980; Rao et al., 1980). Reduction in E.S.R. was noted in both aspirin and trolamiril-treated groups. However, aspirin showed more marked reduction in E.S.R. as compared to trolamiril. Sattur et al. (1980) also reported fall in E.S.R. in trolamiril-treated group which lends further sup-
port to our study. Although raised E.S.R. is an invariable feature of active rheumatoid arthritis, however, Hart and Huskisson, (1972) doubt its utility as an index in evaluating the response of drug in short term clinical studies. Tromaril has been reported to be equipotent with oxyphenbutazone as assessed by improvement in grip strength and reduction in swelling of joints (Rao et al., 1980). Non-steroidal anti-inflammatory drugs like phenylbutazone and paracetamol have been reported to possess antipyretic activity in symptomatic relief of acute rheumatic fever and rheumatoid arthritis (Harper and Bonica, 1979). In the present study, both tromaril and aspirin showed marked reduction in elevated body temperature, which confirms the observations of Gupta et al. (1980). However, aspirin was found to possess more significant anti-pyretic activity as compared to tromaril in onset, degree and duration of pyrexia. Thus tromaril with its reasonable antipyretic action may be of advantage in rheumatic fever and rheumatoid arthritis.

Aspirin was found to show more side effects as compared to tromaril as evidenced by the pattern of side effects in our study (Table-17). Ansell et al. (1978) also reported higher incidence of adverse effects with aspirin than tolmetin. Tromaril has been found to possess minimal side effects and good tolerance and was completely devoid of any adverse effect on G.I.T., cardiovascular or haemopoetic system (Mathur et al., 1980) indicating its