delayed for two or three days; they frequently disappear with continued use but, if they are severe, the drug should be discontinued.

Gastrointestinal reactions (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as being potentially ulcerogenic. It may produce single or multiple ulceration of the esophagus, stomach, duodenum, or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; other patients have developed ulcers after having taken the drug for 1½ to 3 years. Since most patients who developed ulcers had received doses of 150 to 300 mg. a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer, and persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

Leukopenia, purpura, and thrombocytopenia may develop. Agranulocytosis has been reported rarely, but its relationship to indomethacin administration has not been established. Reports of jaundice and hepatitis have also appeared.

Dermatologic or hypersensitivity-type reactions (pruritus, urticaria, rash, angioneurotic edema, loss of hair, acute respiratory distress) and reactions affecting the eye or ear (tinnitus, blurred vision, orbital and periorbital pain) have occurred infrequently.

No significant alterations in the glucose tolerance test, electrolyte balance, or kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged use.

### PRECAUTIONS

Patients who require larger dosages of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Indomethacin is contraindicated in patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, and it should be used wth caution in patients with a history of these disorders. These patients may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems, since the drug may aggravate these conditions.

Because of the possible occurrence of central nervous system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

Indomethacin is contraindicated in patients with asthma who are sensitive to aspirin.

It is now known that indomethacin can mask the signs and symptoms which usually accompany infectious disease. Therefore, the physician must be aware of this possibility to avoid delay in the treatment of an infection, and should use the drug with caution in the presence of existing, controlled infections.

No teratogenic effects have been demonstrated in animal studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman.

A few deaths in children with severe juvenile rheumatoid arthritis who were receiving indomethacin with other drugs have been reported; in two of these cases, death was attributed to intercurrent infections of possibly unrecognized severity. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in infants and children and, at the present time, the drug is considered to be *contraindicated in infants and children* because safe conditions for use have not been established.