The Malignant Neuroleptic Syndrome (M. N. S.) as a relatively uncommon but potentially lethal complication of neuroleptic drug treatment was first described in the French literature by Delay et al. (1960), and several cases of so called 'Malignant Hyperthermia' in relation to neuroleptic drug intake were described. It is only in the last few years that this syndrome has received some attention in the English language literature—Caroff (1980) in his review states that a total of about 60 cases have so far been reported in the world literature. Although exact figures of its incidence are difficult to obtain, Delay et al. (1963) in their series of patients treated with haloperidol reported an incidence of approximately 0.5% to 1.0%. This would suggest that M. N. S. is not as rare as generally believed, considering the large number of patients being treated with neuroleptics, but that probably many cases are not recognised as such and hence go unreported.

Clinical features:

The Malignant Neuroleptic Syndrome is characterised by:

(a) A rise of body temperature—ranging from 38°C (99°F) to as high as 41°C (106°F).

(b) Impairment of Consciousness—which may vary from a dazed mutism through stupor to coma.

(c) Autonomic Dysfunction—eg. labile blood pressure with marked tachycardia, profuse diaphoresis, dyspnoea, dysphagia, urinary retention or incontinence.

(d) Neuromuscular Dysfunction manifesting as catatonic like rigidity, akinesia, dyskinesia, or involuntary movements. The rigidity is generally described as being of lead pipe or plastic type.

Clinical Course:

M. N. S. may occur from hours to months after the initial exposure to the drug but once initiated, signs and symptoms develop rapidly over the next 24-72 hours. It usually starts with a sudden, unexplained rise of temperature with impairment of consciousness, followed by the signs of neuromuscular and autonomic dysfunction. It usually lasts from 5 to 10 days after cessation of neuroleptic drug therapy; and if detected early and intensive supportive therapy instituted, recovery can be expected in a majority of cases.

Of the 60 cases described in the literature, death occurred in 12 patients, giving a mortality rate of 20%. Interestingly, 6 of these 12 cases were being treated with depot fluphenazine preparations. Death, when it occurs, is due either to cardiovascular collapse or respiratory and/ or renal failure. Autopsies performed on these cases have revealed only non-specific or secondary changes. The apparently increased mortality rate with the long acting fluphenazine compounds is probably a function of the long half-life of these drugs, and the resulting prolonged exposure to the agent even after discontinuing medication.

Laboratory Investigations: are generally within normal limits, but nevertheless are necessary to rule out other medical conditions.
that are to be considered in the differential diagnosis. In the literature, leucocytosis has been reported in 14 cases, serum C. P. K. elevations in 7 cases and non-specific, generalised E. E. G. abnormalities suggestive of a diffuse encephalopathy in 6 cases.

**Treatment:**

The main purpose of therapy is to maintain the body temperature, blood pressure and fluid and electrolyte balance. Thus, optimal treatment consists in early recognition, immediate stoppage of all psychotropic medication, and the prompt and energetic institution of intensive medical and nursing supportive care.

There is no specific treatment known that affects either the morbidity or mortality of the M. N. S. Anticholinergic drugs have been tried but without any success; besides, the very fact that a number of these patients were already receiving anticholinergic drugs along with the neuroleptic medication, indicates that it is not effective in preventing the onset of M. N. S. E.C.T. has been used in 2 cases but again the response was equivocal. Antibiotics and dialysis are useful only in cases who develop secondary infection or acute renal failure.

**Differential Diagnosis:**

The acute onset of high grade fever with impairment of consciousness invariably suggests an acute encephalopathy. The common causes that must be excluded are viral encephalitis, enteric encephalopathy, and cerebral malaria; although other bacterial, fungal, and parasitic infections must also be excluded. Some patients with marked catastatic rigidity or akinesia may resemble an acute post-infectious encephalopathy such as encephalitis lethargica, akinetic mutism, or even tetanus. Rarely, strychnine poisoning, myotonia, tetany, and hysterical conversion symptoms may also have to be considered and excluded.

M. N. S. seems to be clinically distinct from heat stroke which has also been reported as a complication of neuroleptic therapy in a hot climate (Itoh et al., 1977). On the other hand, there are striking similarities between M. N. S. and the anaesthetic induced 'malignant hyperthermia' but the defective membrane regulations and transport of calcium into skeletal muscle cytoplasm in presence of inhalation anaesthetics is absent in M.N.S.

**Biology and Predisposing factors:**

All ages and both sexes are affected by M. N. S. It is more likely to occur with the use of high potency neuroleptics in therapeutic doses. Almost half of all the reported cases have been related to the use of haloperidol, and the remaining cases due to piperazine phenothiazines and thiothixene—only one case has been reported after the use of thioridazine (Haberman, 1978). Characteristic features of M. N. S. have been described following the use of neuroleptics in combination with lithium (1 case), and antidepressants (2 cases).

Of the 60 reported cases, only 11 showed evidence of identifiable brain disease prior to neuroleptic exposure. Clinically, the patients had a variety of psychiatric diagnoses including Manic, Depressive, Schizophrenic and Character Disorders. Neuroleptics are necessary but not sufficient in themselves to trigger the onset of M.N.S., apparently other factors must be operating in the initiation of the syndrome in a susceptible person, at a particular time in the course of neuroleptic therapy. Itoh et al. (1977) have suggested that the physiologic state of the patient at the time of drug exposure such as physical exhaustion, or dehydration may be an important additional factor in determining the onset of M.N.S.

**CASE REPORTS:**

**Case 1:**

S. K., 45 years married female was admitted with a diagnosis of Manic-
Depressive Psychosis, currently manic. She had a history of five previous episodes of a similar illness which had been treated successfully with drugs. She was put on oral neuroleptics, and the dosage was gradually increased. Within a period of seven days she responded but she complained of mild tremors of hands. Subsequently, the tremors increased, in addition she developed marked generalised rigidity with impairment of consciousness. She progressed into a state of stupor with gross catatonic features and dysphagia, even after discontinuing the drugs. For the first time she showed a rise of temperature to 102°F without apparent cause. Medical opinion was sought who kept the possibility of either a C.V.A. or viral encephalitis and recommended immediate transfer to the medical ward for investigation and management. She was put on intensive care with four hourly check on vital signs, intake-output chart, and continuous I. V. fluids. Decadron 2 cc and Ampicillin 500 mg were administered along with the parenteral fluids. Temperature ranged between 99°F to 102°F throughout the illness. Patient died on evening of 2-3-77 as a result of acute renal failure.

Haemogram, Blood sugar, C.S.F. and E.C.G. were within normal limits. Urine showed albuminura and Blood urea was raised.

Case 2:

J. R. 50 yrs. old, married male was admitted with a diagnosis of Manic Depressive Psychosis—currently manic. He was started on oral neuroleptics and gradually the dose was increased. After about a weak rise of temperature (102°F) with rigors and chills was noticed. Within next 24 hrs, patient’s B. P. dropped and he appeared confused, restless, muttering to himself with mild generalised rigidity. Medical experts suggested the possibility of Enteric Encephalopathy.

All psychotropic drugs were stopped and patient was given Decadron 2 ml. stat followed by continuous I. V. drip with 6-8 ampoules of mephentine in each bottle to maintain the blood pressure. He was also given Chloromycetin 500 mg I. M. 6 hourly, along with routine supportive therapy. This regimen continued for the next 8 days, when he regained full consciousness, temperature returned to normal., and BP was maintained between 100-110/ 70-80 mm Hg without mephentine. Thereafter, recovery was rapid and patient was discharged after 14 days.

Haemogram, urine and stool examination, Blood urea, C.S.F. were within normal range.

Case 3:

M. D. a 41 years married female, was admitted with a diagnosis of Manic Depressive Psychosis, currently depressed. She was put on antidepressants and phenothiazines. After 6 days she was noted to have a mild temperature for which Paracetamol was prescribed. However the fever did not subside and by next morning it had risen to 102°F and the patient appeared drowsy and unresponsive. The medical consultant could not reach to any definite diagnosis. She was comatous and her BP was very low. All psychotropic drugs were immediately withdrawn. Decadron 1 ml 6 hourly, with 4-6 ampoules of mephentine in each bottle of I.V. fluids was given to maintain the blood pressure. This regime was continued for the next 2 days when she regained full consciousness & her B.P. was stable. Since she was still anxious and depressed, she was restarted on antidepressants and haloperidol, without any adverse effects. Subsequently she was discharged.

Haemogram, blood urea, urine culture, C.S.F. were within normal limits.
DISCUSSION

Having seen two patients (cases 2 & 3) within a period of eight months in which a physically healthy person, while under treatment with neuroleptics, suddenly develops an unexplained fever associated with impairment of consciousness and a severe and prolonged fall in blood pressure; alerted us to the possibility that this may be a complication of neuroleptic drug use. A review of our records revealed one more case who had died from a similar unexplained illness two years earlier (case 1). Thus, over the past six years, i.e. from 1974—1980, we have had three cases of M.N.S. in approx. 1500 patients treated with neuroleptics out of a total admission of 2782 patients—giving an incidence of 0.2%.

While some authors stressed the hyperthermia as the predominant presenting symptom of these cases (Moyes, 1973; Haberman, 1978), others stressed the sudden and dramatic occurrence of a catatonic stupor with fatal outcome (Regestein et al., 1977, Weinberger and Kelly, 1977). A majority now consider the simultaneous presence of hyperthermia, rigidity, and impaired consciousness with autonomic dysfunction as characteristic of the M.N.S. (Delay and Deniker, 1952; Allan and White, 1972; Melzer, 1973; Powers, 1976; Itoh et al., 1977; Grunhaus, 1979, Caroff, 1980). Our patients clearly fulfil these criteria for M.N.S. Although no definite conclusions can be drawn from three cases, it is interesting to speculate that perhaps the patients showing marked catatonic symptoms represent a more severe and diffuse impairment of central neuroregulatory mechanisms, as compared to those showing hyperthermia and fall in blood pressure—in which case the disturbance may be limited to these hypothalamic centres, and hence a more favourable outcome. This would also explain the relatively higher mortality reported in patients with so called malignant or lethal catatonia, and a more favourable outcome in cases of malignant hyperthermia.

Another significant observation made in the present series of cases is that all three patients were receiving butyrophenones. This is in line with previous reports that M.N.S. is more likely to occur on exposure to the potent neuroleptics, especially haloperidol or the long acting fluphenazine. Apparently this reaction to the neuroleptic drug is of an allergic nature and not dose related.

This is the first report of M.N.S. from India, and the purpose of this communication is to highlight the clinical presentation of this syndrome so that clinicians are alerted to the possibility of this complication in their patients receiving neuroleptics. Perhaps other psychiatrists will be moved to report their experience of this reaction, and hopefully, future studies on a larger sample will give us a more accurate estimate of the incidence of this complication; and also help to elucidate the various possible factors operating in its etiology and prognosis.

REFERENCES

ALLAN, R., AND WHITE, H. D. (1972). Side effects of parenteral long acting phenothiazines. Br. Med. J., 1, 221.
CAROFF, S. N. (1980). The neuroleptic malignant syndrome. J. Clin. Psychiat., 41, 79.
DELAY, J., PICHOT, P., AND LEMPERIERE, T. (1960). Un neuroleptique majeur non phenothiazine et non reserpine 1' haloperidol dans la traitement des psychoses. Ann. Med. Psychol. 118, 145.
DELAY, J., PICHOT, P., AND LEMPERIERE, T. (1963). L'emploi des butyrophenones en psychiatrie. Etude statistique et psychometrique. Sumpos internazionale sull'Haloperidol e Triperidol. Milano, 305.
DELAY, J., AND DENIKER, P. (1965). Sur quelques erreurs de presciption des medicaments psychiatriques. Bull. Mem. Soc. Hop. ? Paris. 116, 487.
GRUNHAUS, L., SANCHEZ, S., AND RIMON, R. (1979). Neuroleptic malignant syndrome due to depot Fluphenazine. J. Clin. Psychiat., 40, 99.
HABERMAN, M. (1978). Malignant hyperthermia: an allergic reaction to thioridazine. Arch. Intern. Med., 138, 800.

ITOH, H., OHTSUKA, N., AND OGITA, K. (1977) Malignant neuroleptic syndrome. Folia Psychiatri. et Neurol, JPN. 31, 565.

MELTZER, H. Y. (1973). Rigidity, hyperpyrexia, and coma following fluphenazine enanthate Psychopharmacologia, 29, 337.

MOYES, D. (1973). Malignant hyperpyrexia caused by trimipramine. Br. J. Anaesth., 45, 1163.

POWERS, P., DOUGLASS, T., AND WAZIRI, R. (1976). Hyperpyrexia in a catatonic state. Dis. Nerv. Syst., 37, 359.

REGESTEIN, G., ALPERT, J., AND REICH, P. (1977). Sudden catatonic stupor with disastrous outcome. J. A. M. A., 238, 518.

WEINBERGER, D., AND KELLY, M. (1977). Catatonia and the malignant syndrome; a possible complication of neuroleptic administration. J. Nerv. Ment. Dis., 165, 263.