TABLE II—*Statistical Analysis on Leprosy Patients*

Subjects	<40		40-70		>70	
	Normal	Tuberc.	Normal	Tuberc.	Normal	Tuberc.
Lepromatous	$P < 0.001$	$P < 0.001$	$P < 0.001$	N.S.	$P < 0.001$	$P < 0.05$
Tuberculoid	N.S.		$P < 0.001$		$P < 0.001$	
All leprosy ..	$P < 0.001$		$P < 0.001$		$P < 0.001$	

N.S. = Not significant.

with that among the normal population studied ($P < 0.001$) (Table II).

Of the 212 lepromatous leprosy patients studied it was found that 65 (30·7%) had a D.N. above 70, 130 (61·3%) a D.N. of 40-70, and 17 (8·0%) a D.N. below 40. In each of these the difference was significant compared with the normal population ($P < 0.001$) (Table II).

Of the 178 tuberculoid patients studied 76 (42·7%) had a D.N. above 70, 100 (56·2%) a D.N. of 40-70, and 2 (1·1%), a D.N. below 40. There was no significant difference between the control population and the tuberculoid patients with a D.N. below 40. There was a significant difference between the normal and tuberculoid groups with a D.N. of 40-70 and above 70 ($P < 0.001$).

When tuberculoid and lepromatous patients were compared there was a significant difference in those with a D.N. below 40. At levels of 40-70 the difference was not significant, and above 70 the difference was significant at the 5% level.

Discussion

In this study the esterase values obtained for the normal control sera varied from 56 to 120 units. Similar studies on normal sera give values in the range of 60-125 units (Divekar *et al.*, 1966), showing that the results obtained in this study were in conformity with previous studies. Comparison of the esterase levels between normal subjects and leprosy patients showed no significant difference between the two groups.

The D.N. distribution among the normal subjects in the present study was in conformity with other studies done in India and elsewhere (Kattamis *et al.*, 1962; Omotto and Goedde, 1965; Peters, 1968; Amma and Narang, 1969).

Comparison of the D.N. between leprosy patients and normal subjects showed that in the normal group 95·6%had a D.N. above 70 whereas in the leprosy group only 36·2% had a D.N. above 70. This difference was statistically significant ($P < 0.001$). There were also more patients than controls with a D.N. below 40—4·9% against 0·3%.

The differences in distribution of the D.N. was very marked when lepromatous leprosy patients alone were compared with normal subjects. Of great significance was the high number with atypical enzymes (D.N. below 40) in this type of leprosy. The difference in D.N. distribution was not as marked when tuberculoid patients were compared with normal subjects, especially the group with a D.N. below 40, where there was no statistically significant difference. Thus the distribution of D.N., which indicates the nature of the cholinesterase, was significantly different in lepromatous leprosy patients and the normal population.

In this study it was found that the incidence of atypical enzymes is significantly greater among lepromatous leprosy patients than in normal subjects. Many authors have suggested that susceptibility to leprosy is influenced by various genetic factors even though their studies have not been conclusive (Husen *et al.*, 1963; Spickett, 1964; Mohamed Ali, 1965; Ghosh and Mukerjee, 1970; World Health Organization, 1970). The atypical form of the enzyme which we were trying to detect with the help of the D.N. is the result of a deficiency of an autosomal gene, and sensitivity is expressed clinically when the subject is homozygous for the abnormal gene. This is a pilot study and further studies are required to confirm this.

This study was conducted with the support of a grant from the Indian Council of Medical Research.

Requests for reprints should be sent to Dr. Molly Thomas.

References

Amma, M. K. P., and Narang, R. S. (1969). *Indian Journal of Anesthesia*, 17, 415.
Chatterjee, B. B., and Choudhury, S. R. (1966). *Indian Journal of Experimental Biology*, 4, 178.
Divekar, *et al.* (1966). *Indian Journal of Anesthesia*, 14, 178.
Evans, P. T., Gray, W. S., Lehmann, H., and Silk, E. (1952). *Lancet*, 1, 1229.
Evans, P. T., Gray, W. S., Lehmann, H., and Silk, E. (1953). *British Medical Journal*, 1, 136.
Ghosh, S., and Mukerjee, A. (1970). *Leprosy in India*, 42, 77.
Husen, J., Thomas, E., and Jesudian, G. (1963). *Leprosy Review*, 34, 145.
Kalow, W. (1956). *Lancet*, 2, 576.
Kasliwal, R. M. (1959). *Journal of the Indian Medical Association*, 33, 81.
Kattamis, *et al.* (1962). *Nature*, 196, 599.
Lehmann, H., and Ryan, E. (1956). *Lancet*, 2, 124.
Mohamed Ali, P. (1965). *Leprosy in India*, 57, 272.
Omotto, K., and Goedde, H. W. (1965). *Nature*, 208, 726.
Peters, J. H. (1968). *Annual Review of Pharmacology*, 8, 427.
Phathak, M. A. (1957). *Indian Journal of Medical Sciences*, 11, 588.
Rappaport, F., Fischl, J., and Printo, N. (1959). *Clinica Chemica Acta*, 4, 227.
Spickett, S. G. (1964). In *Leprosy in Theory and Practice*, ed. R. G. Cochrane, 2nd edn. Bristol, Wright.
Steinitz, K., *et al.* (1963). *Lancet*, 1, 227.
Varkey, G. P. (1968). Unpublished observations.
Wahi, P. E., Ramachandran, P. N., and Navani, H. (1959). *Indian Journal of Medical Research*, 47, 13.
World Health Organization (1970). *Technical Report Series*, No. 459.

MEDICAL MEMORANDA

Toxic Effect of Podophyllum Application in Pregnancy

M. J. CHAMBERLAIN, A. L. REYNOLDS, W. B. YEOMAN

British Medical Journal, 1972, 3, 391–392

Podophyllum is an extremely toxic substance whose actions include those of an antimitotic agent. Severe peripheral neuropathy and intrauterine death occurred in a young woman in the 32nd week of pregnancy after the application of podophyllum resin to vulval warts.

Dudley Road Hospital, Birmingham 18
M. J. CHAMBERLAIN, M.B., M.R.C.P., Consultant Physician
A. L. REYNOLDS, M.B., F.R.C.S., Consultant Obstetrician and Gynaecologist
W. B. YEOMAN, A.R.I.C., M.R.C.PATH., Chief Biochemist, Regional Toxicology Laboratory

Case Report

An 18-year-old West Indian shorthand typist was admitted to hospital in the 34th week of a hitherto uneventful first pregnancy because of vaginal bleeding. The blood pressure was 140/90 mm Hg, and examination showed florid vulval warts which were friable and bled easily when touched. She was taken to the operating theatre and under general anaesthesia a 25% solution of podophyllum resin in tincture of benzoin compound was carefully painted on to the warts. A total of 7·5 ml (equivalent to 1·88 g podophyllum) was used.

She was noted to be unusually slow in recovering from the anaesthetic (nitrous oxide and oxygen), and when she did so she complained of paraesthesiae of the hands and feet and generalized weakness. There was noticeable weakness of the limbs, and tendon reflexes were diminished. On the third postoperative day she complained of

diplopia. The neuropathy progressed so that by the ninth day she was dyspnoeic, cyanosed, and unable to cough up secretions. There was profound weakness of the limbs, with absent tendon reflexes and bilateral wrist and ankle drop, and generalized hypoaesthesia of the limbs, with anaesthetic areas on the inner aspect of both thighs. The cerebrospinal fluid was normal on microscopy and contained 21 mg of protein per 100 ml.

On the second postoperative day she had vomited on several occasions and the serum potassium concentration was found to be 2·8 mEq/l. In spite of treatment with intravenous potassium the hypokalaemia persisted, and on the sixth day the serum potassium was 3·1 mEq/l. Subsequent values were normal. There was no diarrhoea at any time.

Two days after treatment of the warts she complained of lower abdominal pain, the uterus became tense, and the fetal heart could no longer be heard. Ten days later a stillborn female infant was delivered. The fetus weighed 2,000 g and was macerated, but no congenital abnormality was found at necropsy. The placenta weighed 340 g and contained numerous infarcts.

The patient required a short period of assisted respiration, but after reaching a maximum on the 10th postoperative day the mixed sensory and motor neuropathy began to improve slowly. Three months later she was walking without aid and was able to type, but very slowly and clumsily. She was discharged to an industrial rehabilitation unit and was lost to follow-up for six months. She then reappeared in the antenatal clinic 24 weeks pregnant. Examination showed complete recovery from the neuropathy. The pregnancy was uneventful and she delivered a normal infant.

Comment

Podophyllum resin is extracted from the dried rhizome of *Podophyllum peltatum* (Mandrake or May-apple). It contains numerous lignins and flavonols, including podophyllotoxin and alpha and beta peltatins, and is a drastic purgative, causing violent peristalsis. It is a powerful skin irritant and caustic and for a long time has been widely used in the treatment of genital warts. More recently podophyllum has been recognized as a powerful antimitotic agent and has been used extensively as a cytotoxic drug (Datta and Biswas, 1968; Kitagawa *et al.*, 1968), although there are few references to this in the English literature.

Experimental animals given podophyllotoxin may develop flaccid paralysis (Sullivan *et al.*, 1951). Severe peripheral neuropathy together with an acute confusional state leading to coma was recorded by Clark and Parsonage (1957) in a young woman who drank 2·8 g of podophyllum resin believing herself to be pregnant. She had made a substantial recovery at six months but some neurological deficit persisted 16 months after ingestion. Schirren (1966) reported loss of consciousness followed by an acute confusional state and peripheral neuropathy in a young man with onset within a few hours of the treatment of anal warts with podophyllum. The author warned particularly against the use of podophyllum in pregnant women. Previously, Ward *et al.* (1954) encountered coma and subsequent death in a young Negro woman after the treatment of vulval warts with podophyllum. Vomiting and an acute confusional state occurred after the use of podophyllum in the treatment of hairy-tongue (Hasler and Standish, 1969).

Podophyllum is teratogenic in rats (Kreybig *et al.*, 1970), and congenital deformities were found in the child of a woman who had taken slimming tablets containing 30 mg of podophyllum from the fifth to the ninth week of pregnancy (Cullis, 1972). Balucani and Zellers (1964) reported the delivery of a normal infant at term three months after the accidental administration of 1 g of podophyllum resin by mouth to the mother. She had developed paroxysms of vomiting, cyanosis, and dyspnoea four-and-a-half hours after ingestion of the resin.

The present patient had hypokalaemia persisting for five days in spite of intravenous replacement and restoration of a normal serum chloride level. This seemed to be out of proportion to the vomiting which occurred on the second postoperative day, and no other cause for hypokalaemia was evident.

There can be little doubt that the severe peripheral neuropathy described in the present case was due to absorbed podophyllum. This is entirely consistent with the known toxicity of the substance and previous clinical reports. That the podophyllum or its secondary metabolic effects were responsible for the intrauterine death is less certainly established but it seems likely.

Genital warts, however troublesome and persistent, are benign conditions, and it is unjustifiable to use so toxic and potentially dangerous a substance as podophyllum in their treatment, particularly when other measures such as diathermy are available. Certainly, podophyllum should never be used in pregnancy or in circumstances where the warts are either so florid, with a large surface area, or haemorrhagic that absorption of the toxic resin is likely. We doubt if the toxic nature of podophyllum is sufficiently appreciated by the clinicians who use it: nor is this toxicity adequately emphasized in many standard textbooks which advocate its use (Jeffcoate, 1967; Baird, 1969; Te Linde and Mattingly, 1970).

References

Baird, D. (1969). In *Combined Textbook of Obstetrics and Gynaecology*, 8th edn., p. 710. Edinburgh, Livingstone.

Balucani, M., and Zellers, D. D. (1964). *Journal of the American Medical Association*, **189**, 639.

Clark, A. N. G., and Parsonage, M. J. (1957). *British Medical Journal*, **2**, 1155.

Cullis, J. E. (1962). *Lancet*, **2**, 511.

Datta, H., and Biswas, S. (1968). *Indian Journal of Cancer*, **5**, 152.

Hasler, J. F., and Standish, S. M. (1969). *Journal of the American Dental Association*, **78**, 563.

Jeffcoate, T. N. A. (1967). In *Principles of Gynaecology*, 3rd edn., p. 476. London, Butterworths.

Kitagawa, S., Nishimura, K., and Motoyama, Y. (1968). *Japanese Journal of Cancer Clinics*, **14**, 1057.

Kreybig, T. von, Reussman, R., Kreybig, I. von (1970). *Arzneimittel-Forschung*, **20**, 363.

Schirren, C. G. (1966). *Hautarzt. Zeitschrift für Dermatologie, Venerologie und verwandte Gebiete*, **17**, 321.

Sullivan, M., Follis, R. H., and Hilgartner, M. (1951). *Proceedings of the Society for Experimental Biology and Medicine*, **77**, 269.

Te Linde, R. W., and Mattingly, R. F. (1970). In *Operative Gynaecology*, 4th edn., p. 670. Oxford, Blackwell Scientific.

Ward, J. W., Clifford, W. S., Monaco, A. R., and Bickerstaff, H. J. (1954). *Southern Medical Journal*, **47**, 1204.