(Carpenter, 1964). The values are comparable to those reported here.

TABLE III.—Comparison of Admission Arterial Blood Studies Between Classical and El Tor Cholera*

	Classical			El Tor		
	No.	Mean	Range	No.	Mean	Range
Plasma specific gravity ..	17	1.0413	1.037–1.048	34	1.0405	1.031–1.048
Total protein (g. %) ..	11	10.6	7.3–13.2	25	10.6	6.1–15
pH ..	14	7.12	7.00–7.28	29	7.17	6.92–7.40
Sodium† ..	14	147.6	130–157	33	151.1	142–161
Potassium† ..	14	7.05	4.6–11	33	6.28	3.3–10.1
Calcium† ..	7	5.6	5.2–6.2	17	5.9	5.1–9.9
Chloride† ..	15	109.2	101–118	32	113.4	101–126
Bicarbonate† ..	17	9.5	1.1–20.1	33	10.8	2.2–24.7

* Pair-wise comparison reveals no significant differences at the 10% level by the "t" test for all comparisons except chloride, which was significant at the 5% but not the 2% level.

† Values in mEq/l. of plasma water.

TABLE IV.—Comparison of Admission Stool Electrolyte Values Between Classical and El Tor Cholera Patients*

	Classical			El Tor		
	No.	Mean	Range	No.	Mean	Range
Sodium (mEq/l.)	3	125.1	124.1–125.8	16	135.0	105.4–153.3
Potassium (mEq/l.)	3	26.6	23.6–32.1	16	19.2	7.3–33.2
Calcium (mEq/l.)	3	9.8	0.5–1.0	14	0.8	0.2–1.5
Chloride (mEq/l.)	3	99.7	92–105	15	98.9	71.8–117

* Pair-wise comparison reveals no significant difference by the "t" test.

All patients had clinical evidence of severe dehydration with poor skin turgor, dry mucous membranes, sunken eyes, and flat neck veins. All patients except two (12%) classical and five (15%) El Tor were cyanotic.

A comparison between the disease course of the two control groups is seen in Table V. It is particularly interesting to note the total volume of diarrhoea, which averaged 13.2 litres for classical cholera and 18.6 l. for El Tor cholera. The variously treated groups were similarly compared, and those pairwise comparisons were not statistically significant. Illustrative of this similarity is the comparison between the 6 classical and 20 El Tor patients who each received 2 g. of tetracycline. The

classical patients had a total stool-volume which ranged from 1 to 17.4 l. and averaged 8.6 l. during the course of the disease. The El Tor patients ranged from 0.3 to 16.8 l. and averaged 5.6 l.

TABLE V.—Comparison of Disease Course During Hospitalization Between Classical and El Tor Cholera Patients Receiving No Antibiotic Therapy*

	Classical			El Tor		
	No.	Mean	Range	No.	Mean	Range
Duration of diarrhoea (hours) ..	5	102.9	67–149.3	6	86	42–127
Amount of diarrhoea (litres) ..	5	13.2	4.3–27.3	6	18.6	5.6–32
Total intravenous fluid (litres) ..	5	14.1	5–25	6	19.4	8–30.5

* Pair-wise comparison reveals no significant difference by the "t" test.

Conclusions and Summary

The above data confirm that there was no significant difference in the clinical and biochemical manifestations between the diseases caused by the classical *Vibrio cholerae* and by the *Vibrio cholerae* biotype El Tor occurring in the same population at the same time. The disease caused by either organism is identical and should be called cholera.

REFERENCES

- Barua, D., and Mukherjee, A. C. (1964). *Bull. Calcutta Sch. trop. Med.*, **12**, 147.
 — and Sack, R. B. (1964). *Ibid.*, **12**, 55.
 Carpenter, C. C. J. (1964). *Indian J. med. Res.*, **52**, 887.
 — Barua, D., Wallace, C. K., Sack, R. B., Mitra, P. P., Werner, A. S., Duffy, T. P., Oleinick, A., Khanra, S. R., and Lewis, G. W. (1965a). *Bull. Wild Hlth Org.*, **33**, 665.
 — Mitra, P. P., Sack, R. B., Khanra, S. R., Werner, A. S., Duffy, T. P., and Wallace, C. K. (1965b). *Bull. Calcutta Sch. trop. Med.*, **13**, 128.
 deMoor, C. E. (1963). *Trop. geogr. Med.*, **15**, 97.
 Gotschlich, F. (1906). *Z. Hyg. Infekt-Kr.*, **53**, 281.
 Mukerjee, S. (1964). *Brit. med. J.*, **2**, 546.
 — Basu, S., and Bhattacharya, P. (1965). *Ibid.*, **2**, 837.
 Wallace, C. K., Carpenter, C. C. J., Mitra, P. P., Sack, R. B., Khanra, S. R., Werner, A. S., Duffy, T. P., Oleinick, A., and Lewis, G. W. (1965). *Trans. roy. Soc. trop. Med. Hyg.*, **59**, 621.

Medical Memoranda

Peripheral Neuropathy due to Disulfiram

Brit. med. J., 1966, **2**, 449–450

Tetraethylthiuram disulphide (disulfiram, Antabuse) has been used extensively for the control of chronic alcoholics since its introduction (Hald *et al.*, 1948). Most workers agree that it interferes with the oxidation of alcohol by blocking hepatic oxidative enzymes, leading to the accumulation of acetaldehyde, which is responsible for the alcohol-disulfiram reaction (Goodman and Gilman, 1955). Minor side-effects of disulfiram are relatively common, including drowsiness, headache, memory impairment, decreased libido, gastro-intestinal symptoms, halitosis, and skin rashes (Martensen-Larsen, 1953). Agranulocytosis (Jacobson, 1952) and thrombocytopenic purpura (Leibetseder, 1952) have been reported, and large doses are goitrogenic in rats (Christensen and Wase, 1954).

Peripheral neuropathy and toxic psychoses may be caused by disulfiram. These complications are not uncommon in chronic alcoholics, and early recognition that they may be due to the drug is important, since the drug-induced cases respond well to its withdrawal. These two side-effects have not been widely reported in Great Britain. To draw attention to one of them

the following case of peripheral neuropathy arising during disulfiram therapy is recorded.

CASE HISTORY

A 39-year-old dentist was admitted to hospital in August 1965. He began drinking to steady his nerves during qualifying examinations 14 years before, and six years later was treated with electric convulsion therapy for paranoid depression. After this episode he began drinking heavily, and in the last five years consumed a bottle of whisky a day. One year before admission he was given disulfiram, for the first time, for two months, and one alcohol reaction was induced.

Seven months before admission he lapsed into another alcoholic bout and was again given disulfiram. At that time neurological examination and E.E.G. revealed nothing abnormal. After two moderate alcohol reactions he continued taking disulfiram, 1 g. daily, faithfully administered by his mother, for nearly seven months. The patient and his mother insisted that he took no alcohol during the whole period. In addition, he regularly took chlorthalidone (Librium) 30 mg. daily, and ethchlorvynol (Arvynol) 500 mg. and trichlorethyl phosphate (triclofos) 1 g. nocte.

Three weeks before admission he developed, within 48 hours, a severe peripheral neuropathy, with paralytic foot-drop, clumsy

hands, and numbness and paraesthesiae extending to the elbows and above the knees. His voice became slurred. Two weeks before this sudden onset he had noticed difficulty in using his fingers for fine tasks, and a change in gait. His mother spontaneously stopped all tablets, including disulfiram, and his family doctor administered Parentrovite.

On admission three weeks after the onset he was thin and haggard, with bilateral complete paralytic foot-drop, weakness extending proximally to the quadriceps and hamstring muscles. The small muscles of the hand were also weak. Loss of all sensory modalities, including joint position, extended to above the knees in a "glove and stocking" distribution. The calves were tender on pressure. He had a slurring dysarthria and slight difficulty in closing the right eyelid.

Electromyography (by Dr. G. Rushworth) was performed on 23 September (seven weeks after the onset of symptoms). "Complete denervation of the extensor digitorum brevis muscle was demonstrated, and partial denervation of tibialis anterior, peronei, and gastrocnemius muscles. The conduction velocity of motor nerve fibres within the lateral popliteal nerve could not be measured because of the complete paralysis of the extensor digitorum brevis, but tibialis anterior responded with a latency of 8 msec. after stimulation of the lateral popliteal nerve at the fibula head (the normal does not exceed 5 msec.). Stimulation of medial popliteal nerve in the popliteal fossa evoked a direct response in gastrocnemius at 7 msec. (normal does not exceed 5 msec.), but there was no H-reflex. No ankle-jerk could be elicited. The left quadriceps gave a normal electromyogram, but the latency of the left knee-jerk was 27 msec. (normal does not exceed 22 msec. by this method). The absent ankle-jerk and H-reflex and delayed knee-jerk (with normal motor innervation of this muscle) are in favour of pathological involvement of large sensory fibres originating in muscle spindles. The increased latency of evoked motor responses in tibialis anterior and gastrocnemius, with partial denervation, indicates peripheral motor-nerve-fibre involvement. In my experience alcoholic polyneuritis usually produces less marked changes of conduction velocity than were demonstrated in this patient, which would tend to support the diagnosis of polyneuritis due to a toxin other than alcohol."

Psychological tests showed an extremely variable performance, with deterioration in arithmetic and visuo-spatial tasks. E.E.G. showed minimal slow-wave abnormalities. Liver-function tests, including bromsulphthalein retention, were normal. The Wassermann reaction was negative. A glucose-tolerance test was normal. Serum vitamin-B₁₂ level was 365 µg./ml. Viral complement-fixation tests showed a titre to influenza A of 1:64 but were otherwise normal. There were no excess urinary porphyrins. Lumbar puncture on two occasions showed normal pressure of clear cerebrospinal fluid, protein 45 mg./100 ml., and no cells.

Further disulfiram was not given, and with compound vitamin-B tablets and physiotherapy the peripheral neuropathy gradually improved. Eight weeks from the onset he was able to walk without a stick, though still with marked paralytic foot-drop, and could do all fine tasks with his fingers. The level of sensory loss was at the finger-tips and ankles.

COMMENT

This patient had probably not taken alcohol for seven months, and alcoholic neuropathy in these circumstances is unlikely. The raised influenza A titre might be significant, since Melnick and Flewett (1964) found increased viral antibody titres in 48% of cases with the Guillain-Barré syndrome compared with 30% of a control series. However, the marked sensory loss, purely distal weakness, and the normal C.S.F. protein exclude the Guillain-Barré syndrome (Osler and Sidell, 1960). Other causes of peripheral neuropathy, other than drugs, appear to have been excluded, and the response to withdrawal of drugs adds support to this conclusion. Neither chlor-diazepoxide nor triclofos nor ethchlorvynol has been reported to cause neuropathy. Chloral has been included among the causes of polyneuropathy (Stewart, 1925; Harris, 1926), though we have been unable to find a case report.

Child *et al.* (1951) reported three cases of "questionable peripheral neuritis" in 120 patients receiving disulfiram. All three had received the drug within four days of an alcoholic bout.

Charatan (1953) reported a case of typical peripheral neuropathy in a patient receiving disulfiram, 500 mg., for four months. Barry (1953) mentioned a further possible case. Hayman and Wilkins (1956) reported six instances of this condition arising in patients taking disulfiram, 250 to 750 mg., with vitamin-B preparations for 4 to 12 months; another patient developed peripheral neuropathy after a severe alcohol-disulfiram reaction. All the cases described in the literature had received such reactions, but only the three cases of Child *et al.* (1951) and the seventh case of Hayman and Wilkins (1956) developed neuropathy in close relation to the reaction. No alcohol was consumed by our patient, and the reason for the rapid onset after premonitory symptoms for two weeks is not clear. In all cases the neuropathy improved after disulfiram withdrawal.

Toxic psychotic states, usually arising early in disulfiram therapy, and of a confusional, paranoid, or expansive type, have been reported (Bennett *et al.*, 1951; Mann *et al.*, 1952; Larimer, 1952; Rathod, 1958). They respond well to drug withdrawal. Disulfiram worsens pre-existing E.E.G. abnormalities, and it has been suggested that it should be withheld from those with evidence of brain damage (Busse *et al.*, 1952).

Disulfiram is a metabolic poison and may lead to the accumulation of toxic derivatives of drugs metabolized by oxidative pathways. Chlordiazepoxide is not so metabolized (Koechlin *et al.*, 1965), and in an acute trial was found compatible with disulfiram (Dimberg, 1962). Our patient was also taking triclofos and ethchlorvynol, both substituted alcohols. Disulfiram completely blocks the oxidation of trichlorethanol (Owens and Marshall, 1955), though oxidative pathways are relatively unimportant in trichlorethanol metabolism (Marshall and Owens, 1954). The metabolic pathways of ethchlorvynol are not known, but oxidation may play a part. These possibilities must be considered in using other drugs with a metabolic poison like disulfiram. It is probably better not to combine substituted alcohols with disulfiram.

We are grateful to Dr. W. Ritchie Russell for permission to publish this case, and to Dr. Geoffrey Rushworth, who performed the electromyography. We also thank Dr. P. J. A. Willems for helpful discussions.

W. G. BRADLEY, M.A., B.M., B.SC.,
Senior House Officer.
R. L. HEWER, M.B., M.R.C.P.,
Senior Registrar.

Department of Neurology,
Churchill Hospital, Oxford.

REFERENCES

- Barry, W. K. (1953). *Brit. med. J.*, 2, 937.
Bennett, A. E., McKeever, L. G., and Turk, R. E. (1951). *J. Amer. med. Ass.*, 145, 483.
Busse, E. W., Barnes, R. H., and Ebaugh, F. G. (1952). *Amer. J. med. Sci.*, 223, 126.
Charatan, F. B. (1953). *Brit. med. J.*, 2, 380.
Child, G. P., Osinski, W., Bennett, R. E., and Davidoff, E. (1951). *Amer. J. Psychiat.*, 107, 774.
Christensen, J., and Wase, A. (1954). *Fed. Proc.*, 13, 343.
Dimberg, A. R. (1962). In *Arbeitsstagung über Alkoholismus*, edited by K. Krypsin-Exner, p. 201. Vienna.
Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed., p. 116. Macmillan, London.
Hald, J., Jacobsen, E., and Larsen, V. (1948). *Acta pharmacol. (Kbh.)*, 4, 285.
Harris, W. (1926). *Neuritis and Neuralgia*. Oxford Univ. Press, London.
Hayman, M., and Wilkins, P. A. (1956). *Quart. J. Stud. Alcohol*, 17, 601.
Jacobson, J. R. (1952). *Hawaii med. J.*, 12, 116.
Koechlin, B. A., Schwartz, M. A., Krol, G., and Oberhansli, W. (1965). *J. Pharmacol. exp. Ther.*, 148, 399.
Larimer, R. C. (1952). *J. Amer. med. Ass.*, 150, 79.
Leibetseder, F. (1952). *Wien. klin. Wschr.*, 64, 431.
Mann, N. M., Conway, E. J., Gottesfeld, B. H., and Lasser, L. M. (1952). *J. Amer. med. Ass.*, 149, 40.
Marshall, E. K., and Owens, A. H. (1954). *Bull. Johns Hopk. Hosp.*, 95, 1.
Martensen-Larsen, O. (1953). *Quart. J. Stud. Alcohol*, 14, 406.
Melnick, S. C., and Flewett, T. H. (1964). *J. Neurol. Neurosurg. Psychiat.*, 27, 395.
Osler, L. D., and Sidell, A. D. (1960). *New Engl. J. Med.*, 262, 964.
Owens, A. H., and Marshall, E. K. (1955). *Bull. Johns Hopk. Hosp.*, 97, 395.
Rathod, N. H. (1958). *Quart. J. Stud. Alcohol*, 19, 418.
Stewart, T. G. (1925). *Brit. med. J.*, 2, 461.