indicated are rigorously observed. In this series this lack of toxicity had several obvious advantages. Because severe bone marrow depression did not occur no access was needed to reverse barrier rooms or to platelet transfusions. In addition, most patients spent only a short time in hospital—that is, three or four days out of 28. Furthermore, though side effects did occur, the quality of the patient's life was not impaired to the extent seen with certain other multiple drug regimens. This meant that even if the treatment should fail, therapy could still be offered to patients in the knowledge that at least it would not make them any worse than they were already. Since the treatment has proved safe over 160 treatment cycles in 40 patients we feel that it should now be used much earlier than has been the case in this preliminary study, perhaps as soon as evidence of metastases first appears.

The overall regression rate in this series seems to be at least comparable to that achieved by other more toxic regimens. There is therefore no evidence that the antitumour effect of these drugs is lessened by giving them in this way. The similarity in response rate between schedules 1 and 2 suggests that the addition of cytosine arabinoside may not contribute any significant antitumour effect.

Thus in answer to the questions posed in the introduction we conclude that the toxicity of multiple antitumour drug

schedules can be reduced to acceptable levels without lessening their antitumour effect. As to whether there exists a particular kind of tumour which might respond especially well to such treatment, we have the impression that carcinomas of the breast and bladder may do relatively well. However, we propose to extend the study to include a further 60 patients to see if such a subgroup can be definitely identified.

L.A.P. wishes to thank all consultants at the Royal Marsden Hospital who referred patients for this trial, particularly Dr. D. A. G. Galton and Dr. E. Wiltshaw, and also wishes to acknowledge the excellent standard of nursing care on Wolrige Ward, Royal Marsden Hospital, London.

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MEDICAL MEMORANDA

Myasthenia with Systemic Lupus and Palmoplantar Keratosis

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A case is described here in which a patient with myasthenia gravis developed tylosis and features of systemic lupus erythematosus.

Case Report

A 20-year-old mill labourer presented in 1963 with a six-month history of increasing weakness of the legs. His previous health had been excellent and the family history contained nothing abnormal. He was noted to have some facial wasting and slight, non-tender enlargement of cervical and axillary lymph nodes. The muscles were normal in appearance but fatigued quickly. Normal power was restored by an injection of edrophonium. The E.S.R. was 15 mm/hr (Westergren) and the W.B.C. 3,700/mm³. Treatment with neostigmine 15 mg four times daily was started.

The weakness slowly returned and ascended, leading him to present again in July 1970 with difficulty in speaking, swallowing, and closing his eyes. In the preceding three years there had been intermittent painful swelling of the knees. Sometime during this period he had noticed painless thickening of the palmar and plantar skin. The increasing weakness had forced him to take lighter employment as a telephonist.

The skin of the palms and soles was transformed into a uniformly thickened orange-yellow keratinized layer. The skin else-

where and the hair and nails were normal. His appearance suggested facial muscle wasting and there was wasting of the lumbar paraspinal muscles. The muscles generally felt flabby and hypotonic, and they were weak and fatigued very quickly. Non-tender enlargement of the cervical, axillary, and inguinal nodes was palpable and a small effusion was present in the right knee.

Edrophonium 10 mg intravenously produced a dramatic response, restoring the muscular strength to normal for one minute. The E.S.R. was 63 mm/hr and the W.B.C. 4,000/mm³. A high titre of antinuclear factor was present and an L.E. cell preparation was strongly positive. Serum IgG 2,012 mg/100 ml, IgM 340 mg/100 ml. Muscle biopsy showed lymphorrhages characteristic of myasthenia gravis and electromyography demonstrated typical motor response fatigability.

The anticholinesterase therapy was increased to neostigmine 15 mg six times daily plus pyridostigmine 60 mg three times daily. Azathioprine 100 mg daily was started. Improvement in muscle power was obtained and though this was not of normal strength he was able to continue work. The serum abnormalities persisted—E.S.R. 44 mm/hr, antinuclear factor + + +, IgG 1,688 mg/100 ml, IgM 424 mg/100 ml.

His parents, four brothers, and two sisters were examined and found to be healthy. None had tylosis, myasthenia, or systemic lupus erythematosus or were positive for antinuclear factor.

Comment

Hyperkeratosis of the palms and soles occurs in pityriasis rubra pilaris, but the skin elsewhere, particularly of the backs of the hands, usually shows the characteristic follicular keratosis. In this patient the skin other than that of the palms and soles was normal. The keratosis resembled that seen in the familial tyloses. These familial lesions may be seen in association with other ectodermal dysplasias (as in the Unna-Thost, Papillon-Lefèvre, and Meleda diseases), with tumours of viscera of foregut origin (oesophagus (Howel-Evans *et al.*, 1958), bronchus (Parnell and Johnson, 1969), larynx and stomach (Haines, 1967), or with hypertrophic spondylitis (Beardwell, 1969).

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The present patient did not have any of these associated conditions, nor were any shown in a limited study of his family. He did have undoubted myasthenia and enough features of systemic lupus erythematosus to fulfil the M.R.C. (1961) diagnostic criteria (high E.S.R., neutropenia, arthritis, lymphadenopathy, strongly positive L.E. cell preparation). The association between these two diseases is known (Harvey *et al.*, 1954), and rarely systemic lupus erythematosus appears to be precipitated by thymectomy in a patient with myasthenia (Alercón-Segovia *et al.*, 1963). It might therefore be argued that thymectomy would be best avoided in the myasthenic patient who has features of systemic lupus erythematosus. In this case azathioprine was given in the hope of preventing the appearance of a more florid systemic lupus erythematosus rather than mitigating the myasthenia, which is affected minimally by immunosuppressive therapy (Namba and Grob, 1969).

My thanks are due to Dr. C. D. Needham for permission to report this case and to Dr. A. W. Downie for the electrophysiological studies.

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Diazepam, Alcohol, and Barbiturate Abuse

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It has been recognized for some time that dependence is a potential hazard of benzodiazepine use (Hollister *et al.*, 1963; Aivazian, 1964; Essig, 1966; Kryspin-Exner, 1966; Relkin, 1966; Holmsberg, 1969). This report is of a case of diazepam abuse in a woman who originally sought treatment for disturbed sleep and who over a period of six years became severely dependent on diazepam, alcohol, and barbiturates.

Case Report

A 39-year-old woman was admitted to the Bethlem Royal Alcoholism Unit for treatment of dependence on alcohol and drugs. There was a strong family history of depressive illness coupled with heavy drinking. As a child the patient had been nervous of the dark, but her school career was normal, and she had then worked for five years as a telephonist. Shortly after marriage at 21 years she suffered her first panic attack when travelling on a train. She was ill at home for two weeks and changed her job, thus avoiding train travel. She had a second panic attack after the birth of her first child four years later. Her second child was born when she was 31, and soon afterwards she became irritable, anxious, and depressed. Her sleep deteriorated, the panic attacks worsened, and she was afraid to go out alone. Her general practitioner prescribed amylobarbitone sodium 390 mg at night. Over a three-year period she increased the dose to 1,170 mg daily, while her symptoms fluctuated. In 1967 she was referred by another general practitioner to the psychiatric outpatient department at her local hospital. She received monthly injections of amylobarbitone sodium for six months, but this was terminated after she became unconscious during a treatment. Her doctor began to reduce the barbiturate prescription. Her symptoms worsened and she began taking alcohol for relief, at first half a bottle of sherry daily, but increasing over 18 months to one or two bottles a day.

In February 1970 she was admitted to the Bethlem Royal Day Hospital and had a withdrawal fit shortly after admission. She was treated for her phobic symptoms with progressive desensitization, barbiturates were discontinued, apart from a night dose, and diazepam by mouth was substituted. After four months she was discharged symptom-free on diazepam 20 mg three times a day

and amylobarbitone sodium 195 mg at night. Within two weeks she had persuaded her general practitioner to increase the diazepam to 90 mg daily and to prescribe the tablets monthly. She increased her consumption steadily and was soon exhausting her monthly supply in 7-10 days, taking up to 500 mg of diazepam daily. Sherry was substituted whenever she ran out of diazepam. During the two months before her readmission she experienced regular morning shakes, slurred speech, gross ataxia, and withdrawal fits, symptoms which she relieved with alcohol or diazepam.

On admission to the alcoholism unit she was undernourished and underweight. There were multiple bruises on her body and one large bruise under her left eye. There was a coarse tremor affecting all her limbs and her deep reflexes were brisk. She was restless, anxious, and continually demanding medication for sleep. There were no depressive or phobic symptoms.

Within seven days she had been withdrawn from all drugs and alcohol. Over the subsequent month she complained of a mild tremor of her arms and legs and an intense craving for tablets. Her sleep remained disturbed throughout her stay and was characterized by short periods of restless light dozing and nightmares. After two months she was discharged, sleeping a little better and not on medication. Follow-up over a period of five months confirmed that she had remained free of symptoms, had obtained a full-time job, and that her sleep had returned to normal.

Comment

Despite a family history of alcohol abuse and a personal history of barbiturate excess this patient was prescribed diazepam in large dose for her phobic symptoms. This reflects the widely held view that the benzodiazepines are non-addictive even in predisposed and highly anxious patients. Glatt (1967) argued that the risk of developing dependence with diazepam is slight but must be considered in those patients on high doses or those treated for lengthy periods. This patient, however, was on diazepam for only a matter of weeks before she began to misuse the drug and manifest signs of dependence.

It is suggested that the sanguine view held by many members of the medical profession towards the minor tranquillizer has been transmitted to the lay public and militates against attempts to remove patients from unnecessary and potentially harmful treatment with these drugs.

I would like to thank Dr. Griffith Edwards for permission to report this case and for his helpful advice.

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