relatively unsuccessful in the treatment of spastic paralysis, for which condition it was particularly indicated on theoretical grounds. Its failure is due chiefly to the difficulty in getting enough of the drug into the patient without causing gastric or cerebral side-effects and to its brief action: intravenous administration in adequate dosage usually gives complete or almost complete relaxation of the most severe spasticity without any concurrent loss of power, although the effect by this route is too brief to be therapeutically useful.

In the treatment of myoclonic epilepsy we have found it necessary to give up to 48.5 g. of mephenesin a day, and, although this is exceptional, doses of that order should be fairly easily achieved, for short periods at least, if attention is given to the timing of the doses. Where possible they should be given on a full stomach, some as alcoholic elixir and some as tablets, although the latter are absorbed less readily and possibly less completely than the elixir.

In a series of 27 spastic patients one of us found that the maximum tolerated dose of the elixir alone varied between 6 and 18 g. of mephenesin a day; these were high doses at the time (1951), and it is now clear that they can be greatly exceeded in some patients and are safe for a period of months at least.

When mephenesin is given intravenously it should be as a 1% solution in saline. At this strength significant haemolysis does not occur and haemoglobinuria has never been reported. The risk of this complication increases as the solution strength rises, but is probably not serious until 4% has been reached. For solutions of over 1.5% it is necessary to use alcohol or propylene glycol to aid solution. The drug is metabolized very rapidly, and the clinical effects of a single intravenous injection may last as little as 30 minutes, or an oral dose only 60 to 90 minutes.

Mephenesin is also a local anaesthetic, and if a patient cannot swallow easily and sips the elixir this may lead to anaesthetization of the throat and inhalation of the drug (Case 2 above and Newhouse *et al.*, 1950).

Summary

It has hitherto been impossible to control the myoclonus of progressive myoclonic epilepsy with drugs.

Five cases are reported, in four of which helpless patients were restored to activity temporarily by intravenous mephenesin; one less severe case was helped by oral mephenesin.

Owing to the very large doses necessary, various side-effects occurred; these were largely overcome.

The mechanism of the action of mephenesin in this disease remains unknown.

We wish to thank Dr. S. P. Meadows for permission to treat Case 1; Dr. M. J. McCormack for referring Case 2 to one of us; and Dr. E. Arnold Carmichael for permission to treat Cases 3-5. We also wish to thank Dr. J. St. C. Elkington for his help and encouragement in carrying out this work; Dr. J. T. Hutchinson for the E.E.G. reports; Messrs. E. R. Squibb and Son, who supplied the mephenesin carbamate; and British Drug Houses, who supplied the control elixir.

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SPONTANEOUS REGRESSION OF A MALIGNANT MELANOMA

BY

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Cutaneous malignant melanoma has a characteristically unpredictable behaviour, and a melanoma which has already metastasized may undergo spontaneous regression (Willis, 1953).

Bennett (1899) described two such cases. The first was in a woman aged 52 who had a malignant melanoma of the foot treated by local excision, followed by Syme's amputation for a local recurrence. She then developed widespread skin and glandular metastases, and the prognosis was regarded as hopeless. Six months later there was no evidence of malignancy. His second case showed spontaneous disappearance of glandular metastases and skin nodules following removal of the primary tumour, a malignant melanoma of the foot.

Gould (1906) saw a man aged 35 who developed widespread skin recurrences following excision of a malignant melanoma on the chest. The liver was enlarged, there were glandular metastases, and melanogen was present in the urine. He was treated with turpentine and sulphur pills, with considerable local and general improvement and disappearance of the skin deposits lasting for five months, though during this time the melanogenuria persisted. Renewed activity then occurred and he died eight months later. Mathews (1915) saw a man aged 45 who had a malignant melanoma over the scapula, with enlarged axillary glands and a fullness above the corresponding clavicle. After incomplete surgery, when the primary tumour and the axillary glands were removed, he remained well for two years and the supraclavicular swelling disappeared.

The histogenesis of intraocular melanoma is unsettled; amongst other hypotheses Willis (1953) suggests that they are of epithelial origin, arising from split-off epithelial cells analogous to the naevus cells of the skin, and that there is a general similarity between the intraocular and cutaneous melanomas. Ocular melanoma behaves slightly differently from the cutaneous type in producing frequent though long-delayed metastases, and in not usually disseminating so widely throughout the body. If, however, Willis's hypothesis is acceptable, then it is reasonable to expect metastases from a malignant melanoma of the choroid to exhibit the same anomalous behaviour as if the primary tumour were in the skin.

Case Report

The patient, a man aged 60, had the right eye excised at Moorfields Eye Hospital on February 21, 1951. The pathological report on the specimen was as follows: "Arising from the choroid in the superonasal quadrant of the eye is a large lightly pigmented mixed-celled malignant melanoma. Many blood sinuses are present in the growth and the reticulin content is light. There is some infiltration of the adjacent deep scleral lamellae, but in the sections examined there is no evidence of extraocular extension. The retina overlying the melanoma has been invaded and there is a retinal detachment on both sides of the growth. Microscopically this is a malignant melanoma of the choroid."

The patient was first seen at Addenbrooke's Hospital on February 26, 1953, when there was no clinical evidence of recurrence and the liver was not palpable. An x-ray film of the chest showed multiple small opacities at the base of the left lung, and examination of the urine at the same time showed melanogens to be present, and he was accordingly regarded as having pulmonary metastases. The presence of melanogens in this urine was shown by the ferric chloride in hydrochloric acid test, and by Thormählen's nitroprusside reaction (Harrison, 1947). No treatment was given.

Re-examination on July 8 showed disappearance of the pulmonary metastases and no melanogens in the urine. Since then repeated clinical and radiological examinations have shown no evidence of recurrence, and melanogens have not been present in the urine.

Discussion

Melanogen, the colourless chromogen of melanin, is excreted in the urine when there are extensive secondary deposits of malignant melanoma. Urine containing melanogen reduces sodium nitroprusside to ferric ferrocyanide (Thormählen's reaction) and reduces ferric chloride to ferrous chloride. Haden and Orr (1924) and Peters (1923) describe cases with apparent melanogenuria with no malignant melanoma in the body, but it seems doubtful if melanogen was really present in the urine in these cases. von Jaksch (1905) claims that a positive Thormählen reaction may be obtained in urine free from melanogen and has seen it in children suffering from chronic constipation; he says an abundance of melanogen occurs in the urine of wasted patients. Harrison (1947) states that he has tested many pathological urines and has never obtained a positive Thormählen reaction except in melanogenuria, and he concludes that if both the ferric chloride test and the nitroprusside reaction are positive it is safe to diagnose melanogenuria. In the case reported here it is considered that, as the choroidal tumour removed was a proved malignant melanoma, the pulmonary opacities were metastases and responsible for the presence of melanogens in the urine.

Spontaneous disappearance of a malignant tumour is a rare phenomenon of considerable interest, and several theories regarding the aetiology have been put forward. Rohdenburgh and Bullock (1918) collected 302 cases in which temporary or permanent regression of a malignant growth occurred. In this series the greatest number of spontaneous regressions followed incomplete surgical removal of the tumour or acute infections with prolonged pyrexia such as erysipelas, and a smaller number were associated with a profound upset of the patients' metabolism such as the menopause. He considered it probable that these conditions act by depressing the proliferative energy of the malignant cell until the defensive forces of the body are able to accomplish its final destruction. Ewing (1940) says the only explanation of many cases of spontaneous cure of highly malignant tumours is a local or general immunity. It is recognized that necrosis, probably starting because the tumour outgrows its blood supply, is a prominent feature of choroidal melanoma, and out of 106 tumours described by Samuels (1934) 24 were completely necrotic. Reese (1951) saw spontaneous necrosis occur in a malignant melanoma of the iris.

In the case reported here there was no obvious cause for the regression of the metastases such as an acute infection. As necrosis can bring about regression and apparent cure of the primary choroidal tumour, it is thought probable that this is the cause in this case rather than the other theories discussed.

Summary

A case of spontaneous regression of pulmonary metastases from a malignant melanoma of the choroid is described. Several theories concerning the aetiology are discussed, necrosis due to the tumour outgrowing its blood supply being considered the most probable.

I am grateful to Professor J. S. Mitchell for permission to publish details of this case and for his help, to Dr. N. R. Lawrie for assistance with the biochemical details, and to Dr. N. Ashton for supplying me with the pathology report.

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THERAPY IN EXPERIMENTAL HEPATIC FAILURE

BY

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It is difficult to assess the effect of any drug in the treatment of acute hepatic failure in man. A few patients will recover spontaneously, and any method of treatment used will then be given credit for the successful outcome. No satisfactory therapeutic trial comparing similar groups of treated and untreated cases has ever been carried out, and the difficulties in the way of such a trial are formidable, for the condition is uncommon and may be due to a variety of causes.

A controlled trial of the efficacy of some of the measures advocated for the treatment of acute hepatic failure in man has therefore been carried out on rats in which the syndrome has been reproduced experimentally.

Methods

It has been shown that the injection of 0.02 to 0.04 ml. of carbon tetrachloride into the mesenteric vein of the rat will reproduce many of the clinical and pathological features of the syndrome of acute liver failure seen in man (Reynell, 1953). A large proportion of the rats so treated will die within 48 hours. The procedure was designed to produce severe hepatic necrosis without damaging other tissues. Adult male rats of the Wistar strain (200–400 g. body weight) and free of Bartonella infection were used in these experiments.

Experiment I: Vitamin Supplements by Mouth.—Thirty-four rats reared on stock diet were each given 10 g. of a synthetic diet daily for two days before the injection of carbon tetrachloride into the mesenteric vein. The diet was made up as follows: cornstarch, 71 parts; casein, 26 parts; and salt mixture, 3 parts. During the three days after operation each rat was offered 5 g. a day of the same diet, although even this reduced amount was not always consumed. Half the rats were given the following vitamin supplement, which was mixed with the diet: 2 mg. of nicotinic acid, 1 mg. of thiamine, 1 mg. of riboflavin, 1.5 mg. of tocopherol, and 30 mg. of choline chloride per rat daily. This supplement resembles the parenteral vitamin mixture advocated by Latner (1950) for the treatment of hepatic failure.

Experiment II: Large Doses of Parenteral Liver Extract.—Of 24 rats fed on stock diet and subjected to the injection of carbon tetrachloride into the mesenteric vein, 12 were given 0.25 ml. of commercial liver extract daily by subcutaneous injection for two days after operation.