In this case air-dried films stained with Leishman's stain and wet films fixed in Schaudinn's fluid before being stained with Meyer's haemalum and eosin were both satisfactory, though the latter method gave greater cytological detail. In either case it was necessary that the centrifuged deposit be suspended in the minimum amount of fluid consistent with spreading a film.

In the cases hitherto described the commonest sites of primary growth have been stomach and bronchus. With regard to the dissemination of malignant cells in the C.S.F. Willis (1953) has suggested that this usually occurs from secondary deposits involving the ventricular walls, the choroid plexus, or the leptomeninges. The extensive involvement of the leptomeninges and choroid plexus in the present case together with the constant finding of carcinoma cells in the C.S.F. supports this, and it is clear that dissemination would be particularly easy from such a large surface area in contact with C.S.F.

Carcinomatosis of the meninges frequently produces a lymphocytic response in the C.S.F. In this case 87% of the cells present were lymphocytes. In cases such as this, which present clinically as subacute or chronic meningitis, this may lead to a misdiagnosis of tuberculous meningitis unless the carcinoma cells are also found. The absence of fever in these cases is significant, and should stimulate an adequate search for atypical cells.

Another finding frequently associated with carcinomatosis of the meninges is a low glucose level in the C.S.F. The mechanism of this change is uncertain, some observers believing that the fall is due to increased metabolism by the tumour cells, others that a mechanical block of the blood-brain barrier would prevent the passage of crystalloids, while still others believe that a combination of both these factors is usually present (McMenemey and Cumings, 1959). However, the general belief that the glucose level is lowest in those cases where there is extensive meningeal involvement is supported by this case, where the glucose level in all three samples of C.S.F. was extremely low, and indeed absent in one sample, and the meningeal involvement particularly diffuse.

The successful identification of malignant cells in the C.S.F. is primarily dependent on a satisfactory film for cytological examination, as it is most unlikely that the atypicality of any carcinoma cells present would always be apparent in the counting-chamber. It is suggested that films should be carefully examined in all cases of cerebrospinal pleocytosis of unknown aetiology, particularly where there is an associated cerebrospinal lymphocytosis, when the glucose level is unexpectedly low, or when a patient with subacute or chronic meningitis is afebrile.

It is also emphasized that the diagnosis of carcinomatous meningitis may be missed at necropsy unless a thorough histological examination is carried out.

Summary

A case of carcinomatosis of the meninges is reported. Malignant cells were found in the cerebrospinal fluid *in vivo*, and this was associated with an extremely low glucose level in the fluid. Histological evidence of diffuse carcinomatous involvement of the leptomeninges was found at necropsy, though there was no naked-eye evidence of tumour.

The difficulties of diagnosis in this condition are discussed.

I wish to thank Dr. Evan Jones for permission to quote from the case history, Dr. R. Vaughan-Jones for the cytological preparations, and Professor R. C. Curran for the photomicrographs.

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DIAGNOSTIC VALUE OF A SINGLE PLASMA PEPSINOGEN ESTIMATION

AN ASSESSMENT IN 500 CASES

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The study of peptic ulceration has included a search for methods which will provide a reliable indication of total gastric activity. The clinician is particularly interested in those tests which will help him to decide whether or not there is an ulcer, and how he can cure it or relieve its symptoms. Edwards, Jepson, and Wood (1960) reviewed the relationship between gastric pepsin secretion and the uropepsinogen and plasma pepsinogen levels, and suggested that single estimations of the plasma pepsinogen would prove a helpful diagnostic test. There are many difficulties in transferring a research test satisfactorily to general diagnostic work. It has to be done by different people in different departments and under different conditions, of which pressure of other work is perhaps the most exacting. Only the most robust and reliable tests survive and prove suitable for indiscriminate use. We have used the method proposed by Edwards *et al.* in 500 cases under busy routine diagnostic conditions and have failed to substantiate their hopes for it.

Method

The method was based on that described originally by Mirsky *et al.* (Edwards *et al.*, 1960).

Each batch of tests was done on the same batch of reconstituted plasma substrate, and only substrate which reconstituted completely was used. The substrate and patients' plasma mixture was initially standardized to a pH of 2, estimated electrically. The tyrosine standard was prepared by dissolving 100 mg. of tyrosine and making up to 100 ml. with N/10 HCl. A working standard was prepared freshly each day from this by diluting 5 ml. of the stock standard to 100 ml. with water.

The final steps, in which all tubes were treated identically, were as follows. 2 ml. of filtrate and 3 ml. of dilute Folin and Ciocalteu reagent (B.D.H. reagent diluted one part reagent to two parts of water) were

added to 20 ml. of N/4 NaOH. Results were read on the Spekker absorptiometer using an Ilford No. 8 red filter. Standard curves were prepared as follows: into three tubes were added (1) 0.5 ml. of working standard and 1.5 ml. of water; (2) 1 ml. of working standard and 1 ml. of water; and (3) 2 ml. of working standard. To each tube were then added 20 ml. of N/4 NaOH and 3 ml. of dilute Folin and Ciocalteu reagent, which were mixed and read on the Spekker absorptiometer. Calculation was as described by Edwards *et al.* (1960).

Results

Accuracy of Method.—The 44 estimations made on 12 specimens of plasma gave a coefficient of variation of 17.8%.

Variation of Plasma Pepsinogen in Patient.—A total of 107 serial estimations were made on 26 patients on a two-hourly basis beginning at 7.30 a.m. The coefficient of variation proved to be 31%.

Random Levels on Patients.—The Table shows a frequency distribution of various levels of plasma pepsinogen in 521 patients with various diagnoses. The diagnosis of non-organic dyspepsia was established by radiographic exclusion of peptic ulcer, gastritis, and

Frequency Distribution of Grouped Random Single Plasma Pepsinogen Levels in 521 Patients with Various Diagnoses

		Plasma Pepsinogen (units/ml.)					Total
		0-96	104-194	200-296	304-398	400-500+	
Non-organic dyspepsia	Male	53	46	17	3	1	120
	Female	32	33	12	0	0	77
Duodenal ulcer	Male	25	58	52	23	3	161
	Female	18	35	7	4	2	66
Gastric ulcer: both sexes		19	25	8	1	0	53
Pernicious anaemia: both sexes		14	5	1	0	0	20
Gastritis: both sexes		4	2	8	5	5	24

The group or two groups which include two-thirds or more of the cases in that diagnosis have been boxed in.

carcinoma in the presence of a long history of dyspepsia; duodenal and gastric ulcer were established by radiographic demonstration, gastritis by the typical radiographic appearance in the absence of demonstrable ulcer, and pernicious anaemia by blood and sternal marrow films. High levels did not occur in female non-organic dyspepsia or in pernicious anaemia. Male duodenal ulcer alone was distinguished by a different frequency distribution and had significantly more cases in the range of 200 to 400 units. Female duodenal ulcer was not so distinguished.

Discussion

Our coefficient of variation for the method of 17.8%, and for the patients over one day of 31%, compared unfavourably with the 8% average (range 2 to 22%) which Edwards *et al.* quoted Mirsky *et al.* as finding from hour to hour on any day on their patients, and the 12-18% which they claimed for daily specimens spread over a month. Our results were obtained under representative general diagnostic hospital conditions

and showed the test to be unsuitable for use in these conditions. It is basically complicated and the results have not proved satisfactorily reproducible. Single estimations gave no reliable or decisive diagnostic information.

Summary

The Mirsky method of estimating plasma pepsinogen as proposed by Edwards *et al.* (1960) has not given satisfactory results when used under general diagnostic conditions. Single plasma pepsinogen levels did not give reliable or decisive diagnostic information.

We thank Dr. Robert Kemp for his interest and the use of his records.

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PENICILLAMINE AS LEAD-CHELATING SUBSTANCE IN MAN

BY

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Ever since dimercaprol (B.A.L.) came into use in 1945 much interest has been devoted to chelating agents, not least in connexion with lead poisoning. After only a few years, however, it became clear that dimercaprol was not particularly suitable as an antidote to plumbism. About the same time the first favourable reports of treatment with sodium calciumedetate (calcium disodium ethylenediaminetetra-acetic acid; $\text{CaNa}_2\text{E.D.T.A.}$) were published (Belknap, 1952; Bessman *et al.*, 1952; Karpinski *et al.*, 1953; Ohlsson, 1954; Rieders *et al.*, 1955; Sidbury, 1955; Glömme and Swensson, 1956). But this substance also gave rise to disappointments; for several cases of renal damage, some of them fatal, occurred after excessive dosage (Dudley *et al.*, 1955; Foreman *et al.*, 1956; Moeschlin, 1957).

Penicillamine (β - β -dimethylcysteine) was introduced by Walshe (1956) for the treatment of Wilson's disease. He reported good effects on the urinary excretion of copper when penicillamine was given intravenously or by mouth.

The formulae of these three chelating agents are as follows:

Since the beginning of 1957 penicillamine has been used at this hospital in the treatment of lead poisoning. At first administration was by intravenous drip—1 to 3 g. of penicillamine in 500 ml. of physiological NaCl over two to three hours. The effect on the urinary excretion of lead was compared with that of CaNa_2