

symptoms and signs of subacute combined degeneration of the cord. Haemoglobin, 9.47 g. per 100 ml.; red cells, 2,130,000; M.C.V., 128 c $\mu$ ; reticulocytes, 3%; white cells, 6,300 (neutrophil polymorphs, 2,331; eosinophil polymorphs, 378; basophil polymorphs, 63; lymphocytes, 3,402; monocytes, 126).

TABLE I.—Sternal Marrow Counts representing Percentage of 500 Nucleated Red Blood Cells in Each Film

	Type				Mitoses
	I	II	III	IV	
Before folic acid	46.0	22.8	12.4	17.0	1.8
6 hours after	22.8	27.2	33.2	14.6	2.2
12 " "	10.0	18.4	48.4	20.4	2.8
24 " "	7.0	17.4	56.6	16.8	2.2
58 " "	8.4	19.0	45.0	26.2	1.4
Davidson <i>et al.</i> :					
Case 1 { Before anaheim	42.0	28.3	24.0	5.7	9.0
6 hours after	25.7	38.5	25.5	10.3	12.4
Case 2 { Before anaheim	46.2	30.4	9.8	13.6	10.2
10 hours after	35.8	44.2	13.8	6.2	18.4
32 " "	8.4	53.6	30.8	7.2	14.3
Case 3 { Before anaheim	40.2	38.4	15.0	6.4	14.4
8 hours after	19.8	51.7	19.7	8.8	11.5

Type I: Cell of average 18  $\mu$  diameter; pale nucleus with fine lattice of chromatin, sometimes with nucleoli. Type II: Average 14.2  $\mu$  diameter; nucleus more deeply staining and coarser chromatin pattern. Type III: Average 11  $\mu$  diameter; cytoplasm basophilic, polychromatic, or orthochromatic; deeply staining nucleus with lumpy masses of chromatin. Type IV: Average 9  $\mu$  diameter; polychromatic or orthochromatic, with pyknotic nucleus. Mitotic erythroblasts: Characterized by deeply staining chromosomes (cf. LaCour, 1944). For the cases of Davidson *et al.* mitotic cells are listed separately, but are also included in the figures under Types I-IV.

It is thus seen that folic acid by mouth effected as rapid and extensive a decrease in Type I cells as did intramuscular refined liver extract. The increase in Type III erythroblasts following folic acid as compared with Type II in the series of Davidson *et al.* may be due to a difference in assessment rather than in quality of response.

The rapidity of the change in the bone marrow from a megaloblastic to a normoblastic picture was thought by Davidson *et al.* to support the view "that normoblasts can be derived directly from megaloblasts" and "that megaloblasts and normoblasts belong to one developmental series." Table II shows, however, that the proportion of nucleated red blood cells with deeply basophilic—that is, non-haemoglobinized—cytoplasm is considerably larger six hours after treatment than it was before treatment, the basophilic cells belonging to Types I to III. I have in the past observed the same phenomenon in all cases of pernicious anaemia in which I have examined sternal-marrow films before and shortly after liver treatment.

TABLE II

	Basophilic	Polychromatic	Orthochromatic
Before folic acid	24.8	59.4	15.8
6 hours after	57.6	32.2	10.2
12 " "	43.4	40.6	16.0
24 " "	57.4	34.0	8.6
48 " "	45.8	43.0	11.2

Percentages represent 500 nucleated red cells.

The objection that the figures in Table II do not necessarily indicate an absolute increase in the number of basophilic erythroblasts seems refuted by Table III, which shows a probably significant rise, and in any case not a fall, in the erythroblast population.

TABLE III.—Myelo-erythroblastic Ratio

	Cells of Myeloid and Lymphoid Series	Nucleated Red Blood Corpuscles
Before folic acid	363	137
6 hours after	340	160
12 " "	350	150
24 " "	337	163
48 " "	294	206

As it seems scarcely possible that a partly or fully haemoglobinized megaloblast should lose all its haemo-

globin during its further development, this finding shows that repair in pernicious anaemia is effected by newly produced cells of a non-megaloblastic series. Naegeli (1931) described as late megaloblasts fully or nearly fully haemoglobinized large oval-shaped rather than spherical cells, with an eccentric rather than central, deeply staining, more or less pyknotic nucleus; Israëls (1939) and Wilson (1942) reached the same conclusion. The number of these cells in the films after treatment is quite consistent with the view that they are the cells derived from the early, partly, or not yet haemoglobinized megaloblasts of the untreated marrow, and that they play quantitatively no material part in the repair of pernicious anaemia.

The disturbance of granulopoiesis characterized by the presence in large numbers of giant metamyelocytes and giant band-shaped granulocytes—due, according to LaCour (1944), to nucleic acid shortage of the promyelocytes producing incomplete spiralization of their chromosomes—showed no appreciable change in the four marrow films made after the administration of folic acid. This is in agreement with previous personal observations on marrow films examined one to two days after the beginning of liver treatment, and with the findings of Zuelzer and Ogden (1946) in cases of megaloblastic anaemia in infancy treated with folic acid in which they observed its disappearance only after two to four weeks, whereas in at least one of their cases the megaloblastic pattern had disappeared two days after parenteral folic acid treatment.

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## Medical Memoranda

### A Rare Form of Tuberculous Meningitis

Four cases of an unusual variety of tuberculous meningitis occurred in adults in Singapore during the period 1938-42. Each case presented the following features: a period of pyrexia, a period in which spinal symptoms predominated, and a period of meningism passing on to coma and death. Each period lasted about a week.

CLINICAL FEATURES

*Pyrexial Period.*—There were no pronounced distinguishing features during this time. Three cases were admitted for routine investigation for fever of unknown origin, and the fourth, Col. Rogan's case, for fever associated with diarrhoea. The pyrexia was of a regular remittent type, not rising much above 102° F. (38.9° C.). It was associated with a mild leucocytosis up to 12,000 (80% polymorphs).

*Spinal Symptoms.*—These were the first symptoms of major importance which distinguished the illness from the ruck of tropical fevers undergoing routine investigation. The first manifestation in all cases was difficulty in passing urine, leading to retention. This was followed within 24 hours by a paresis of the lower extremities which gradually deepened but never became complete. There was diminution of muscle tone, loss of superficial and deep reflexes, and an absent or equivocal Babinski sign. These findings were associated with a rising sensory level, which was peculiar in that it was patchy and extremely difficult to determine precisely. Sensory loss was most marked to pin-prick; hot and cold, postural sensibility, vibration sense.

and touch were little affected. The calves were not unduly tender. There were no root pains. From a consideration of the Chinese cases alone, this might have been beriberi occurring during the course of tuberculous meningitis, in which disease early bladder symptoms are common; particularly as pyramidal release was never demonstrated. The fact, however, that a case occurred in a Sikh and a British soldier practically rules out this possibility. Lumbar punctures performed at various periods during the second week showed: spinal block, a yellowish fluid more green than is usual in Froin's syndrome, and an excess of cells, mainly lymphocytes, up to 500. The protein rose as high at 900 mg. per 100 ml. The tubercle bacillus was never found. In three cases radiology of the spine revealed no pathological change.

*Period of Meningism.*—This period lasted up to 10 days. It was associated with headache, and as this disappeared the patient became confused. Brudzinski's neck sign was usually not markedly present until well on in the second week—that is, after the spinal symptoms had been in evidence for some days.

#### PATHOLOGY

A full necropsy was performed on two cases; in two the brain and spinal cord alone were available. Both cases in which necropsy was made revealed subclinical fibroid phthisis without cavitation. The appearance of the spinal cord was characteristic. It looked as if a yellow jelly had been poured into the subarachnoid space and had been allowed to set, but that this had been incomplete in the lower cervical areas. A few tubercles could be found in the meninges of the cord. The brain showed typical small tubercles in the arachnoid, in which acid-fast bacilli were demonstrated. The fluid in the basal cistern was relatively clear. It contained considerably less protein and fewer cells. Section of the cord showed very little save peripheral commencing degeneration of myelin round the full circumference of the cord (ösmic acid) to the depth of about 2 mm.

#### COMMENT

This syndrome is recorded mainly because, though known to occur, its features are not referred to in standard works. On this account the first case caused considerable difficulty; in fact it was not diagnosed correctly until the necropsy. Since that time we have not seen an exactly similar case, though Dr. Purdon Martin recently had one at Queen Square, in which the cerebrospinal fluid findings early on tallied with the above. Dr. Greenfield, in discussing this case, remarked that in his experience when the cerebrospinal fluid protein was very high he has been unable to demonstrate tubercle bacilli. In view of the necropsy findings cisternal fluid might be more productive. It is worthy of comment that Lieut.-Col. J. M. Rogan, to whom our thanks are due, correctly diagnosed the British case during the period of the spinal phase from his knowledge of the Asiatic cases.

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### Nicotinamide and Diabetes Mellitus

The water-soluble vitamins have been shown to play a part in enzyme systems involved in the oxidation and fermentation of glucose, and the beneficial action of yeast in the treatment of diabetes mellitus has been recognized for over 50 years. Dienst in 1939 reported the results of experiments on six human diabetics: his patients were given diets of known carbohydrate, protein, and fat content, and after stabilization and control over a period of several weeks the diets were supplemented with vitamin B (whole group) and ascorbic acid. He reported that the sugar tolerance in all cases was much improved thereby, and concluded that this was due to the action of thiamine and ascorbic acid. In 1937 Martin had shown that the existence of a multiple vitamin deficiency increased the insulin requirements of depancreatized dogs, but did not form any definite conclusion as to the precise role of the vitamins in treatment. Gaebler and Ciszewski (1945) fed three depancreatized dogs on a standard diet with added pancreatic enzymes and yeast. The minimal dose of insulin necessary to control glycosuria was inadequate when yeast was removed from the diet, and glycosuria was abolished after 12 days when the

ingestion of yeast was resumed. The effects of yeast could be produced with thiamine, riboflavine, nicotinic acid, inositol, pyridoxine, pantothenic acid, and para-aminobenzoic acid. In one animal no relation between the insulin requirements and the water-soluble vitamin intake could be demonstrated, and in the other two dogs thiamine, riboflavine, and nicotinic acid given together only delayed the onset of glycosuria. From this it may be concluded that although yeast prevents glycosuria in depancreatized dogs under the conditions of this experiment it is not possible to state which component of yeast is solely responsible. They were unable to confirm Dienst's view that an excess of ascorbic acid was beneficial in reducing the insulin requirements.

#### PRESENT INVESTIGATION

There is then some clinical and experimental evidence that yeast and the water-soluble vitamins can reduce the insulin requirements in human diabetics, but there still exists considerable doubt not only as to the active principle concerned but also as to its mode of action. The case described by Gordon in a recent letter of a male diabetic aged 40, not on insulin, who seemed to have his tolerance for sugar increased by large doses of nicotinamide (1,200 mg. daily for one month) is therefore of considerable interest in this connexion. We decided to investigate further the effect of nicotinamide on diabetics under control conditions in hospital. Accordingly six adult diabetics who were adequately stabilized without insulin on a fixed diet of 1,800 calories were chosen. They fell in the age group 40–65. Sugar tolerance estimation was performed after a few days' observation, and nicotinamide in a dose of 600 mg. t.i.d. was given by mouth for 14 days. Sugar tolerance estimation was repeated at the end of this period, and meanwhile daily blood sugar estimations had been performed. Surprisingly few side-reactions were observed from this large dose of nicotinamide, the most constant being a general feeling of warmth and occasional severe flushing and tingling of the skin, face, and extremities. In no case did the sugar tolerance curve improve on this therapy, and the daily blood sugar levels were consistently steady throughout. As an example, one case will be described in more detail.

#### CASE REPORT

This was a married woman aged 52, with no family history of diabetes, who had been a known diabetic for 12 months. She was admitted to the Manchester Royal Infirmary, under the care of Prof. T. H. Oliver, from the diabetic clinic. The sugar tolerance on July 4, 1946, was as follows:

Fasting blood sugar	.. .. .	216 mg. per 100 ml.
Blood sugar 1/2 hour after 50 g. glucose	.. .. .	310 " "
" 1 " "	" "	320 " "
" 1½ hours	" "	340 " "
" 2 " "	" "	310 " "
" 2½ " "	" "	255 " "

Sugar was present in the urine throughout. She received 1,800 mg. nicotinamide daily for 14 days with only slight flushing of the face and occasional tingling of the hands and feet. A sugar-tolerance test was repeated on July 18, with the following result:

Fasting blood sugar	.. .. .	226 mg. per 100 ml.
Blood sugar 1/2 hour after 50 g. glucose	.. .. .	300 " "
" 1 " "	" "	335 " "
" 1½ hours	" "	365 " "
" 2 " "	" "	350 " "
" 2½ " "	" "	315 " "

She has been seen on subsequent occasions in the out-patient clinic and there has been no change in her diabetic condition.

#### COMMENT

Although it is realized that the findings in six cases are inadequate for definite conclusions, there is no evidence that nicotinamide alone does influence the sugar tolerance or improve the diabetic condition.

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