Further research might follow two lines. First, an attempt might be made to identify in more detail the family and community factors which lead to a demand for hospital care, and to study preventive measures and alternative ways of meeting needs. Second, an investigation of the trends in birth and death rates of subnormal individuals would allow predictions to be made of the size of the future population from which hospital cases will arise.

Summary

In the Manchester Region the characteristics of the admissions and applications for admission of patients to mental deficiency hospitals for the period 1954–8 are described, together with those of a 20% sample of patients who left hospital during this period, and a 20% sample of hospital in-patients.

About one-third of the admissions were of high grade, and many of these were young people without families who were committed to hospital for social, not medical, reasons. It was suggested that community care, with hostel accommodation and psychiatric and social support, might be considered as an alternative to hospital care, or as aftercare for those discharged, and might reduce the number of high-grade patients who spend all their adult lives in institutions. At present about one-third of the in-patients are of high grade, and in the past such patients, who were in hospital when they were 45 years old, had little chance of being discharged.

Low-grade patients presented the most acute accommodation problem, and the waiting-list for places for them rose throughout the period studied. Many of these patients were helpless children who actually needed nursing care, but it was questioned whether the hospitals were in a position to provide it for all those in need.

The demand for hospital care for medium-grade patients, who made up nearly half of the hospital population, might be reduced by early community support for their families, and by training and the provision of suitable jobs and hostels for the patients. The investigation of these possibilities and the study of the present prevalence of mental subnormality would render it possible to make meaningful predictions of the future need for services.

My thanks are due to the Manchester Regional Hospital Board, and to Professor Fraser Brockington, of the Department of Social and Preventive Medicine, for enabling me to carry out this research, and to the Officers of the Board and the staffs of the mental deficiency hospitals for their assistance in its execution. I am also grateful to Dr. Mervyn Susser and other colleagues in the Department of Social and Preventive Medicine, Manchester University, for their help and criticism, and to Mrs. A. Pendred, Mrs. R. Platt, and Mrs. A. Fish for help in extracting and tabulating the data.

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CLINICAL USEFULNESS OF URINARY FIGLU TEST IN MEGALOBLASTIC ANAEMIAS*

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Bakerman *et al.* (1951) discovered a product in the urine of folic-acid-depleted rats which was later identified by Borek and Waelsch (1953) as formiminoglutamic acid (Figlu). Since that time much work has been done in this field. Excessive Figlu excretion after a load of histidine was found in patients who were folic-acid deficient (Luhby and Cooperman, 1961; Spray and Witts, 1959). Increased amounts of Figlu in the urine have also been found in other conditions, such as liver disease (Carter *et al.*, 1961), thalassaemia (Luhby and Cooperman, 1961), and pernicious anaemia (Herbert *et al.*, 1960).

The most sensitive and accurate method for the estimation of Figlu in the urine is an enzymatic one (Tabor and Wyngarden, 1958). A simpler method was developed by Knowles *et al.* (1960), and modifications of this (Kohn *et al.*, 1961; Husain and Ellis, 1961; Knowles, 1961) have been made in an attempt to establish the simplest and most practical technique. Modifications have also been introduced to make the test more quantitative (Zalusky and Herbert, 1962) or sensitive (Lewis and Moore, 1962), but these make the test less simple. We have used the simple electrophoresis of untreated urine to assess its usefulness as a clinical test.

We have studied the excretion of Figlu in the urine of patients with megaloblastic anaemia and related haematological conditions, in order to throw further light on the interrelationship of vitamin B_{12} and folic-acid deficiency in these conditions.

Materials and Methods

The 50 patients studied may be grouped as follows: group 1, 11 patients with pernicious anaemia in remission; group 2, 8 patients with pernicious anaemia in relapse; group 3, 8 patients with the malabsorption syndrome; group 4, 6 patients with hepatic cirrhosis; group 5, 5 patients with dietary insufficiency of folic acid; group 6, 12 patients with miscellaneous conditions.

The patients were selected almost entirely from those attending the clinics of Charity Hospital, New Orleans. The patients attending these clinics represent an

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economically poor section of the community, and the majority of them are coloured. Many of the patients subsist on diets which are poor in animal protein and dairy produce, but it was only in the group of patients labelled " dietary insufficiency " that the diet was thought to be frankly deficient.

All the patients with pernicious anaemia had the diagnosis established by finding a megaloblastic marrow, histamine-fast achlorhydria, and a typical Schilling test (delayed when necessary until after the folic-acid studies). The patients in remission were all being treated with 1–2 mg. of vitamin B_{12} by mouth weekly. The patients with the malabsorption syndrome were diagnosed by routine absorption tests, including the Schilling test, and all had a megaloblastic anaemia at the time of diagnosis. All but one of these patients had been treated before the test, four with folic acid and vitamin B_{12} and three with vitamin B_{12} alone. No folic acid, however, had been received for at least one month prior to their first Figlu test. Five of the six patients with cirrhosis were cases of heavy alcoholism. Five of the six had megaloblastic bone-marrow changes at the time of test, while the sixth patient had previously responded to folic-acid therapy. The patients with a dietary insufficiency of folic acid all gave a history of food intake inadequate in folic acid. All had normal absorption tests, and all had a megaloblastic anaemia which did not respond to vitamin B_{12} injection. One of these patients had a large oesophageal diverticulum.

The miscellaneous group included five patients with leukaemia and three patients with erythraemic myelosis, and all of them had megaloblastic changes in the bone-marrow at the time of the test. The remaining patients were a case of thalassaemia undergoing a mild crisis, with a megaloblastic marrow; a patient with lupus erythematosus and a malabsorption type of Schilling test, but who had no anaemia; a patient with post-operative regional ileitis who had no anaemia; and a woman with gout who developed a megaloblastic anaemia while on treatment with colchicine, " benemid " (probenecid), and " aralen " (chloroquine). Her bone-marrow failed to respond to vitamin B_{12} and folic acid, but six weeks after all drugs were stopped her bone-marrow had reverted to normal.

All the patients were given 15 g. of L-histidine monochloride in 200 ml. of orange juice early in the morning. A five-hour urine sample was collected, starting three hours after the histidine was given, and 2 ml. of 4 N hydrochloric acid and 1 ml. of toluene were added to the sample as preservatives. A horizontal type 1,000-volt electrophoresis instrument, provided with a cooling system, was used. 25 lambda of urine and 25 lambda of standard were run for two hours. A standard Figlu solution obtained from Dr. Luhby was used initially, but subsequently samples of previously tested positive urine were used instead. The technique employed was essentially the same as that described by Knowles *et al.* (1960), using a pyridine acetate buffer *p*H 5.4 and Whatman paper No. 3, staining with ninhydrin. Consistently negative results were obtained in normal people. Control urines tested in patients without the histidine load were also consistently negative.

Results

The numbers of patients in the different groups showing positive Figlu tests in the urine are given in the Table. Serial tests were performed in patients showing positive tests, to study the conditions under which the tests reverted to normal.

Incidence of Positive Urinary Figlu Tests

Group	Diagnosis	No. of Cases Tested	No. with Positive Tests
1	Pernicious anaemia in remission	11	0
2	" " " relapse	8	5
3	Malabsorption syndrome ..	8	3
4	Cirrhosis	6	4
5	Dietary deficiency	5	5
6	Miscellaneous	12	4

Group 1.—No patient with pernicious anaemia in remission showed a positive test.

Group 2.—Five patients out of the eight with pernicious anaemia in relapse showed a positive test. All five, four women and one man, were coloured.

Case 12 had no change in her positive test 11 days after receiving 1,000 μg. of vitamin B_{12} intramuscularly as part of the Schilling test. She was then placed on folic acid, 15 mg. daily by mouth, and four days later still had a strongly positive Figlu test. She was then given 15 mg. of folic acid by intramuscular injection, and within 48 hours the Figlu test was negative. This patient has subsequently been maintained on injections of vitamin B_{12} without further folic-acid therapy, and her tests have remained consistently negative over a six-months period.

Case 13 received 1,000 μg. of vitamin B_{12} as part of a Schilling test, and one week later her Figlu test had become negative. She did not receive any folic-acid therapy.

Case 14 was treated with folic acid 0.4 mg. daily by intramuscular injection without any vitamin B_{12}. Ten days later his urine was still Figlu-positive, and his bone-marrow had shown some change towards normal. After 20 days' therapy with 0.4 mg. of folic acid intramuscularly his bone-marrow was normal and his urinary Figlu test negative. He did not receive any vitamin B_{12} during this time, but subsequently his Schilling test showed a typical pernicious-anaemia pattern. This patient has been maintained on vitamin B_{12} without further folic-acid therapy, and his tests have remained consistently negative.

Case 15 received 0.4 mg. of folic acid daily by intramuscular injection, and 10 days later her bone-marrow was still megaloblastic and her urine still Figlu-positive. She then received a Schilling test, and one week later the urine was Figlu-negative.

Case 16 received 100μg. of hydroxocobalamin injection, with a good haematological response, and 12 days later her urine still showed a weak positive. The next test was negative. She received no folic acid.

Three of these patients with pernicious anaemia in relapse therefore showed some resistance to folic-acid therapy in reversing the Figlu test to normal. Vitamin B_{12} alone reverted two of the patients to normal, but in another patient it failed to do this and she required intramuscular injections of folic acid.

Group 3.—Three out of eight patients with the malabsorption syndrome had positive tests.

Case 20 developed a positive test when folic acid had been stopped for one month, and subsequently the test became negative without further folic-acid therapy.

Case 21 developed a positive test after folic acid had been stopped for one month. It became negative when folic acid was restarted, and became positive again when folic acid was stopped again.

Case 23, with a negative test, who originally had presented with a megaloblastic anaemia some years earlier, was placed in the metabolic ward on a diet calculated to be deficient in folic acid. The intake from standard food tables was 60 μg. of folic acid daily. Despite continuing evidence of severe malabsorption of fat (for instance, he excreted 43%

of a labelled triolein sample in the stool) the Figlu test remained consistently negative, and for a period of six months' observation in the metabolic ward he did not have a single positive urine test for Figlu. At the end of the six-months period his bone-marrow was normal.

Group 4.—Four of the six patients with cirrhosis had positive tests. Two of those with positive Figlu tests received 0.4 mg. folic acid by intramuscular injection daily for 10 days, and their tests became negative and the bone-marrow reverted to normal. One patient was placed on gradually increasing doses of folic acid by injection, starting with 0.05 mg. daily for 10 days, then 0.1 mg. for 10 days, then 0.2 mg. for 10 days. After this his bone-marrow had reverted to normal, but the urinary Figlu test was still positive. He then received 0.4 mg. daily for 10 days and the Figlu test became negative.

Group 5.—All five patients with megaloblastic anaemia due to dietary insufficiency had positive Figlu tests. Two of these received intramuscular injections of 0.4 mg. daily of folic acid for 10 days, and this reverted the Figlu test to negative. Another patient received larger doses, with a similar response.

Group 6.—The patient with thalassaemia had a megaloblastic marrow on admission. He was treated with bed rest and a normal hospital diet, and one week later his bone-marrow had reverted to a normoblastic one. The Figlu test, however, remained positive. It was still positive six weeks later, when the patient had had a good haematological response, with a haemoglobin rise from 4 to 10 g./100 ml. He was then given 5 mg. of folic acid daily by mouth, and subsequently all urine tests have been negative for Figlu. He has been maintained since this time with supplementary folic acid, and his haemoglobin has remained about 10 g./100 ml. He has required no further transfusions, although prior to this admission he had required intermittent transfusions and consistently had a haemoglobin lower than 8 g./100 ml. One of the leukaemia patients with a positive Figlu test was treated with 0.4 mg. of folic acid by intramuscular injection daily for 10 days, and his Figlu test became negative. The other one did not respond. A patient with gout, whose megaloblastic marrow was attributed to a drug reaction, had a negative test at the time of her anaemia. Six weeks later, however, after the drugs had been discontinued and her bone-marrow had reverted to normal, with a good rise in haemoglobin, the urinary Figlu test had become positive, presumably owing to rapid folic-acid utilization.

Discussion

In discussing the significance of these tests we should like to emphasize that the test as we have used it is a qualitative and not a quantitative one. Even so, it seems an adequate and useful test for detecting cases of clear-cut deficiency of folic-acid metabolism. It is interesting that several patients with pernicious anaemia give a positive test, although they are suffering primarily from failure to absorb vitamin B_{12}. This has, of course, been found by others (Herbert *et al.*, 1960). It is clear that the test cannot be used as a means of distinguishing pernicious anaemia from a folic-acid deficiency type of megaloblastic anaemia.

The fact that in some of our pernicious anaemia patients the Figlu test reverted to normal with vitamin B_{12} therapy alone and normal hospital diet is in keeping with the fact that it is a deficiency of vitamin B_{12} that interferes with folic-acid metabolism. The fact that in some patients the test reverted to normal with folic-acid therapy without any vitamin B_{12} therapy is in keeping with the fact that the interference with folic-acid metabolism takes the form of an increased requirement rather than an absolute block. It is not clear whether this increased requirement is just a partial metabolic block that occurs after absorption or whether it is partly due to impaired absorption as well, but the lack of response of one patient to 15 mg. of folic acid by mouth for three days suggests that, in this patient at least, there was impaired absorption. It may be relevant that in our pernicious-anaemia patients the positive tests were all found in coloured patients with a relatively poor dietary intake. There may be a parallel here with the megaloblastic anaemia of pregnancy and with that of anticonvulsant drugs, where an increased requirement for folic acid becomes evident in patients on a low folic-acid intake.

The fact that patients with cirrhosis of the liver and anaemia may have a positive Figlu test in the urine raises the question of whether this is just a dietary deficiency or whether there is a lack of liver storage for folic acid. Little is known about the storage of folic acid in the body, and it is interesting that one patient with known malabsorption who had previously developed a megaloblastic anaemia responding to folic acid remained free of bone-marrow deficiency or a positive Figlu test in the urine after six months on a diet calculated to be deficient in folic acid. One wonders whether he had stored in his body enough folic acid from previous folic-acid therapy to last this length of time.

The traditional view that folic acid is absorbed mainly in the jejunum, rather than the lower ileum, in which vitamin B_{12} is absorbed, is in keeping with the fact that the Figlu test was negative in a patient who had a megaloblastic anaemia secondary to resection of the lower ileum. The persistently positive Figlu in the patient with thalassaemia suggests an increased requirement for folic acid in this condition. It has been suggested (Luhby and Cooperman, 1961) that folic-acid therapy may help patients with haemolytic anaemia, such as thalassaemia, to maintain higher haemoglobin levels than they can otherwise do, and this patients' course would certainly suggest this. The urinary Figlu test might, in these conditions, well be helpful in showing a latent folic-acid deficiency. Megaloblastic bone-marrow changes do not necessarily mean vitamin-B_{12} or folic-acid deficiency. Cases of erythraemic myelosis, some cases of leukaemia, and perhaps other cases such as our gout patient with drug reaction, may have megaloblastic marrows but do not respond to either vitamin B_{12} or folic acid. These cases apparently have negative tests for Figlu in their urine.

Studies to determine the usefulness of the urinary Figlu test are as yet at an early stage, but it seems likely that it will prove useful in the elucidation of some cases of megaloblastic anaemia. It may help to uncover other states of relative folic-acid deficiency, and it is simple enough for routine clinical use.

Summary

Simple electrophoresis of untreated urine in patients receiving a histidine load (15 g. of L-histidine monochloride) has been used to detect the excretion of

abnormal amounts of formiminoglutamic acid (Figlu). A horizontal type, 1,000-volt electrophoresis instrument was used and a clearly recognizable spot of Figlu on the paper strip (a positive test) has been considered indicative of a deficiency in folic-acid metabolism.

The patients studied were 50 cases of megaloblastic anaemia or related conditions. It was found that all of five patients with dietary deficiency of folic acid, four of six patients with cirrhosis, and three of eight patients with a malabsorption syndrome had positive tests, which were easily reverted by the administration of folic acid.

Eleven patients with pernicious anaemia in remission had negative tests, but five out of eight patients with pernicious anaemia in relapse had positive tests. Three of these five patients showed some resistance to folic-acid therapy in reversing the Figlu test to normal. Vitamin B_{12} alone reverted two of the patients to normal, but in another patient vitamin B_{12} failed to do this and she required injections of folic acid to achieve it. Other patients tested included cases of erythraemic myelosis and leukaemia with megaloblastic bone-marrow.

It is considered that a positive Figlu test may result from dietary insufficiency of folic acid, malabsorption of folic acid, or from metabolic disturbances in the action of folic acid in the body, one important factor in this regard being vitamin B_{12} metabolism.

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"' Psychosis arctica ' has been described in the Lapps, and ' kaamos,' or depressions, are said to be common in the dark season. It isn't clear that these are true depressive states, for other observers report that the winter months may be a period of relaxation and enjoyment for northern peoples. The mental problems that result from cultural change are much better known and they are encountered in indigenes and immigrants. The sudden change from modern city life to an apparently unchanging world, devoid of stimuli, can be disturbing for civil servants, settlers, seasonal workers and the personnel of scientific expeditions. They may become desolate and despondent, full of resentment towards families, friends and colleagues whom they believe to be leading an easier life in a more friendly climate and atmosphere. That they volunteered for the work makes no difference. They experience ' Arctic imprisonment ' which sometimes ends in suicide. Personnel, especially for small expeditions, must be carefully selected, with no history of mental disease, drug addiction, alcoholism or homosexuality. A conference on medicine and public health in the Arctic and Antarctic, which was sponsored recently in Geneva by the World Health Organization, expressed the opinion that especial attention should be given to the study of mental health problems in the high latitudes, particularly of transients and station personnel." (*World Health*, January 1963.)

A SECOND AND A THIRD ABNORMAL HAEMOGLOBIN IN NORFOLK

HAEMOGLOBIN $G_{Norfolk}$ and HAEMOGLOBIN $D_{Norfolk}$

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In 1958 Ager, Lehmann, and Vella reported that they had discovered a family in Norfolk possessing a new abnormal haemoglobin — haemoglobin Norfolk. To determine the incidence of this haemoglobin in the County of Norfolk 1,000 unrelated inhabitants were examined for the presence of abnormal haemoglobins (Huntsman, 1963). Though no further examples of haemoglobin Norfolk could be traced two Norfolk families with other abnormal haemoglobins were found.

HAEMOGLOBIN $G_{Norfolk}$

Propositus.—The propositus (W. A.), a young married man with two children, was at the time attending the Norfolk and Norwich Hospital for a routine follow-up of tuberculosis of the spine. He was fit and all physical and laboratory examinations yielded normal results. In particular there was no anaemia and all haematological examinations were within normal limits.

Examination of Haemoglobin

No haemoglobin F was found, but on paper electrophoresis at *p*H 8.6 and 8.9 a slow-moving fraction was seen to separate from haemoglobin A; it amounted to about 20% of the total pigment (Fig. 1). The exact position was at all times between haemoglobin A and

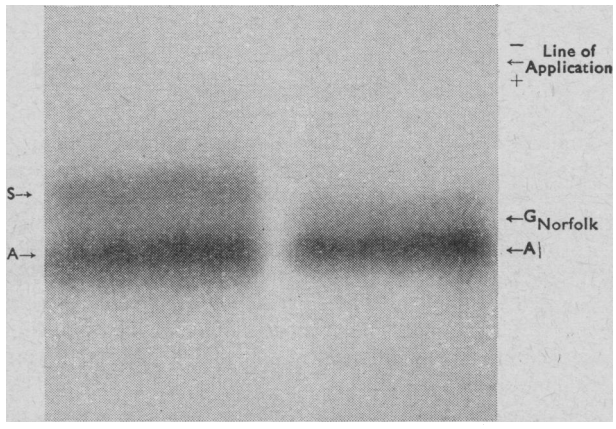

FIG. 1.—Filter-paper electrophoresis, *p*H 8.9, TRIS buffer (Cradock-Watson, Fenton, and Lehmann, 1959). Haemoglobin $G_{Norfolk}$ moves behind haemoglobin A but faster than haemoglobin S.