period of six months before and after treatment, the number of attendances at the surgery for the treatment of sore and bleeding finger-tips fell from 192 to 21. The result of this small series would appear to make further trials on a larger scale worth while.

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A THERAPEUTIC TRIAL OF CHOLINE CHLORIDE IN INFECTIVE HEPATITIS

BY

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Choline is a powerful lipotropic agent (Best and Huntsman, 1932), and in experimental animals has been shown to have the effect of reducing the cirrhosis which follows the infiltration of the liver with fat after taking a high-fat diet (Daft, Sebrell, and Lillie, 1942; György and Goldblatt, 1942). It is considered to exert its lipotropic effect by promotion of lecithin (phospholipid) synthesis in the liver, as phospholipids are actively concerned with the transport of fat and cell structure.

The action of choline in preventing cirrhosis is different when methods other than dietetic are used for the production of fatty livers (McHenry and Patterson, 1944). It has no effect in preventing the accumulation of cholesterol esters in "cholesterol" fatty livers, and while in curative experiments it causes a rapid decrease in glycerides, the reduction of cholesterol esters is slow. The fatty liver produced by the ketogenic fraction of the anterior pituitary is not prevented by choline, and large doses are required to prevent damage in carbon tetrachloride poisoning or to increase the disappearance of fat from the liver in the recovery period of phosphorus poisoning.

Himsworth and Glynn (1944) have distinguished two distinct types of liver injury due to diet. One follows long-continued fatty infiltration of the liver due either to excessive intake of fat or to deficiency of lipotropic factors such as choline, and the second results from lack of amino-acids in sufficient amounts in the diet. The injury resulting from the amino-acid deficiency is characterized by necrosis, and against this choline has no beneficial effect—in fact, Himsworth and Glynn suggest that it tends to aggravate the hepatic necrosis by reducing the high fat content of the liver. It will be seen, therefore, that though choline prevents fatty infiltration and the consequent cirrhosis that results from the intake of an excessive amount of fat, there are various experimental conditions in which it is unlikely to have a beneficial effect on the liver.

The work that is recorded here was started at about the same time as Higgins and his associates began their investigations into the therapeutic effect of methionine in infective hepatitis at Oxford (Higgins *et al.*, 1945). There was, however, a distinct difference in the circumstances under which the trials were undertaken, as 21 of our cases were patients in a general hospital over-seas, and thus it was not possible to carry out the detailed biochemical study to which reference is made in their paper.

The Trial

No attempt was made to select cases so as to get those of comparable severity, but alternate patients were given choline chloride 1.5 g. a day for the first eight days following admission. All the patients were serving soldiers between 20 and 50 years of age, and their diets were similar except for the plentiful supply of fresh fruit for drinks that was available for those treated in Algeria. Both the treated and the control series received vitamins A and D (and K in 21 cases) as an addition to a low-fat high-carbohydrate diet. The amount of protein in the diet was left largely to the patient's preference, and under the conditions of the experiment it was not possible to determine the quantities each patient consumed.

Considerable care was taken to exclude liver disease from other cause and the presence of any intercurrent infection—a very important precaution in a hot climate. Special attention was paid to the possibility of men having received an organic arsenical for any reason, and no case in which there was any doubt was included. The patients were treated in bed. The decision as to when they should get up was recorded, as well as the length of stay in hospital, as a substantial reduction in either would be a very practical way of demonstrating therapeutic efficiency. The day on which their appetite returned was noted for a similar reason, but the date of disappearance of jaundice was not, as discoloration of the conjunctivae persisted in several cases after the patient was considered fit to leave hospital. The only biochemical investigations that were undertaken were repeated estimations of the serum bilirubin and examination of the urine for the presence of bile pigments.

Results

The level of the serum bilirubin was estimated on admission. This, coupled with the number of cases that had a rising serum bilirubin while under observation, was used as a means of assessing the comparability of the treated and control series. The number of days of malaise and the length of icteric period before admission are shown for a similar reason in Table I.

TABLE I

	Subjects	
	Treated 16	Control 16
Duration of illness before admission, in days ..	8.3 (3–29)	8.1 (2–21)
Icteric period before admission, in days ..	1.4 (1–5)	1.7 (1–7)
Serum bilirubin on admission (mg./100 c.cm.) ..	4.7 (1.0–12.2)	6.1 (1.25–14)
Number of cases with rising serum bilirubin ..	5	6

The average number of days and the levels of serum bilirubin in milligrammes re shown—the variations are in brackets.

In such a small series, when much larger numbers would be required to be statistically significant, the importance of finding means of showing that the cases were of comparable severity is obvious. It is thought that Table I shows this to be so, although it will be noted that the level of the serum bilirubin on admission was lower in the treated than in the control cases.

The results of giving choline chloride can be seen in Table II, and it may be mentioned here that they were closely similar in cases treated at home and those treated over-seas.

TABLE II

	Subjects	
	Treated 16	Control 16
Maximum serum bilirubin (mg./100 c.cm.) ..	6.0 (1.5–15)	7.9 (2.0–14.0)
First day of fall of bilirubin to 0.6 mg./100 c.cm. ..	25.1 (11–50)	30.1 (10–55)
First day urine bile-free ..	20 (10–29)	22.2 (10–42)
First day of return of appetite ..	15 (2–33)	14.4 (4–33)
First day allowed up ..	30 (13–54)	28.8 (13–46)
Duration of stay in hospital ..	35 (13–79)	40.7 (27–56)
Number of relapses known ..	4	5

Discussion

We were fortunate in getting our cases early on, in the period of the disease that was accompanied by jaundice. The average number of days that the urine was dark before admission to hospital was 1.4 in our cases, compared with 4.4 in the methionine-treated cases reported by Wilson, Pollock, and Harris (1945). The dose of choline chloride that we gave—1.5 g. daily—is approximately one-third of that of methionine used by the Oxford and Cambridge workers. This gives comparable dosage as regards methyl equivalents, and is probably adequate.

The figures shown in Table II for the first day on which the serum bilirubin fell to 0.6 mg. per 100 c.cm. and for the duration of stay in hospital are a little lower for the treated than for the untreated cases. It is thought, however, that these results, as a whole, must be taken to show that choline chloride, under the conditions of the experiment, had no therapeutic value.

Summary

Alternate cases of infective hepatitis were given 1.5 g. of choline chloride as a supplement to a low-fat high-carbohydrate diet with the addition of vitamins. Sixteen cases were so treated, and no significant benefit over 16 control cases was noted.

Our thanks are due to Prof. L. J. Wits for suggesting the work and sending us the choline chloride, and for his generous advice and help. We also wish to thank Col. W. H. O'Riordan, M.C., for permission to forward this paper for publication.

REFERENCES

- Best, C. H., and Huntsman, M. E. (1932). *J. Physiol.*, **75**, 405.
 Daft, F. S., Sebell, W. H., jun., and Lillie, R. D. (1942). *Proc. Soc. exp. Biol.*, N.Y., **50**, 1.
 György, P., and Goldblatt, H. (1942). *J. exp. Med.*, **75**, 355.
 Higgins, G., O'Brien, J. R. P., Peters, R. A., Stewart, A., and Wits, L. J. (1945). *British Medical Journal*, **1**, 401.
 Himsworth, H. P., and Glynn, L. E. (1944). *Clin. Sci.*, **5**, 93, 133.
 McHenry, E. W., and Patterson, J. M. (1944). *Physiol. Rev.*, **24**, 128.
 Wilson, C., Pollock, M. R., and Harris, A. D. (1945). *British Medical Journal*, **1**, 399.

Medical Memoranda

Palindromic Rheumatism

This syndrome was described by Hench and Rosenberg (1941) on the basis of their findings in 34 cases; of these 19 were males and 15 females. They recorded multiple afebrile attacks of acute arthritis, peri-arthritis, and sometimes also para-arthritis with pain, swelling, redness, and disability. The attacks appeared suddenly, developed rapidly, and lasted for a few hours up to about 24, and recurred at short or long irregularly spaced intervals. The blood sedimentation rate was normal between attacks, but rose to an average of 24 on the uncorrected Westergren scale. The history in these patients extended over periods varying from 1 to 25 years, with from 2 up to 250 attacks a year. The attacks lasted from 3 hours to 6 days, and successive attacks affected different joints. The authors recognized the similarity to the angio-neural arthrosis described by Solis-Cohen (1911, 1913, 1914) and to the allergic arthritis described by Kahlmeter (1939), but the syndromes reported by the latter authors show certain fundamental differences from that of Hench and Rosenberg. Intermittent hydrarthrosis, excellently described by Garrod (1907), also differs from palindromic rheumatism in that the attacks generally recur in the same joint and at mathematically regular intervals. Cain (1944) recorded a single case apparently conforming exactly to the picture of palindromic rheumatism. No other case reports appear to have been published.

The following case seems to conform to the typical description:

A Port official was admitted to the Seamen's Hospital on Sept. 1, 1943. He gave a history of flitting pains in the joints, first noticed in 1930 after he had fallen into the river. The joints became painful and repeatedly swollen, and the disability lasted from 1 to 2 days at the most. There was great variability in both the type and the situation of the pain and also in its duration, but almost every joint in the body had at one time or another been affected. He had no constant symptoms except excessive perspiration. On examination tachycardia was present, but there was no other evidence of systemic disease. Temperature was normal throughout his stay in hospital. On the second day after admission he had swelling of the right knee-joint with erythema and tenderness. On the following day the left ankle-joint was affected. At subsequent periods during a six-weeks stay in hospital almost every joint in the body was involved. Blood sedimentation tests gave the following readings at approximately weekly intervals: 75/200, 43/200, 47/200, 51/200, 82/200, 30/200, and 23/200. A careful search revealed no focal sepsis. Radiographs of the chest were within normal limits. Electrocardiograms and the urine were normal. The Wassermann reaction, Kahn test, and gonococcal C.F.T. were negative. The white blood count was 9,000 per c.mm. (polymorphs 52%, eosinophils 1%, large mononuclears 3%, large lymphocytes 2%, small lymphocytes 42%). The blood serum did not agglutinate *Brucella abortus*. X-ray examination of bones and joints showed no pathological changes.

Various lines of treatment were tried, including a prolonged course of sulphathiazole, intramuscular injections of contramine, and the salicylates. The condition showed no improvement, and during the months which succeeded his stay in hospital the attacks continued almost exactly as before.

This complete therapeutic failure conforms to the experience of the authors quoted, and when the patient was last seen in Jan., 1945, his condition was virtually unchanged.

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REFERENCES

- Cain, J. C. (1944). *J. Amer. med. Ass.*, **125**, 1037.
 Garrod, A. E. (1907). In Allbutt and Rolleston's *System of Medicine*, **3**, 60, London.
 Hench, P. S., and Rosenberg, E. F. (1941). *Proc. Mayo Clin.*, **16**, 808.
 Kahlmeter, G. (1939). *Acta med. scand.*, **102**, 432.
 Solis-Cohen, S. (1911). *Trans. Coll. Phys. Philad.*, **3** s., **33**, 309.
 — (1913). *Trans. Ass. Amer. Phys.*, **28**, 739.
 — (1914). *Amer. J. med. Sci.*, **147**, 228.

Reviews

NEUROLOGY, PSYCHIATRY, ENDOCRINOLOGY

The 1944 Year Book of Neurology, Psychiatry and Endocrinology. Neurology, edited by Hans H. Reese, M.D. Psychiatry, edited by Nolan D. C. Lewis, M.D. Endocrinology, edited by Elmer L. Sevringhaus, M.D. (Pp. 712; illustrated. 18s. 6d.) Chicago: The Year Book Publishers; London: H. K. Lewis and Co. 1945.

The mass of medical literature continually poured out makes the busy practitioner more and more dependent on critical summaries and reviews such as are provided by the *Year Book of Neurology, Psychiatry and Endocrinology*. The current volume maintains the standard of its predecessors. Choosing articles almost at random, we note that Dr. Denny-Brown has concluded that epilepsy is an infrequent complication of injury to the head in general, and that laceration of the brain is an essential factor, particularly if resulting in a cerebro-dural scar. Early convulsions within the first eight weeks must be distinguished from true epilepsy, which is of later onset. The electro-encephalogram naturally receives attention from various writers. Now that so much interest is taken in the scientific study of delinquency it is important to observe that the E.E.G. has not proved of value in diagnosing the criminal mentality. It is of course abnormal when the criminal has an organic disease of the brain, but the psychopath shows the same departure from normal, whether a criminal or not, while the non-psychopathic offender shows a normal rhythm. Post-mortem records bring to light a much larger number of abnormalities of endocrine glands and of new growths in paranoid than in non-paranoid psychotics. Dr. Nolan Lewis is very cautious in his assessment of the value of shock therapy. He agrees with the general experience that insulin is preferable for schizophrenics and electric shock for the manic-depressives. Psychoneurotics show questionable benefit. There is no good evidence that damage is done to the brain, and fractures and dislocations are not frequent enough to interdict the treatment in carefully selected cases. It now seems to be established that the muscular weakness of myasthenia gravis is due to a failure in the synthesis of acetylcholine. The serum of a myasthenic patient can inhibit this synthesis *in vitro* and can produce the curage phenomenon in the isolated muscle-nerve preparation from a frog. The action of thiouracil is the subject of several papers. If rats are injected with radio-active iodine the drug can be traced to the gland and the consequent inhibition by thiouracil of its synthesis into di-iodotyrosine and thyroxine observed. The production of thyroid hormone stops promptly and almost completely when thiouracil is given. Clinically it brings down the basal metabolic rate, though this response is delayed when iodine has been previously administered. These few examples will give some idea of the varied interest of the *Year Book* for 1944.

AMERICAN MEDICAL PRACTICE

American Medical Practice in the Perspectives of a Century. By Bernhard J. Stern, Ph.D. (Pp. 156. 8s. 6d.) New York: The Commonwealth Fund; London: Oxford Medical Press.

This is a preliminary statement made by a committee of the Council of the New York Academy of Medicine, instructed to review the nature, quality, and direction of the economic and social changes taking place and to be anticipated in the U.S.A., and to report what the medical profession can do about it. It included doctors, dentists, nurses, and laymen. The book is well documented and contains a valuable series of monographs designed, presumably, to serve as a basis for a later report and recommendations. The problems dealt with have a strong resemblance to those which face the medical profession everywhere. The development of medical practice in the U.S.A. and the gradual rise of the doctor in the public estimation are well told. The question of "specialism" receives much attention because it is largely responsible for the rise in the cost of medical care, and has influenced the distribution of the profession. Its growth is traced largely to the introduction of expensive diagnostic instruments needing special competence to handle. There are no fewer than 14 certifying boards for "specialism" in the United States, and in 1942 there were 49 "specialists" to every 51 general practitioners. As they require elaborate hospital facilities they are found mainly in the large and more wealthy centres of population. "Specialism