equal, the superficial reflexes were normal save for the plantar responses, which were extensor in type on both sides.

The cardiovascular system showed little abnormality for a man of his years; there was no evidence of congestive failure, the pulse was regular except for an occasional extrasystole, and the blood pressure was 190/110 mm. Hg. Radiography confirmed the clinical findings concerning the size of the heart, and revealed it to be of a shape usually associated with hypertension. The basal blood pressure at this time was 128/84 mm. Kidney-function tests were normal, and examination of the other systems showed no evidence of gross pathological change. Improvement was complete in the course of four weeks, and a diagnosis of essential hypertension of a labile variety with encephalopathy was made.

In January, 1947, when the symptoms and clinical manifestations had completely disappeared, it was decided to treat him with potassium thiocyanate in an attempt to reduce his blood pressure so as to minimize a recurrence of the complication: the accompanying chart shows the course of the treatment. He maintained high concentrations of the drug with great improvement in his general well-being, but later developed mild diarrhoea as a toxic manifestation and continued on treatment for 10 days without indicating this. The drug was stopped temporarily.

Comment

Attention was drawn to the following: (a) The casual systolic and diastolic pressures began to fall soon after treatment was instituted. (b) At the end of 17 weeks the casual blood pressure had fallen from 190/110 to 125/84, and the basal from 128/84 to the low figure of 88/52. These reductions represent a response to treatment to the extent of 65 mm. systolic and 26 mm. diastolic in the casual blood pressure, and in the basal of 40 mm. systolic and 32 mm. diastolic. (c) The withdrawal of the drug was followed by a rise of both casual and basal pressures, which two weeks afterwards had returned to the levels found before treatment was begun. (d) On treatment being restarted the casual and basal pressures showed the same tendency to fall again.

Conclusions

In some patients with essential hypertension treatment with thiocyanate causes a well-marked fall in blood pressure.

The reductions in pressure are due partly to decreases in the basal and partly to decreases in the supplemental pressures.

The falls in basal pressure are good evidence that the effect of adequate thiocyanate therapy is pharmacological and not psychological.

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TREATMENT OF ANGINA PECTORIS BY REDUCTION OF BASAL METABOLISM

BY

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From the therapeutic point of view sufferers from angina can be divided into three types: obese, anaemic, and slim. The first two groups are amenable to treatment by reduction of weight and correction of anaemia respectively. The others can only be given nitroglycerin either to shorten attacks or occasionally to prevent them. These comprise, in my experience, more than half the victims of the disease.

Some fifteen years ago American workers first conceived the idea of reducing the demand upon the failing heart by reducing the oxygen demand of the organism. This was achieved by total surgical removal of the thyroid gland, followed by medication with thyroid extract sufficient to prevent myxoedema but not enough to restore the basal metabolism to normal. A new principle was thereby introduced into cardiological treatment: instead of trying to boost the output of the failing heart, the principle of "load shedding" was substituted. In many cases the results of total thyroidectomy were good, but there are objections to radical surgery in a cardiac invalid, and these, together with the inherent technical difficulties, prevented the method from attaining any great popularity.

Thiouracil and its derivatives have now given the physician the means of suppressing thyroid activity, but rather surprisingly these means have not yet been widely exploited in cardiology. In America, W. Raab (1945) treated a small group of cases of angina, with promising results, and in this country a number of cases of heart failure have been given methylthiouracil (Sharpey-Schafer, 1946).

Three cases of angina treated ambulant with methylthiouracil are here described. All had typical angina of effort, exhibited electrocardiographic abnormalities corroborating the diagnosis, and suffered from three to six attacks daily in the course of their routine activities. Two had previously had a coronary thrombosis—one four years and one nine months before the start of treatment. Their daily routine was not altered in any way during the treatment. Since it is well known that the effect of methylthiouracil is to reduce basal metabolism and eventually produce myxoedema, no attempt was made to follow up changes in basal metabolism. It was felt that this treatment had two possible end-points: the cessation of angina before the onset of myxoedema, and the onset of myxoedema without amelioration of the angina. Each of these two end-points could be determined by clinical observation and by regular control of weight, without estimations of the basal metabolism.

Case 1

R. D., a male clerk aged 64, had no history of previous illness. In March, 1946, he suffered an attack of severe substernal pain lasting for 36 hours. Heart sounds were normal, blood pressure was normal and remained so, and ectopic beats appeared during the first two days. An electrocardiogram taken on the fourth day showed the typical changes of a recent coronary thrombosis. After six weeks' rest in bed he was allowed up, but he did not resume work because of two or three attacks of anginal pain daily on minimal physical effort. A chest film showed considerable enlargement of the heart to the left, with elongated and uncoiled aorta. Methylthiouracil, 0.6 g. daily, was started on Dec. 10, 1946. It was reduced to 0.4 g. daily four weeks later. After ten weeks' medication the patient reported complete cessation of angina, and methylthiouracil was thereupon reduced to 0.1 g. a day. His weight had remained constant throughout this period.

The Hon. Secretary of the West Derbyshire Medical Society, Dr. H. Rhys Davies, reports that at a meeting held at Matlock on Jan. 25 the following resolution was passed *nem. com.*: "That this meeting is of the opinion that the omnipotence of the Minister under the Act in general, and in particular in regard to the power of dismissal without appeal to the courts, is contrary to the interest of the community and justifies the profession in abstaining from the Service."

Twelve weeks after the start of treatment he gained 6 lb. (2.72 kg.) in one week and developed typical myxoedematous facies. Treatment was then stopped completely for a week, during which time the gain in weight was lost and the facial expression returned to normal.

Throughout this episode the patient was not aware of anything unusual happening. Treatment was then restarted with 0.05 g. daily, and has continued up to the time of writing (June, 1947). He has remained free from angina, and maintains that he feels generally better than before the treatment (presumably because of the absence of attacks). He had retired from work, but now contemplates looking for a light job. The heart has not changed in size or shape. The electrocardiogram was still grossly abnormal at the start of the treatment and remained virtually unchanged (Fig. 1).

FIG. 1.—Electrocardiogram of Case 1, leads I and III.

Case 2

R. J. H., a male clerk aged 55, had coronary thrombosis four years previously. Since then regular attacks of angina, relieved by nitroglycerin, occurred approximately six times a day during mild weather and considerably more often during cold and windy spells. Two years later he had a gastric ulcer, which healed after six weeks' treatment, including rest in bed, and has since caused no trouble. Attacks of angina occurred on walking more than a quarter of a mile (400 metres), on walking up three flights of stairs (which he had to do three to four times a day in the course of his work), and on leaving the office for shopping after lunch.

FIG. 2.—Electrocardiogram of Case 2, leads I and III.

The electrocardiogram was characteristic of long-standing myocardial damage, and has remained unaltered since 1944 (Fig. 2). His heart was radiologically normal. Treatment with methylthiouracil was started on Dec. 10, 1946, with 0.6 g. daily for 5½ weeks; it was then reduced to 0.2 g. a day until March 29, 1947, when it was increased again to 0.6 g. a day.

The patient reported no change in his condition for the first 10 weeks, but improved to a certain extent thereafter. He was then able to negotiate the three flights of stairs at his office without any discomfort, but still had angina on walking to or from the station and on shopping after lunch. A week after reintroducing the larger dose of 0.6 g. of methylthiouracil daily he lost the attacks that had occurred regularly when he went out shopping after lunch, and the attacks on going to and from the station diminished considerably in intensity and no

longer occurred regularly. He now has only one slight attack each day, which is rapidly relieved by nitroglycerin, whereas before treatment he had at least six severe attacks a day. At the time of writing he had not reached the stage of myxoedema; his weight has in fact dropped by 4 lb. (1.81 kg.) during the treatment.

He says that he is at least as active at his work as before, and that his general condition has been much improved. Neither his chest film nor his electrocardiogram has shown any changes since the start of the treatment.

Case 3

F. W. B., a road surveyor aged 55, has had typical angina of effort for ten years, and latterly it had been getting worse. Because he could not walk to the station in the morning or walk any distance during the day, he reluctantly contemplated retirement. The number of attacks varied, but there was hardly ever a day without at least one, and usually there were several.

On examination the heart sounds were muffled, and the blood pressure was 190/110. Screening revealed a moderate enlargement of the heart to the left and an elongated aorta. The electrocardiogram showed evidence of myocardial damage (Fig. 3). Treatment with methylthiouracil, 0.6 g. daily, was started on Feb. 22, 1947, and 2½ weeks later the patient noted that for the past few days he had been able to walk to the station in the mornings without stopping. On April 1 and 10 he reported that he had had one very mild attack of angina during each of the previous weeks. He had walked to and from the station at a normal pace without difficulty, had walked

FIG. 3.—Electrocardiogram of Case 3, leads I and III.

for 15 to 20 minutes in the course of his work without having to stop and without pain, and on several occasions had done a test walk after tea over a course that previously he had never been able to traverse at this time of day without at least one attack.

His weight remains steady, his electrocardiogram and blood pressure are unchanged, and he has given up thoughts of retirement.

Discussion

No dogmatic conclusion can be reached from a study of only three cases, but angina is a condition not prone to spontaneous fluctuations in severity; thereafter daily observations on a small number of cases may have more value in this complaint than in many other pathological conditions.

In the above investigation it was a salient point that the patient should not change his daily routine. It was therefore essential to select patients who could be treated in private practice. White cell counts were checked at 48-hour intervals. In each case one or more occasions arose when the drug was discontinued for 24 hours because of a fall in the white cell count. Clearly, the number of cases treated had to be limited, but in view of the promising results obtained it might be considered worth while to treat similar cases in hospital until the onset of myxoedema and then discharge them on a maintenance dose in order to observe the results after their return to full activity.

It would seem that in order to reduce thyroid activity to any appreciable extent it is often necessary to give much

larger doses for a comparatively longer period to those with normal thyroid activity than to those with hyperthyroid activity. Since this paper was written Cases 2 and 3 have developed myxoedema and have recovered as rapidly as Case 1 did.

Summary

Three cases of angina of effort are reported. Treatment with methylthiouracil was successful in either abolishing or markedly reducing the frequency of attacks. On the whole, comparatively large doses were required. This treatment has possibilities in that patients may be restored to their former earning capacity.

I wish to thank Dr. A. Morton Gill for his advice and help in the preparation of this paper.

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CHRONIC HEPATITIS TREATED WITH METHIONINE AND CHOLINE

BY

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Experimental studies and clinical observations in recent years have focused attention on the importance of dietetic factors in liver disease. Witts (1947) gives a valuable list of references. Neither the exact effects of these factors nor their value as therapeutic agents have as yet become clearly defined. It seemed interesting, therefore, to study the effects of large doses of methionine and choline as an adjunct to the treatment of a group of patients suffering from chronic hepatitis.

Clinical Material.—Six cases of chronic hepatitis were selected for this study. The salient clinical features of each are presented in Table I. Biochemical tests showed impairment of liver function in each case, and a feature common to all was a low level of the plasma albumin with inversion of the albumin-globulin ratio (Table II).

Method.—The patients were placed on a high-protein diet, which consisted of the national ration supplemented by the extra meat and milk which are authorized for this condition. It is estimated that each patient received a daily intake of 120–150 g. of protein throughout the period under review. Case 6 had been on the diet for the previous

eighteen months, and the other five for only two to four weeks before the course of methionine was started. The dose given was 1 g. five times daily by mouth, increasing on the third day to 3 g. five times daily for six weeks. The methionine was then discontinued and choline chloride in similar doses was prescribed for a further period of three months.

A careful clinical assessment of each case was made immediately before the beginning of treatment and at the end of the courses of methionine and choline. It seemed probable that any real clinical progress would be reflected in an improvement of the plasma albumin level, with a return towards normal of the albumin-globulin ratio (Higgins *et al.*, 1944). Levels of total plasma proteins, plasma albumin, and plasma globulin were consequently estimated at the times of the clinical examinations (Table II).

Results.—No reactions to either of the drugs were observed, but the patients stated that the tastes were extremely unpleasant. In Case 5 the course of choline was abandoned for this reason. No striking clinical changes were observed in any of the patients during the period of treatment. One (Case 5) has since died in cholaemia, one (Case 3) is deteriorating rapidly, and the condition of the other four remains unchanged. There was a small rise in plasma albumin in Cases 3, 4, and 6, a small drop in plasma albumin in Cases 2 and 5, and no appreciable alteration in the plasma albumin of Case 1. It is apparent that there has been no consistent alteration of the biochemical findings attributable to the treatment. These results confirm the view that supplementation of diets already containing adequate amounts of choline and methionine is not likely to be effective (Miller *et al.*, 1947).

Summary

Six patients suffering from chronic hepatitis were treated on a high-protein diet with a supplement of 15 g. of methionine daily for six weeks and choline chloride in the same dose for a further period of three months.

There was no change in the clinical condition of the patients during this time, and the variations in the plasma proteins did not seem to be due to the treatment.

It is a pleasure to acknowledge the help of the Department of Biochemistry and to thank Mr. George Higgins for the plasma protein estimations. We also wish to thank the Medical Research Council for *DL*-methionine.

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TABLE I.—Clinical Features

Case No.	Age	Sex	Duration (Years)	Aetiology	Jaundice	Haemorrhage	Ascites Oedema	Palpable Liver	Palpable Spleen
1	67	F	5	Insidious onset	Intermittent attacks	Epistaxis	Oedema of ankles	4 cm.	2 cm.
2	34	M	10	Infectious hepatitis	" "	"	Nil	2 cm.	Nil
3	54	M	4	Alcoholic history	" "	"	Oedema and ascites	12 cm.	Nil
4	61	M	10	" "	Nil	Nil, but oesophageal varices present	" "	8 cm.	4 cm.
5	60	F	4	Insidious onset	Intermittent attacks	Haematemeses	" "	2 cm.	4 cm.
6	26	F	7	Splenic anaemia	" "	"	Oedema ascites and pleural effusion	Nil	Splenectomy 2 years ago

TABLE II.—Plasma Proteins in Grammes per 100 ml.

Case No.	Before Treatment			After Methionine			After Choline		
	Albumin	Globulin	Total	Albumin	Globulin	Total	Albumin	Globulin	Total
1	3.10	4.17	8.10	3.15	4.10	7.80	3.05	4.00	7.10
2	3.50	3.85	8.00	—	—	—	2.90	4.20	7.70
3	2.40	5.40	8.10	3.20	4.60	8.40	2.80	4.80	8.35
4	2.50	2.90	5.75	3.00	3.70	7.00	3.45	3.07	6.60
5*	2.51	4.79	7.63	2.40	4.40	7.10	1.90	3.69	6.15
6	2.00	4.00	6.35	2.30	4.00	6.50	2.45	3.75	6.25

* Course of choline not completed.