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RAPIDLY ACTING THYROID HORMONES AND THEIR CARDIAC ACTION

BY

K. IBBERTSON, M.B., M.R.C.P., M.R.A.C.P.

RUSSELL FRASER, M.D., F.R.C.P., D.P.M.

AND

D. ALLDIS, M.B., D.C.P.

*Departments of Medicine and Biochemistry, Postgraduate
Medical School of London*

Those two synthesized thyroid hormones triiodothyronine and triac (Pitt-Rivers, 1953) not only can provide full thyroid replacement therapy for myxoedema, but will do this more rapidly than the main thyroid hormone L-thyroxine (Asper *et al.*, 1953; Trotter, 1955). The discovery of the rapid action of triiodothyronine initially led to the suggestion that it may be the form in which the thyroid hormone acts in the tissues (Gross and Pitt-Rivers, 1952) but this hypothesis was abandoned when triiodothyronine was found to have no action on tissue slices *in vitro* (Thibault and Pitt-Rivers, 1955). The second analogue, triac, which is the acetic acid derivative of triiodothyronine, was found in its first clinical and biological trials to have at least as rapid an action (Trotter, 1955, 1957; Frazer *et al.*, 1956; Zondek *et al.*, 1956; Macgregor, 1957; Goolden, 1957) and to have also an immediate action on tissue slices *in vitro* (Thibault and Pitt-Rivers, 1955; Thibault, 1957), although this latter finding has not been confirmed (Barker and Lewis, 1956; Wiswell and Asper, 1958).

Other clinical studies have also claimed that small doses of triac can lower blood cholesterol without other equivalent thyroid effects (Lerman and Pitt-Rivers, 1955; Trotter, 1956, 1957). Thus triac might have special clinical uses, both when the rapid restoration of thyroid function is desired, as in cases of myxoedema coma, and also possibly for lowering blood cholesterol in, for example, patients with coronary atheroma. The following studies were therefore undertaken to assess how soon triac acted and whether it did specifically lower plasma cholesterol; the studies were made on myxoedematous subjects, and its action was contrasted with that of triiodothyronine, the more familiar rapidly acting thyroid hormone. In the first studies the metabolic effects of a single large oral dose of triac or triiodothyronine, given to myxoedematous subjects, were observed closely for the first 24 hours, and thereafter for several days. Where possible, the effects of both drugs were observed on each patient, the second dose being given after an adequate interval of 7 to 28 days. In the later studies the pattern of the restoration of thyroid function was observed after administration of various graded daily dosages of triac, noting also its cardiac effects and contrasting it with triiodothyronine.

Material and Methods

The large single dose of triac or triiodothyronine was given only to myxoedematous subjects who were judged unlikely to have coronary artery disease. These patients were therefore without any clinical or E.C.G. evidence of this disease, and were also under 40 years or had only had a short period of myxoedema, or had previously had full thyroid replacement therapy without disability. Of the six patients, all showed the signs of complete thyroid failure, and two had an associated hypopituitarism (Ibbertson and Fraser, 1956). The six patients observed for longer periods on various daily dosages of triac included two of the above patients and also four others with complete thyroid failure. Some incidental observations made on other patients given triac are also noted.

Dosage of Triac and Triiodothyronine

For the single-dose experiments, triac was given in oral doses of 18 and 12 mg., which is about three times the full daily replacement dose (occasional doses of 6 and 10 mg. being also used). Triiodothyronine was given in a single oral dose of 0.5 mg., which is about seven times the daily replacement dose. These doses were chosen to obtain a readily measurable effect, with the balance set in favour of triiodothyronine, since it was planned to ascertain whether there was any earlier action of triac not attributable merely to the size of the physiological dose of hormone given. For human myxoedematous subjects the daily full replacement dosage has been estimated as about 4-6 mg. of triac (Lerman and Pitt-Rivers, 1955; Trotter, 1956, 1957) and 0.07-0.1 mg. a day of triiodothyronine (Selenkow and Asper, 1955a). Doniach *et al.* (1958) found some metabolic effects from 0.08 mg. of triiodothyronine a day given to normals but little if any from 4 mg. of triac, suggesting that this is slightly more than the replacement dosage for triiodothyronine, but about that for triac.

Procedure for Studies after a Single Dose

With the scheme of sedation described below, comparable observations of six patients were made under basal conditions during 18 test days. With four patients three test days were observed—that of the placebo, of the triac, and of the triiodothyronine dose, usually in that order; with one patient (J. W.) the triiodothyronine day preceded the triac day. A further two patients received one or other of these drugs on a single test day. During each test day serial measurements of the B.M.R., E.C.G., plasma cholesterol, and urine volume, creatine, and creatinines were made on all patients; and also of urine phosphate on one patient. To permit comparison of the effect observed in the different patients, the metabolic effects measured are presented as a percentage of each patient's initial value for that test day.

Maintenance of Basal State During Test Days.—The study of the changes in the B.M.R. within a 24-hour period was made possible by an extended use of the sedated B.M.R. procedure. Thus on a "test day" the

patient was first sedated with sodium amylobarbitone 200 mg., given at 7 a.m. and 9 a.m. The test dose of the drug to be studied was given at 9 a.m. The patients were allowed to sleep throughout the day, being wakened to pass urine only after the two-hourly B.M.R. and E.C.G. estimations. A further dose of sodium amylobarbitone was given if signs of rousing were observed during the day. Sips of water were allowed throughout the day if desired. On the morning following each trial day the patients were similarly sedated, and after a B.M.R. recording were wakened for breakfast with oral doses of bemegride (Ibbertson *et al.*, 1957). By these means, reliable serial B.M.R. readings were obtained without inconvenience to the patient. The adequacy of the attainment of basal conditions was confirmed by the observations on four of the patients made throughout a control day under exactly the same conditions after giving placebo tablets instead of triac or triiodothyronine (see Fig. 1).

FIG. 1.—Early effect of 10 single doses of triac on the B.M.R. compared with the range observed on four control days (on myxoedematous subjects)

Measurements

Sleeping B.M.R. determinations were performed by the method described by Fraser and Nordin (1955), using Benedict-Roth apparatus and the standards of Robertson and Reid (1952). The results were first calculated as a percentage of the mean expected normal for age and sex.

E.C.G. recordings were made after each B.M.R. determination on both test days and control days. Although changes were observed in the potentials of both T and R waves, the latter were more easily measured and proved the more sensitive index of the minimal thyroid hormone effect. Standard lead 1 was usually measured, although lead 2 occasionally showed a more obvious change.

Serum cholesterol determinations were performed in duplicate by the method of Zlatkis *et al.* (1953), and urine phosphate and creatinine by the method of King and Wootton (1956).

Effects Within 24 Hours of a Single Dose

(a) B.M.R.

Serial measurements of the B.M.R. throughout a day are feasible only if the patient can be maintained in a basal state, which is not possible under normal resting

conditions (Lerman and Pitt-Rivers, 1955). In these studies, as described under "Methods," heavy sedation throughout the test day ensured a basal state, and incidentally minimized the boredom of the procedure of a test day for the patient. The adequacy of the procedure in maintaining a basal state is shown in the results obtained with four patients on the control days when they were given placebo tablets (Fig. 1). Initial B.M.R. values ranged from -6 to -39%, and each patient's subsequent measurements were within a range of 71-108% of these initial B.M.R. values. Thus on control days there was some tendency for the B.M.R. to fall even lower as the day wore on; clearly, therefore, any rise observed during the test days after triac or triiodothyronine was likely to be due to the drug.

After the single large oral dose of triac (6-18 mg.) there was within the 24 hours a definite rise in the B.M.R. in all 10 test days on the six patients (Fig. 1). This rise was evident at least by the fourth hour, when the values were over 120% of the initial reading. The peak effect was achieved between the 6th and 24th hours, usually with a rise of at least 50% above the morning's initial value.

Since other workers have not observed so early a rise with triiodothyronine, it seemed important to determine whether a similar early effect could be achieved with rather more than the physiologically equivalent dose of triiodothyronine. Fig. 2 contrasts the results obtained

FIG. 2.—Early effects of a single dose of triac or triiodothyronine on the B.M.R. of the same four myxoedematous subjects. after single oral doses of 0.5 mg. of triiodothyronine with those observed after doses of 10-18 mg. of triac in the same four persons. A very comparable rise in the B.M.R. is seen; the mean B.M.R. values during the first 24 hours after either drug are practically identical, though there is a hint that the peak may be achieved later at a slightly lower level after triiodothyronine.

(b) E.C.G.

During the first 24 hours after triac the E.C.G. voltage also rose in all patients. There was a rise by the fourth hour in four out of seven, and by the ninth hour in six out of seven patients. Full restoration of the E.C.G. to normal was not achieved with the single dose, but the R wave usually rose by 60-100%; the extent of this

response was not related to the size of the dose or to the initial R-wave voltage. Fig. 3 compares these E.C.G. changes after triac with those observed in the same patients on another day following use of triiodothyronine.

FIG. 3.—Early effect of a single dose of triac or triiodothyronine on late E.C.G. of the same four myxoedematous subjects.

After triiodothyronine the rises in R-wave voltage were later and less marked than after triac; only two E.C.G.s showed a change at four hours, and only three at nine hours.

(c) Cholesterol (Fig. 4)

One patient (N. C.) is exceptional in showing a poorly sustained fall after either drug, possibly because previous thyroid hormone administration had been stopped only

FIG. 4.—Early effect of a single dose of triac or triiodothyronine on the plasma cholesterol of four myxoedematous subjects.

45 days previously. Otherwise, after both triac and triiodothyronine a fall is discernible within the first 24 hours. After triac it is discernible at 6–18 hours, and at 24 hours it was approximately maximal at about 15% below the initial level. On the other hand, the fall after triiodothyronine was not clearly discernible before 24 hours, though it fell about as far as after triac.

(d) Urinary Creatine (Fig. 5)

After triac an increased creatine excretion was observed in six out of eight tests on three of four patients, beginning at the 8th to 12th hour and with a

FIG. 5.—Early effect of a single dose of triac on the urinary creatine of four myxoedematous subjects.

peak at the 9th to 17th hour. No change was observed in urinary creatine after triiodothyronine with two of these patients, nor with three of them on control or placebo days.

(e) Urinary Phosphate

In one patient a rise in urinary but not plasma phosphate was observed after both triac and triiodothyronine, with maximal levels between the 6th and 24th hours, and an earlier and greater effect was seen after triac, as also seen by Rall *et al.* (1956) on 24-hour samples.

(f) Varying Responsiveness Among the Patients

While both hormones produced responses in all the patients tested, the main variations seen in the speed and extent of action seemed to be a feature of the patient, more than of the dose or type of hormone. The patients whose E.C.G. or B.M.R. responded slowly to triac also responded slowly to triiodothyronine. Thus, patients A. W. and F. B., the two patients showing the slowest and weakest B.M.R. responses to triac, were similarly slow and weak in their E.C.G. response to it and also in both these responses to triiodothyronine. When one of these patients was given a smaller dose of triac (1 mg.), the responses were still slight. Both patients were previously untreated, one having primary myxoedema and the other hypopituitarism with complete thyroid failure. Slowness in response might have depended in part on the duration of previous hypothyroidism (Thibault, 1957), for the "early responders" were all patients who had previously been maintained on thyroid hormone, and in one instance it had been withdrawn only 45 days before the tests. As already noted, after either drug responses were seen in all the parameters observed; excepting only the creatine response, which failed in one of four patients after triac and in both patients tested after triiodothyronine. A larger dose would probably be needed for the regular production of this effect.

Persistence of Effects of a Single Oral Dose of 12–18 mg. of Triac (Fig. 6)

As noted above, the peak effect was achieved within 24 hours; after which the effects on the B.M.R., E.C.G., and cholesterol slowly subsided, reaching the basal level within 6 to 10 days, at approximately equivalent speeds. The rise in urinary creatine, however, lasted only until the third day. One patient's cholesterol level seemed exceptional in remaining low for longer. It is of interest to contrast this declining effect from 24 hours after the single dose with the steadily rising effect over the first week, seen when the maintenance dose is given daily (Fig. 7).

% Deviation
from
resting levels

FIG. 6.—Duration of effects of a single dose of triac in four myxoedematous subjects. (Dose range, 12–18 mg.)

FIG. 7.—Effect on a myxoedematous subject of daily triac administration begun at maintenance dosage.

Effects of Daily Administration of Triac

Five patients with myxoedema were treated with triac for periods of 3 to 10 months before transferring them to thyroxine maintenance. Dosages ranged from 0.5 to 6 mg. a day. In two patients full maintenance dosage (4–6 mg. a day) was used from the start, and in three patients the treatment was begun with small doses and gradually increased to full maintenance dosage.

(1) When 5 mg. of triac a day was given from the start, a gradual restoration to normal was attained over 7 to 10 days (Fig. 7). The plasma cholesterol, E.C.G., and B.M.R. all showed the same rate of change.

(2) During the phase of lower initial triac dosage (0.5–1 mg. a day) all three patients showed a fall of plasma cholesterol, and in two this occurred without change in the B.M.R. or E.C.G. (Fig. 8). This pattern of change

FIG. 8.—Effect on a myxoedematous subject of daily triac administration begun at small dosage.

corresponds to the apparently predominant cholesterol effect observed with triac by other workers. The third patient showed responses by all criteria even at the 1–2 mg. dose level, suggesting a heightened sensitivity to the drug. In all three patients the B.M.R. rose rapidly to normal levels after the increase of the dose to 4 mg. a day.

(3) For comparison, triiodothyronine was given similarly to two other myxoedematous subjects. During the early period of low dosage a similar phase of lowered cholesterol without discernible B.M.R. or E.C.G. change was also seen (Fig. 9).

FIG. 9.—As in Fig. 8, but using triiodothyronine.

(4) *Frequency of dosage* (Fig. 10). The B.M.R. was twice studied throughout the day, on each of three patients, while they were being maintained on a constant total daily dose of triac (4, 4, and 2 mg. respectively). Throughout each day the patient was kept sedated and so basal, but the day's triac dose was subdivided on one day into 12-hourly and on the other into three-hourly doses. On both of the study days the patients were awakened to pass urine and drink water with each B.M.R. estimation, so that the regimes were comparably basal. On the 12-hourly triac regime (6 a.m. and 6 p.m.) the B.M.R.s were lowest in the morning, and all tended to be lower than those of the three-hourly regime. Thus each triac dose still shows some acute B.M.R. effect like that observed after the single large

FIG. 10.—B.M.R. under the same daily dose of triac given three-hourly or 12-hourly (mean and ranges of the same three patients).

doses—that is, one beginning at about four hours and maximal at about eight hours. Consequently, a slight B.M.R. response from doses given only in the morning might not be discerned by the usual morning B.M.R. procedure.

Cardiac Effects of Small Doses of Triac

Myxoedematous subjects with known or suspected coronary ischaemia were given triac in small doses. Since triac has been suggested for patients with coronary disease (*Lancet*, 1956), thyroid function was cautiously restored with it in a series of 14 myxoedematous patients—in three a previous history of angina was elicited, in four there was no such history but an E.C.G. suggestive of coronary ischaemia, and in seven there were no such suggestions.

With the last group, satisfactory restoration of normal thyroid function was obtained without ischaemic episodes, using doses initially ranging from 0.25 to 0.5 mg., which were gradually increased to a maintenance dose of 4–6 mg. a day. The E.C.G. and plasma cholesterol were restored to normal within an average period of 10 days, though early changes were observed within 48 hours in all patients. The four patients with merely suggestions of coronary ischaemia on the E.C.G. were rendered euthyroid similarly—that is, by triac in commencing doses of 0.25 mg., increasing to a maximum of 4 mg. a day. No ischaemic symptoms were observed. In one patient the E.C.G. showed the normal evolutionary changes described without increase in ischaemia. In the other three, although the cholesterol fall followed the usual pattern, the E.C.G. showed little change in voltage and certainly no increase of ischaemia. It appears that ischaemic myocardial damage may in some way impair the ability of the E.C.G. to reflect changes in myocardial metabolism.

However, all three patients with a previous history of angina suffered ischaemic symptoms when triac therapy was begun (details are given in the Appendix)—in one previously untreated patient within 1½ hours after the first dose. The rapidity with which angina may be precipitated by even a small dose offers further evidence that these doses are not merely cholesterol-lowering in their action, as has previously been suggested from crude B.M.R. measurements. Barker (1955, 1957) has observed a similarly early cardiac effect from triac in thyroidectomized animals.

Clinical Uses of Triac

Diagnostic.—The rapid acute effects of triac on the E.C.G. may be of value in confirming the diagnosis of hypothyroidism in young subjects. For example, in a

5-months-old cretin, at eight hours after 0.5 mg. of triac by mouth, there was an obvious increase in the R and T waves of the E.C.G. The diagnosis of hypothyroidism was not obvious on clinical examination, but was later confirmed by radioiodine.

Therapeutic.—Where, as in this child, there is no reason to suspect coronary ischaemia, our studies have indicated that considerable restoration of thyroid function may be safely achieved within 24 hours by using triac or triiodothyronine. Optimal dosage should probably be a loading dose of 12–18 mg. of triac followed by 4–6 mg. a day in three divided doses. But where there is any history suggesting angina these rapidly acting thyroid hormones should be avoided. Where the subjects are over 40 years of age or there are E.C.G. or other suggestions of cardiac abnormality, the commencing dosage of triac should not exceed 0.25 mg a day, which may be cautiously increased towards a full maintenance dosage over 10 or more days.

Discussion

It is clear from these studies that single doses of either triac or triiodothyronine produce discernible effects beginning at about four hours and maximal at about 8 to 12 hours, which involve evidently all parameters of thyroid function. Other workers in the clinical field have also testified to the rapid effect of these hormones. After each of these, Rall *et al.* (1956) and Wiswell and Asper (1958) have observed within 24 hours, and maximally within at least 48 hours, increased urinary volume, Na, Cl, N, P, creatine, and perhaps also calcium, and usually a rise in B.M.R. Occasionally effects have been observed before 24 hours: warming of the skin at four hours by Wiswell and Asper (1958) and a possible rise in B.M.R. at eight hours by Rawson *et al.* (1953). The sedation procedure which we have used has permitted the detection of these early B.M.R. changes well before 24 hours, which has not hitherto been practicable. The E.C.G. has also proved a convenient method of demonstrating these early thyroid effects.

These early B.M.R. and other changes contrasted with those observed after single doses of thyroxine, when they have not been discerned for several days or been maximal till about the tenth day (Asper *et al.*, 1953; Rawson *et al.*, 1953; Lerman and Pitt-Rivers, 1955; Fraser, 1958). Kyle *et al.* (1958) claim to have observed similarly rapid effects after 2 or 3 mg. of thyroxine, but their two patients had previously received a dose of triiodothyronine within 14 days, which would have altered their responsiveness. They also report observing an effect within two days after single 1,500-mg. doses of thyroid extract, but this rapidity may have been due to its content of triiodothyronine.

In speed of action there is little difference between triac and triiodothyronine, though our results suggest a slightly more rapid action from triac. While this observed difference might have depended merely on the dose of triac being physiologically greater, this is unlikely since this dose was about three to four times the daily maintenance dose while the triiodothyronine dose was about seven times. However, it is difficult to assess the physiologically equivalent single doses from the daily maintenance doses, as the persistence of their effects is different. We have observed the effects of triac persisting for only 7 to 10 days after the single dose, while Blackburn *et al.* (1954) have observed that the decline

of the effects from triiodothyronine has a half-life of 7.4 days and from thyroxine one of 11.9 days. The less persistent action of triac does suggest that its action may also be more rapid in onset.

It is of some theoretical interest that after a single dose of triac there is a maximal effect within 24 hours which gradually declines over the subsequent week, while the daily administration of a maintenance dosage of triac causes a steadily rising effect throughout the first week. This suggests that the full effects of the chronic administration of thyroid hormones are achieved in part by some responsive increase in tissue enzymes, such as that demonstrated by Smith and Williams-Ashman (1951). Our observations that the level of the B.M.R. throughout the day depends on the frequency of administration of the maintenance dosage of triac suggest that each dose still has an acute metabolic effect, while also maintaining some such increased enzyme responsiveness.

Our results do not reveal any qualitative difference between the effects of triac and those of triiodothyronine, the other thyroid hormone tested, contrary to certain previous claims (Lerman and Pitt-Rivers, 1955; Trotter, 1955, 1957; *Lancet*, 1956; Oliver and Boyd, 1957). While we have confirmed that small doses of triac may lower the cholesterol without any apparent effects on the morning B.M.R. or E.C.G., this has also been seen with small doses of triiodothyronine, and might possibly also be seen with equivalent doses of thyroxine (Strisower *et al.*, 1957). Further, small metabolic effects are difficult to measure, and frequent sedated B.M.R. estimations taken throughout the day have indicated that the usual morning B.M.R. may not reveal the maximal afternoon response which follows triac given only in the morning. In any case, cardiac stimulation has been observed within 1½ hours of giving these same small doses of triac to certain myxoedematous subjects.

Our observations have confirmed those of others (Mackay *et al.*, 1957; Oliver and Boyd, 1957) that even small doses (1/16 of the daily maintenance dose) of triac may precipitate angina in myxoedematous subjects with a history of angina. Hence any cautious restoration of thyroid function in such subjects should be done instead with the slower-acting thyroid hormones such as thyroxine (Wolff and Goldberg, 1957).

There are, however, two indications for the clinical use of these rapidly acting thyroid hormones: either for the cautious restoration of thyroid function over several days with E.C.G. control in cases of myxoedema coma, or for the recognition of suspected hypothyroidism in young subjects. In young subjects without any suspicion of cardiac disease, triac can correct the familiar hypothyroid abnormalities on the E.C.G. within eight hours, and so offers a useful quick therapeutic test. In older subjects such a test may be neither safe nor valid, for in myxoedematous subjects with coronary disease triac may not correct the E.C.G. abnormalities, and may precipitate angina.

APPENDIX

Acute Precipitation of Coronary Ischaemia by Triac

The three patients with a previous history of angina all suffered ischaemic symptoms when triac therapy was begun.

Case 1.—A 53-year-old woman, with myxoedema and hypoparathyroidism complicating thyroidectomy five years previously, suffered from angina on moderate effort.

Examination revealed the presence of rheumatic heart disease with aortic stenosis and incompetence, and the E.C.G. showed a left bundle-branch block pattern. As she also suffered severe intractable (post-operative) tetany resistant to normal therapy, the restoration of thyroid function was thought desirable. Triac was begun in a dose of 0.25 mg. and gradually increased to 2 mg. a day. At this level she suffered a paroxysmal attack of precordial pain with collapse. Despite the L.B.B.B. pattern, the E.C.G. showed changes suggesting myocardial infarction. When the triac was stopped and anticoagulants were given, she recovered from this episode. This patient died five months later while on thyroid, siccum, ¼ gr. (16 mg.) daily, and the post-mortem examination showed severe aortic stenosis, but no evidence of myocardial infarction.

Case 2.—A woman of 75 had been admitted to the surgical wards with large-bowel obstruction due to faecal impaction. She gave a history of sudden precordial pain some two to three months previously. Her myxoedema was obvious and the E.C.G. showed evidence of old posterior myocardial infarction. Treatment was begun with 0.5 mg. of triac daily. At 1½ hours after the first dose, she collapsed with palpitations and Cheyne-Stokes respiration. The E.C.G. showed sinus tachycardia with numerous extrasystoles, but no evidence of recent infarction. The patient was subsequently maintained on L-thyroxine, but died three weeks after the initiation of treatment. Post-mortem examination revealed extensive old and recent myocardial infarction.

Case 3.—A housewife already under treatment was first given triac at the age of 61. She had then suffered from angina on easy effort for five years, and had been diagnosed and treated as having myxoedema, after obtaining radio-iodine, cholesterol, and clinical evidence. Thus before giving triac, it had been ascertained that more than 0.05 to 0.1 mg. of L-thyroxine per day increased her liability to angina on effort, and so she was maintained on 0.05 mg. L-thyroxine per day. Then the thyroxine was stopped, and on three different days she was given single doses of triac of 1 mg., 0.75 mg., and 0.75 mg. On the first occasion, 2½ hours later she was giddy for one hour, on the second occasion, two hours later she had an angina attack for one hour; and on the third, three hours later she had an angina attack for five minutes. Subsequently she was stabilized on 0.25 mg. triac q.i.d., on which her clinical state was similar to that while receiving 0.05 to 0.01 mg. of thyroxine per day—that is, partial relief of her myxoedema, and probably less angina than without the thyroid hormone.

Summary

After single oral doses of 12–18 mg. of triac and of 0.5 mg. of triiodothyronine, effects were observed in myxoedematous subjects at as early as four hours and were maximal within 24 hours. These doses caused rises in sedated B.M.R., in the R wave of the E.C.G., in urinary creatine and phosphate, and a fall in plasma cholesterol.

Triac acted slightly more rapidly than triiodothyronine, and its effects lasted 7 to 10 days.

The daily administration of triac in maintenance doses to myxoedematous subjects, however, only gradually achieved a full effect within seven days. In smaller doses triac or triiodothyronine could induce a fall in plasma cholesterol without apparent B.M.R. or E.C.G. effect.

However, on constant daily dosage, triac given 12-hourly showed a lower B.M.R. in the morning than in the evening, or when given in three-hourly doses.

Even small doses of triac could rapidly induce angina in myxoedematous subjects who had given a history of

angina; but triac may be the best thyroid hormone for treating subjects with myxoedema coma who do not give a history of angina

An E.C.G. may be taken eight hours after a dose of triac to confirm the diagnosis of hypothyroidism in young subjects

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MASSIVE JEJUNAL DIVERTICULOSIS WITH STEATORRHOEA AND MEGALOBlastic ANAEMIA IMPROVED BY EXCISION OF DIVERTICULA

BY

G. WATKINSON, M.D., M.R.C.P.
Senior Lecturer in Medicine

D. B. FEATHER, Ch.M., F.R.C.S.
Consultant Surgeon

F. G. W. MARSON,* M.D., M.R.C.P.
Lecturer in Medicine

AND

J. A. DOSSETT, M.B., B.S.
Senior Registrar in Pathology

From the Department of Medicine, University of Leeds,
and St James's Hospital, Leeds

Diverticulosis of the small intestine, located largely in the jejunum, is a not uncommon pathological finding in elderly subjects, generally causing no symptoms and, incidentally, found radiologically or at necropsy. Rarely diverticula are found to induce physical disorders. Taylor (1930) described the case of a patient with pernicious anaemia and a gastro-enterostomy in which numerous diverticula of the jejunum were found at necropsy. Montuschi (1949), Zingg (1950), Spang (1954), and Krevans, Conley, and Sachs (1954) described further cases in which jejunal diverticulosis had induced a sprue-like syndrome with diarrhoea, fatty stools, and hypoproteinaemia. The triad of jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia was first recognized by Bauenoch and Bedford (1954) and by Dick (1955). A review of the literature reveals that only 21 cases have as yet been described, and 17 of them showed an associated megaloblastic anaemia. It is not yet firmly established that jejunal diverticulosis may itself be the cause of an associated malabsorption syndrome, which might be a chance association with the not uncommon lesion of the small intestine.

In this paper we are reporting a further case, not only because of the rarity of the condition, but also because elective surgical removal of the diverticula has brought a prolonged improvement in the patient's condition, with correction of both anaemia and steatorrhoea.

Case Report

A man aged 64, a finisher in a dye-works, was first seen at the Leeds General Infirmary in December, 1956. For 25 years he had had attacks of upper abdominal pain occurring about twice weekly. The pain was severe and colicky, persisting a few hours, and was accompanied by nausea and vomiting; his longest remission from pain was three months. In August, 1951, a particularly severe attack of pain with vomiting and diarrhoea necessitated admission to hospital. Blood examination revealed a haemoglobin of 60% (8.9 g./100 ml.) and a red-cell count of 3,400,000. Rapid improvement followed treatment with phthalylsulphathiazole and a blood transfusion. A diagnosis of acute gastroenteritis was made. Later a barium-meal study in November, 1951, revealed multiple diverticula of the upper jejunum to be present with prolonged retention of the bowel contents in them (Fig. 1).

In December, 1953, ligation and excision of third-degree haemorrhoids was performed, and after this operation the mild diarrhoea from which the patient had suffered since

*Now at Hamilton General Hospital, Ontario, Canada