anginal pain in one case in which there was probable pre-existing myocardial degeneration.

4. As regards regulation of dosage, our results bear out the dictum of Means (1935) to the effect that the proper dosage of thyroid for a patient with myxoedema is the smallest dose which will relieve the symptoms. Although in our cases we usually succeeded in restoring the basal metabolic rate and serum cholesterol level to within normal limits, it was notable that the patients were usually more comfortable at a lower dosage than that required for this purpose. In such cases there was a tendency for old symptoms of past disorders to be resurrected—e.g., dyspepsia, pains in shoulders, arthritic pains, etc.—which had been, as it were, submerged in the myxoedematous state. It is probably better, therefore, not to attempt complete restoration of normal metabolism in the average case of myxoedema, and if the B.M.R. is to be used as a check on treatment a figure of 90% of normal would be an appropriate level at which to aim.

5. The thyroxine has been administered to most of our patients in a single daily dose after breakfast, and it appears from the metabolic data that there would be no advantage in giving the drug more frequently than this (Table I).

6. It is of theoretical interest that the iodine equivalent of our average maintenance dose of L-thyroxine sodium (0.2 mg.—0.13 mg. iodine) is approximately the same as that of an average maintenance dose of thyroid extract (1.5 gr.—0.1 mg. thyroxine iodine). This would suggest that the former drug is absorbed from the alimentary tract about as well as the active principle of thyroid extract.

Conclusion

While we are not in a position to say that L-thyroxine sodium is any better in the treatment of myxoedema than a reliable thyroid extract, in our opinion it is certainly equally satisfactory. It would appear, therefore, that there might be definite advantages in its use on the score of greater reliability. Since synthetic thyroxine does not require any biological or chemical standardization it provides a substance which can be used with equal confidence in any part of the world.

Summary

Nine cases of myxoedema have been treated orally with various synthetic thyroxine preparations over a period of 18 months.

All the drugs tested gave perfectly satisfactory clinical results, though L-thyroxine sodium (average daily dose 0.15–0.3 mg.) was the most active of the compounds used. With a suitable dosage all symptoms of myxoedema were relieved and the metabolism could be restored to normal.

There were no untoward side-effects except those which might be due to overdosage—a real danger. The results bear out the dictum that the proper dosage in myxoedema is the smallest one that will relieve symptoms.

We consider L-thyroxine sodium to be as satisfactory as thyroid extract in myxoedema. Its use might therefore be of definite advantage because of its greater reliability and because it does not need biological or chemical standardization.

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PROTHROMBIN ESTIMATION AND DICOUMAROL THERAPY

BY

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Since the advent of anticoagulant therapy, with the widespread use of dicoumarol, prothrombin estimations have assumed a much greater clinical significance. Numerous modifications of Quick's (Quick *et al.*, 1935) original one-stage method have been introduced, and on the whole with satisfactory results. Much confusion exists, however, regarding the interpretation of the results obtained in different laboratories, a circumstance which tends to bring prothrombin estimations for clinical use somewhat into disrepute. The prevailing practice is to plot a curve showing the actual clotting-times obtained with varying percentages of prothrombin and giving the final result as a percentage of normal. Many authorities express the result as a prothrombin index. In order to clarify the present position it is important that certain principles should be fully understood.

1. It has been definitely proved that in carrying out Quick's method of prothrombin estimation optimal concentrations of the thromboplastin and calcium are necessary, and that varying the concentration of these will give different clotting-times, especially with plasma having a low prothrombin content. The concentration of calcium can be easily controlled so that this becomes a stable factor. Not so, however, with the thromboplastin, and it is this which gives the varying readings obtained in different laboratories. The ideal is to prepare a standard thromboplastin solution which will give identical results in different laboratories.

2. In preparing a prothrombin percentage curve plasma is diluted with either saline or prothrombin-free plasma, the latter being obtained by absorption with aluminium hydroxide or barium chloride. The curves produced by diluting with saline vary from those obtained by diluting with prothrombin-free plasma, and different curves result from the use of aluminium hydroxide or barium chloride. A further difficulty is that in practice one has to vary the concentration of thromboplastin when using weaker percentages of plasma if optimal plotting-times are to be obtained. It is with these diluted plasmas having a low prothrombin content that the concentration of thromboplastin, and to a less extent of the calcium, becomes critical. Different prothrombin preparations which give apparently equal clotting-times with undiluted plasma may give widely different clotting-times with diluted plasma.

Thromboplastin Preparations

Various methods have been adopted, the most common of which are a dried extract of rabbit brain as originally described by Quick, and Russell-viper venom.

Dried Brain Extract.—This is widely used in America, and is prepared commercially. It keeps well and gives clotting-times of approximately 12 seconds with normal controls. These preparations contain an excess of thromboplastin and when used with diluted plasmas or plasma with low prothrombin content the concentration of thromboplastin may therefore not be optimal.

Russell-Viper Venom.—Venom as a source of thromboplastin is very commonly used in this country in a 1 in 10,000 or weaker concentration. The advantage of venom is the ease of preparation, which simplifies prothrombin estimations. In my experience it has proved unreliable when used with low prothrombin plasmas such as are obtained with dicoumarol. It tends to give false low clotting-times, and when compared with brain extract it "lags" so that it leads to a false and dangerous appreciation of prothrombin content—for example, several of my patients who had haemorrhagic manifestations on dicoumarol gave short (near normal) clotting-times with venom. For this reason I firmly believe that venom solution is dangerous and should be discarded. Its false low clotting-times have been observed by various authorities (Wilson, 1947; Macfarlane, 1948).

Saline Emulsion of Brain Extract

Quick originally used rabbit-brain emulsions but very soon discarded them for that of acetone-dried brain extract. For the last seven years I have used saline emulsions of human-brain extract with consistently good results. The main advantages are the ease of preparation, the stability, and the consistent results obtained. The preparation of these saline emulsions and the results obtained with them have been fully described elsewhere (Toohey, 1941; Owen and Toohey, 1941); I have, however, slightly modified these preparations since then.

Fresh human brain is used, as it is readily obtained from the post-mortem room. Human-brain extract also keeps for longer periods than rabbit brain. It is freed of all membranes and blood vessels and washed in saline. A small portion, enough to cover a shilling, is emulsified in a mortar with approximately 20 ml. of normal saline to which has been added 0.5% of phenol as a preservative. The emulsion is filtered through gauze to remove all gross particles and the resulting solution should be of milky opacity. When this is tested with normal plasma it invariably gives a clotting-time of 10 to 15 seconds. This emulsion, however, contains a considerable excess of thromboplastin, and, while it will normally give good and reliable results with low prothrombin plasma, it tends in some cases to inhibit clotting and may occasionally for this reason give falsely high clotting-times. I therefore dilute the emulsion to a weaker concentration.

A convenient method of dilution is to prepare a solution which is approximately equivalent to that in the tube containing 150 mg. of protein as used for estimation of cerebrospinal fluid protein. This concentration (150 mg.) will give a clotting-time of 13 to 16 seconds with normal controls.

It will be found that the 150-mg. thromboplastin solution will tend to decline in activity to the extent of only three to four seconds over a period of a month, and many preparations will keep for much longer. Several have kept for as long as six months, with a prolongation of only five to six seconds with normal plasma. Many of the more concentrated thromboplastin preparations have remained stable for one year, with a prolongation from the initial clotting-time of only five to six seconds. The

weaker the initial concentration of thromboplastin preparation the quicker it tends to become inactive. The simplicity with which these preparations are made renders it unnecessary to keep them for long periods.

It is essential that, in preparation, the emulsion be thoroughly shaken for at least five minutes so that the thromboplastin goes into solution. The preparations are kept in a tightly stoppered container at 4° C. Before use they should again be thoroughly shaken and be left at room temperature for 15 minutes. The addition of 0.5% phenol to the saline prevents bacterial contamination, which I have found is a common cause of rapid deterioration of these saline-brain emulsions. In my opinion it is not necessary to prepare dried brain extract, thus greatly simplifying prothrombin estimations.

Prothrombin Estimations

The difficulty encountered in prothrombin estimation lies in expressing results and also in deciding to what extent the level of prothrombin should be lowered. Most authorities recommend a lowering to between 10 and 30% of normal—a safe level, as bleeding seldom occurs when the prothrombin content is above 10%. Some authorities recommend a prolongation of the clotting-time to twice the normal; this roughly corresponds to 20% of normal. The difficulty in practice of expressing a definite percentage of normal is that prothrombin clotting-times will vary according to the prothrombin content of the plasma and also with the concentration of thromboplastin used. I think that a much simpler interpretation which is of benefit to the clinician can be adopted.

(a) A thromboplastin preparation made as described above, which will give a normal clotting-time of 13 to 16 seconds, is used. I do not employ a preparation which gives a normal clotting-time of above 20 seconds, as at that level it tends to decline in activity too rapidly, and it is important to be certain that the thromboplastin is active. Conversely, I do not advocate a more concentrated preparation of thromboplastin with its much shorter clotting-times, usually 10 to 12 seconds, as this strength is not optimal for low prothrombin plasmas and may, as already mentioned, give false longer times. A saline emulsion of brain diluted to 150 mg. of protein as described above will be found in practice to be most convenient.

(b) The prothrombin level of the patient on dicoumarol should be maintained between 30 and 50 seconds, using the above thromboplastin preparation. With more than 50 seconds we are veering to the danger level, though many patients have given clotting-times of 60 to 70 seconds without haemorrhagic manifestations. In a carefully controlled series of 30 patients treated with dicoumarol the shortest clotting-time found with haemorrhage was 85 seconds. I consider the absolute time to be of greater importance than a percentage reading, as, when preparing prothrombin percentage curves, plasma is diluted with saline or prothrombin-free plasma, which is an artificial procedure in that one may well dilute other factors taking part in blood coagulation that does not bear a direct relation to what happens *in vivo*.

I do not recommend making prothrombin estimations on diluted plasma, which many authorities do in order to bring out a minor reduction in prothrombin content. In actual practice bleeding has never occurred with a clotting-time of less than 50 seconds. Conversely, whether a clotting-time of 30 seconds is sufficient to prevent the occurrence of thrombo-embolic accidents remains to be proved. In my small series of 30 patients no such accidents did occur when the clotting-time was maintained within the range of 30 to 50 seconds.

Dicoumarol Therapy

Dosage.—It must be clearly understood that there is no standard dose of dicoumarol, and that the reactions vary greatly with different patients. For this reason it is essential that prothrombin estimations should be carried out at regular intervals. Many workers recommend daily estimations. I have found that estimations on alternate days are sufficient, except during the initial stages of treatment—that is, for the first four or five days—and in those cases with widely fluctuating clotting-times that sometimes occur. One factor of great importance with regard to dicoumarol dosage is the age and general condition of the patient. The older and more frail the patient is the more susceptible is he to dicoumarol—so much so that I give a reduced dosage to all those over 65 years. Of six patients who had haemorrhages all but one were over 65. It is important to remember that some patients are much older than their years, and vice versa; and this factor should be borne in mind when using dicoumarol. Some patients are very susceptible to dicoumarol, and haemorrhages can occur with a very small dose: one patient, aged 69, had serious bleeding with a total dose of only 550 mg. of dicoumarol.

Scheme of Dosage.—For younger patients: First day, 300 mg.; second day, 200 mg.; third day, 200 mg.; and then a daily dose of 50 mg., to be varied according to the prothrombin clotting-time. Many young robust people are relatively insensitive to dicoumarol and will need larger doses—for example, 100 mg. daily instead of 50 mg. to keep the prothrombin at a therapeutic level. For older patients (65 years and over): First day, 200 mg.; second day, 200 mg.; third day, 100 mg.; and then 50 mg. daily, to be varied according to prothrombin clotting-time. In the initial stages it is better to give dicoumarol in small divided doses than in a single large dose.

Most authorities usually give an initial dose of 300 mg. of dicoumarol followed by 200 mg.; they then give it according to the prothrombin content as ascertained by daily estimations. I find, however, that this method tends to produce a fluctuating curve. I therefore prefer to give a small daily dose of dicoumarol after the initial heavier dosage—omitting the drug, of course, if the prothrombin falls to a dangerously low level.

In practice I have found the daily microscopical examination of urine for red cells very useful. In many cases their presence foreshadows an impending gross haemorrhage, and as soon as any quantity appear dicoumarol must be stopped.

Conclusions and Summary

Estimation of prothrombin has assumed a greater clinical significance since the use of dicoumarol. Practical difficulties in carrying out the test are mainly due to the inability to standardize and prepare thromboplastin. Quick's method is a simple one, and most convenient for clinical use. The commonly used method of diluting whole plasma with saline in order to bring out an early fall in the prothrombin level is not advocated.

A simple method of preparing a stable and active thromboplastin preparation is essential. The most frequently used preparations are Quick's original acetone-dried brain extract and Russell-viper venom. The latter often gives false low clotting-times, with the consequent danger of overdosage with dicoumarol and subsequent haemorrhage. Preparation of acetone-dried brain extract usually requires skilled technical ability.

A description is given of an alternative and simple thromboplastin preparation made by emulsifying human brain with normal saline to which has been added 0.5% phenol as a preservative.

A thromboplastin preparation which will give a prothrombin clotting-time with normal plasma of 13 to 16 seconds is advised. This preparation usually corresponds with the 150-mg. tube as used in cerebrospinal fluid protein estimations.

For effective dicoumarol therapy a prothrombin clotting-time of 30 to 50 seconds is advised. It is not essential to record the prothrombin level as a definite percentage. The absolute clotting-time is considered of much greater clinical importance, and, using an active thromboplastin preparation which gives a clotting-time of 13 to 16 seconds with normal plasma, it is sufficient to maintain a clotting-time of 30 to 50 seconds.

Dicoumarol varies in its activity in different people, some being very susceptible to small doses. This is especially so with the elderly and the frail, who should be given a reduced dose. Conversely, the young and robust will stand much larger doses. After the initial heavier medication to lower the prothrombin to the required therapeutic level, a small daily dose is advocated. In the majority of cases it will suffice to estimate the prothrombin level on alternate days after the first four to five days of treatment. A scheme of dosage which has been found in practice to give adequate treatment is outlined. Daily microscopical examination of the urine for the presence of red cells is of value as an indication of the likelihood of more serious haemorrhage occurring.

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IODINE AND GASTRIC FUNCTION

BY

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A great number of papers have been written on the influence of iodine and its derivatives on the function of the stomach. The most important question is whether the gastric mucosa has the ability to secrete iodine introduced intravenously or to absorb it. Rose (1930) first presented evidence that the gastric mucosa has this ability. His evidence was confirmed by experiments in animals and men by Pentzold and Faber (1897) and Nencki and Schoumow-Simanowsky (1894). The last-named authors came to the conclusion that it is possible for the gastric mucosa to replace the hydrochloric acid in small part by hydroiodic acid. This conclusion corresponds with that of Lipschitz, who found that the ability of the gastric mucosa of the rabbit to secrete iodine is almost comparable to that of the kidneys. As pointed out by Heilmeyer and Sturm (1928), iodine begins to be secreted by the gastric mucosa while it is still in the peripheral circulation.

This ability of the gastric mucosa to secrete iodine led me to investigate the influence this secretion had on stomach