

THE ADMINISTRATION OF THYROID GLAND TO PREMATURE BABIES

BY

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As far as can be ascertained from the literature, the administration of thyroid gland to premature babies was first suggested by Pritchard (1934). He then described its use in his book on 'The New Born Baby,' but he was certainly advocating this therapeutic measure long before this time. The underlying principle for this form of treatment is of much earlier date and goes back to the classical experiments of Gudernatsch (1913-14), on the feeding of tadpoles with thyroid gland to speed up their development into frogs. This pioneer's conclusions were as follows:

'The experiments of 1911 and 1912 leave no doubt that the mammalian thyroid contains an agent which, when given as food, calls forth a rapid differentiation in a developing vertebrate organism.'

The object of administering thyroid gland to the premature baby is to hasten maturation, so that the various essential functions, such as those of respiration, digestion and heat regulation, may be more expertly undertaken than in the immature state. It is differentiation of function and structure which is achieved in the tadpole, and not growth. In fact, the resulting frog will usually be undersized and its length of life is generally shorter than the average. In the premature baby the use of thyroid should be limited to such a period as seems necessary to improve functional development. The gland is not being used to supply a deficiency, but merely to act as a stimulant to remove the inertia which makes the premature baby so difficult to manage.

This point on the question of a possible deficiency of thyroid secretion in the premature baby must be elaborated briefly, for Collis (1936), in strongly supporting the use of thyroid for premature babies, has suggested that new-born babies do not in general secrete thyroxin in the first few weeks of life, implying that the premature baby may be handicapped on this account. Histological evidence (Murray, 1927) does not support this view. The thyroid gland in the full-term human foetus and in the newly born infant presents a normal colloid

state provided that careful precautions are taken to prevent degenerative changes in the course of preparing histological specimens. A biochemical study (Elmer and Scheps, 1935) indicates that the amount of thyroxin in the thyroid gland of the foetus and new-born baby is of the same order as in a normal adult. Aldrich (1936) has also pointed out that one of a set of twins may be a cretin, indicating that normally a foetus develops its own thyroid secretion which is not dependent upon a maternal supply. This author also emphasizes the fact that in general thyroid gland speeds up development rather than the promotion of growth or gain in weight.

These introductory considerations will be referred to again below in a discussion on the assessment of results. The main object of this communication is to set out such results, obtained in a controlled therapeutic trial at Queen Charlotte's Maternity Hospital between November 1935 and January 1937.

Method of investigation

It has been already pointed out (Moncrieff, 1936) in connexion with a similar investigation of the use of oestrin for premature babies that what may be termed 'contemporary controls' are essential. So much depends upon the general management and nursing care, the ward, temperature, the feeding and the risks of infection that the value of any procedure for premature babies can only be judged if at the same time of year, in the same ward and looked after by the same nurses there are similar babies not submitted to the method of treatment or management under trial. At the same time it is important that so far as possible the nursing staff should be unaware of which babies are receiving special treatment, so that any bias may be absent from their views on the value of such treatment. In the present investigation this was achieved (at least at the onset) by the use of 'dummy' thyroid tablets. The nursing staff, however, early in the investigation, was convinced that the thyroid-treated babies were easier to feed and manage, and since the thyroid tablets were slightly browner in colour than the dummy tablets, the nurses soon ceased to be unaware of which babies were treated and which were controls. This was to some extent unfortunate as possibly affecting the results. However, as will be shown below, the main point in favour of the use of thyroid gland for premature infants which emerges from this investigation is a lowering of the mortality rate, and this can scarcely be attributed to any decreased care of the control babies.

For the period mentioned above every baby of 5 lb. or under at birth came under the scheme. It would be out of place to argue here on the definition of prematurity and to what extent weight is a reliable guide. At Queen Charlotte's Hospital the weight standard has been in use for a long time, and it certainly serves as useful arbitrary measure. (In passing it may be remarked that the standard has now been raised to 5½ lb. in view of certain developments recorded in American and European literature.) There were during the period chosen one hundred and three such babies born alive. Of these forty-one were excluded from the experiment for the following reasons :

Thirty-two died shortly after birth or were very ill for several days (subsequently dying) or suffered from severe disease (hæmorrhagic disease) or from severe congenital malformation.

Nine were nearly 5 lb. in weight, not at all immature in function and treated as completely normal babies from the beginning.

With regard to this second group it should be explained that the arrangements at the hospital are such that each of three floors has a side ward in which small and ill infants are nursed. These nine infants never came into the side wards at all, being regarded as essentially small normal babies.

The remaining sixty-two babies came into the investigation ; all were identically treated as regards room temperature and humidity, general hygiene and feeding. Each baby was seen by the author as soon as possible after birth and at intervals during its stay in hospital. Breast milk was always used in the early days of life for all the premature babies, obtained at first from a ' pool ' of surplus milk and later, if possible, from the baby's mother. Weak milk mixtures (' humanized ' dried milk or peptonized milk mixtures) had to be introduced in some instances, but rarely before the end of the first week of life, and since the results here presented refer to the first two weeks of life only, it may be assumed that the qualitative feeding conditions were identical. It is, of course, fundamental to the problem that the quantities of milk were dependent largely on the baby's ability to suck and swallow. The stronger and more mature the baby the more feed would be taken, and it was to promote such strength and maturity that thyroid was being given.

Alternate babies received thyroid extract in lactose tablets or plain ' dummy ' tablets (all kindly supplied for the investigation by Messrs. Oxo Limited). Each tablet of thyroid extract contained 1/20 grain, and these were labelled ' thyroid A.' The lactose tablets were labelled ' thyroid B.' The dosage used was on a basis of 1/20 grain (i.e. one tablet) daily per lb. body weight. This was continued for at least a fortnight unless the baby was fit enough to leave hospital before this time. The tablets were crushed and given from a spoon with a little water. The dose chosen was more or less arbitrary. Pritchard (1934) has recommended 1/10 grain per lb. body weight daily as a maximum, and half this seemed a safe amount to employ. Careful records were kept of the temperature (rectal) night and morning and of the weight. Unless the baby was obviously unfit, daily weighing has been practised. With twins one received ' thyroid A ' and the other ' thyroid B.' This somewhat upset the ' alternative baby ' plan and in the end it was found that thirty-three babies had received ' thyroid A ' and twenty-nine ' thyroid B.' These numbers appeared near enough for comparison purposes.

The assessment of results

It is first necessary to discuss how the results may be assessed. As was remarked in connexion with the oestrin investigation (Moncrieff, 1936), when nursing skill is of a high standard the general mortality and morbidity rates are already so low that it is difficult to achieve improvement with any special form of treatment. Thus of the sixty-two babies who came into the investigation there were only seven deaths, and anyone with experience of managing premature babies will realize that a mortality of 11 per cent. is low. (Of the whole one hundred and three babies born alive during the period there were thirty-eight deaths. Deducting the seven deaths already mentioned, this means that thirty-one out of the thirty-two babies classified as being too

ill or weak for treatment died, most of them within forty-eight hours after delivery.) Despite this small number of deaths a point will be made later about the mortality rates, since there appeared to be a difference between the group receiving thyroid and the group which did not.

The question of gain in weight, used as the main test in the oestrin experiment, presents a great difficulty. Thyroid gland presumably stimulates metabolism and may promote a loss rather than a gain in weight. Nevertheless the 'stimulated' baby will probably take its feeds better than the 'unstimulated' baby (if thyroid is to have any effect) and thus a better gain might be expected. At any rate, it seems fair to assume that no very clear-cut results can be expected from the weight charts and any attempt to obtain such results by increasing the dosage of thyroid will produce the opposite effect. It may be remarked in passing that with the dose employed (1/20 grain per lb. body weight daily) no toxic symptoms were ever observed and there was no case of diarrhoea.

The temperature range has been considered for each baby, since it has been suggested by Pritchard that it was especially in the inert baby with subnormal temperature that good results were obtained. For the purpose of these results the records in the first forty-eight hours have been disregarded, since violent fluctuations may occur during this period. The highest and the lowest recorded temperatures in the subsequent stay in hospital has been taken for each baby and averaged for the group.

Analysis of results

The results can now be summarized in the form of a table (table 1).

TABLE 1
ALL 'TREATED' BABIES (62)

	NO. OF BABIES	AVERAGE WEIGHT AT BIRTH	AVERAGE WEIGHT 7TH DAY OF LIFE	PER CENT. DECREASE IN WEIGHT 7TH DAY	AVERAGE WEIGHT 14TH DAY	PER CENT. INCREASE OR DECREASE OVER BIRTH WEIGHT 14TH DAY	AVERAGE TEMPERATURE RANGE	DEATHS
Group A (received thyroid).	33	4 lb. 3 oz.	3 lb. 15 oz. (32 babies)	6	4 lb. 0 oz. (21 babies)	- 4.5	96.5° F. -98.5° F.	2 ; 6 per cent.
Group B (no thyroid).	29	4 lb. 7 oz.	4 lb. 4 oz. (21 babies)	4.2	4 lb. 11 oz. (17 babies)	+ 5.6	97.1° F. -98.3° F.	5 ; 17 per cent.

Both groups consisted of babies whose estimated maturity lay between thirty-two weeks and term. The causes of the prematurity—toxaemia, antepartum haemorrhage, and multiple pregnancy—appeared to be the same in both groups. The lowest weight in both groups was 3 lb. 2 oz. It will be noticed in table 1 that only fifty-seven out of the sixty-two babies remained for comparison of weights on the seventh day. In group A one baby had already died (on the

second day of life) and in group B four babies had died (on the third, fourth, sixth and seventh day, respectively). Similarly by the fourteenth day the numbers had again been decreased. There had been one more death in each group and seventeen had been discharged from hospital, ten in group A (32 per cent. of survivors) and seven in group B (29 per cent. of survivors). Although this decreases the already small number of babies available for study, a separate analysis of the babies followed through to the fourteenth day is given below (table 2). It is obvious that the effect of deaths in both series is to remove those babies who were doing badly, and since there were two deaths in group A and five deaths in group B this gives a certain bias to the results in favour of group A. On the other hand the discharges of babies who were doing well—largely because the mothers were anxious to get home and only when the babies were well established on the breast or on mixed breast and complementary feeds—were about equal in the two groups.

TABLE 2
'SURVIVORS' (38)

	NO. OF BABIES	AVERAGE WEIGHT AT BIRTH	AVERAGE WEIGHT 14TH DAY OF LIFE	PER CENT. INCREASE OR DECREASE OVER BIRTH WEIGHT 14TH DAY
Group A (received thyroid).	21	4 lb. 1 oz.	4 lb. 1 oz.	- 1.5
Group B (no thyroid) . .	17	4 lb. 7 oz.	4 lb. 8 oz.	+ 1.8

Before proceeding to a discussion of the results in more detail, the weights at birth, seventh day and fourteenth day of four sets of twins are given in table 3.

TABLE 3
FOUR SETS OF TWINS

GROUP	BIRTH WEIGHT	7TH DAY WEIGHT	14TH DAY WEIGHT
A	4.14	4.12	5.3
B	4.5	4.8	4.11
A	4.3	4.0	4.3
B	4.8	4.4	4.8
A	3.15	3.4	3.15
B	4.10	4.6	4.7
A	3.11	3.6	3.5
B	4.11	3.13	Died

General discussion

It is proposed to consider the general results of thyroid administration under the headings of effects on weight, effects on temperature, mortality and sex differences. The last section is included because the present study must be regarded as a continuation of the work already mentioned in connexion with

the use of oestrin for premature babies, in which a sex difference appeared to be present.

Weight.—It has already been explained that any striking effect on the weight of the babies receiving thyroid was not to be expected, since its stimulating action on appetite and digestion might well be counterbalanced by its general raising of the metabolic rate, tending to produce a weight loss. In table 1 it will be seen that at the end of a week the percentage decrease in weight was similar in the treated and untreated groups, although slightly more in the former (6 per cent. and 4.2 per cent. respectively). By the end of fourteen days the untreated group appears to show a great advantage (a gain of 5.6 per cent. as compared with a loss of 4.5 per cent. in the treated group), but this may well be accounted for by the removal of certain unsatisfactory babies from the final figures, since in all there had been five deaths in this group and only two in the treated group. In fact, between the seventh and fourteenth day only one baby died in each group, but the final comparison is made between birth weight and fourteenth-day weight. The figures in table 2 tend to bear out this contention, since after removal by death or discharge of babies not available for comparison on the fourteenth day, the two groups show little difference in the weight. The twenty-one treated babies are on the average 1 oz. under birth weight and the seventeen untreated babies are 1 oz. over birth weight. Table 3, giving the results in four sets of twins, shows also little difference between the weights of the treated and untreated babies. In general the effect on weight may be summarized by the statement that thyroid administration in the dosage employed in this investigation (1/20 grain of thyroid extract per lb. of body weight daily) does not produce any obvious beneficial results on the weight curve.

It must, however, be borne in mind that the nursing available for the premature babies at Queen Charlotte's Hospital is of a high standard. The more permanent nursing staff have had extensive experience, and the skill displayed in getting small babies to take their feeds is great. Thyroid might have the effect in making this procedure easier for less experienced nurses. In the course of this investigation the opinion was frequently expressed by the nurses in charge that the 'treated' babies were definitely easier to manage. In fact, as already mentioned, it soon became impossible to conceal that the 'dummy' tablets labelled 'thyroid B' did not contain any thyroid, for the babies receiving them were thought by the nursing staff to be more difficult to feed and to keep warm than those in group A receiving thyroid extract.

Temperature.—Rectal temperatures were taken night and morning for all the babies in the series. The records of the first two days of life have been neglected, since violent fluctuations may occur during this period. The highest and lowest average temperatures for each group of babies is given in table 1. The upper limits are similar and the lower limits appear to show a slight advantage in favour of the untreated group. All the premature babies here described are clothed in gamgee jackets, with separate gamgee coverings for the head, hands and feet in the smallest babies. In addition, electric pads of the 'Thermega' pattern are placed over the bed-clothes in all premature babies. These pads allow of three grades of temperature, and they are con-

stantly adjusted by the nursing staff according to the temperatures of the babies, as well as by the results of observation. Although the untreated babies appeared to have a higher lowest level, on the average there was no doubt about the effect of thyroid in raising the temperature in some of the treated series (fig. 1), and here again the opinion of the nursing staff was emphatic that the thyroid-receiving babies are easier to keep warm.

Mortality.—It will be remembered that of the whole series of one hundred and three premature babies born alive at Queen Charlotte's Hospital during the period of the investigation, forty-one were excluded from the numbers accepted for 'treatment' and observation, thirty-two of whom died shortly

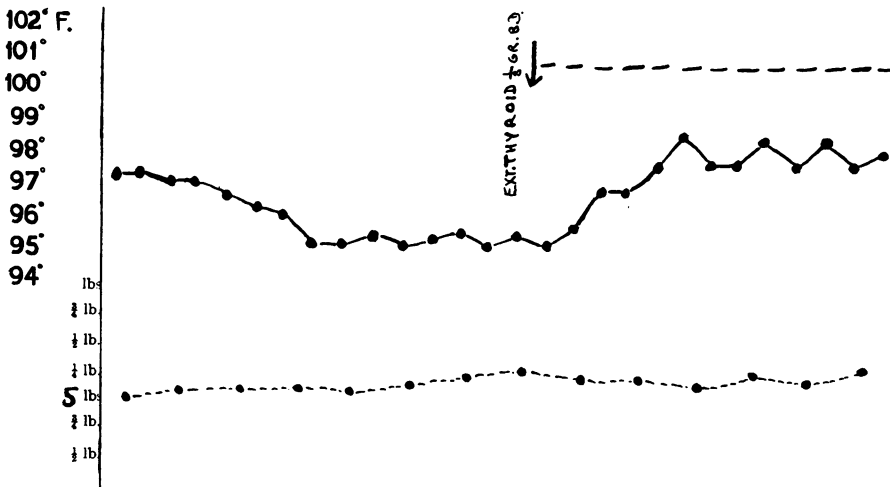


FIG. 1.—Effect of ext. thyroid ($\frac{1}{8}$ grain twice a day) upon the temperature curve (upper line) of a new-born baby weighing 5 lb. at birth. The lower dotted line shows the weight curve and there is a slight arrest in the upward curve when thyroid is begun. The records for the first three days have been omitted. The thyroid was given on the eleventh day of life because of the sub-normal temperature.

after birth or were very ill, suffering from some severe disease or congenital malformation. The sixty-two remaining for the purpose of the controlled experiment were, therefore, reasonably 'good starters.' Of those receiving thyroid two died and of those not receiving thyroid five died. In other words, the mortality rate of the selected babies was 6 per cent. in those receiving thyroid and 17 per cent. in those not receiving thyroid, nearly three times as high. Of the seven deaths, two, one in each group, occurred during the first forty-eight hours of life, so that the untreated group shows four deaths after this period as against one only in the treated group. One of the deaths in group B was in the larger of twins, the smaller, treated baby surviving. The figures are small, but since all other conditions as regards nursing care and feeding were identical and carried on by the same staff at the same period of time, the difference may be regarded as significant and, indeed, represents the main argument in favour of thyroid administration.

Sex differences.—In the oestrin-treated series previously reported (Moncrieff,

1936), thirty-three out of the total series of fifty-four babies were females, a curious sex preponderance. Further, the slight but definite improvement in the weight by the fourteenth day in the oestrin-treated series appeared to be mainly due to improvement effected in the female babies. Since a sex hormone was involved in the oestrin series such results may have some special significance. In the present series the thirty-eight babies followed through to the fourteenth day show a predominance of the male sex, the number of male babies being twenty-three and females fifteen. The present investigation followed immediately after the oestrin series, and the curious difference in the two series serves to emphasize the importance of large numbers of cases spread over a long period before altogether satisfactory results can be obtained. Analysing this group of thirty-eight babies according to sex shows approximately equal results for the males and females. In the thyroid-receiving group the males were 1 oz. under birth weight by the fourteenth day and the females had just recovered the birth weight. In the control group the males were 2 oz. over birth weight by the fourteenth day and the females were 2 oz. under birth weight. These observations have a more important bearing in retrospect on the oestrin series than upon the present investigation, since there is no evidence of any great difference in the two sexes when thyroid is used.

Conclusions

The administration of thyroid extract (1/20 grain per lb. body weight daily) to premature babies appears to exert a beneficial effect in speeding up maturation. In a controlled investigation the mortality rate in a group receiving thyroid was only one third that in the control group. Reasons are adduced why better gains in weight are not obtained, and the opinion of the nursing staff is mentioned as emphatically in favour of thyroid administration as rendering small babies easier to manage as regards feeding and keeping them warm.

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