

Bromocriptine for the suppression of lactation was superior to quincœstrol or placebo, as judged by the patient's symptoms. It was also effective when given to women in whom lactation has already started. Headache and nausea, sometimes observed in non-puerperal patients receiving bromocriptine, did not occur in this series. Also there are no known serious side-effects, such as changes in coagulation status.¹⁷ Rolland and Schellekens⁷ found no changes in hepatic and renal function tests. This may be of particular advantage in patients in whom the risk of thrombosis is increased by factors such as operative delivery. Early restoration of ovulation has been reported.⁵ Patients should be made aware of this and contraceptive advice should be given.

Comparison of a 14-day course of treatment with bromocriptine with a single dose of quincœstrol may be criticised, and the practical disadvantages of a long course are obvious. However, the single-dose quincœstrol regimen is widely used and is reputedly as effective as a longer course of other œstrogen preparations. Although shorter courses of bromocriptine are under trial, they may prove unsatisfactory in the light of the rebound effect observed by us even after 14 days of treatment. A long-acting or depot preparation with similar prolactin-inhibiting properties would be advantageous.

We thank Mrs J. Webster for her detailed follow-up and domiciliary studies on the patients and for obtaining blood-samples: the many general practitioners who allowed us to study their patients; and Sandoz Ltd for financial support.

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"Traffic accidents in the youthful nations of Africa amount to a social scourge. Even a cursory survey of a handful of these countries shows that all too often the victims of such accidents are young Africans, whose rising earning power has enabled them to invest in a motorcycle or a car. Yet it is just this group of promising youngsters whose social and economic contribution Africa can least afford to lose . . . Statistics often lend themselves to various interpretations. But one report originating in Kenya expresses the situation succinctly by contrasting the number of road deaths per 100 million passenger miles in different countries:

United States	6
United Kingdom	13
Kenya	55
Uganda	65

In several countries, road accidents over a ten year period have increased at the alarming rate of between 85 and 100 per cent."—*World Health*, October, 1975, p. 14.

TRIODOTHYRONINE AND THYROID-STIMULATING HORMONE IN PROTEIN-CALORIE MALNUTRITION IN INFANTS

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Summary Protein-calorie malnutrition (P.C.M.) in a group of 43 Senegalese children aged eighteen to thirty months was characterised by a sharp fall in serum-triiodothyronine (T₃) concentration to 25.3% of the mean value in healthy age-matched controls. This decrease in T₃ was significantly (P<0.001) more pronounced in kwashiorkor of recent onset than in long-term P.C.M., a finding which suggests that impaired thyroxine (T₄) monodeiodination in the liver was responsible for the fall in serum-T₃ concentration rather than a reduction in the secretion of T₃ by the thyroid. Serum-T₃ concentrations became normal in both malnourished groups after two weeks of appropriate nutrition. Serum-T₃ concentrations in healthy, euthyroid, Senegalese children were higher than in White children. In frank kwashiorkor in Senegalese children, serum-thyroid-stimulating-hormone (T.S.H.) concentrations were within the normal range throughout the entire course of dietary therapy, indicating that the children remained euthyroid. In contrast, protracted P.C.M. led to impairment of the T.S.H./T₃ feedback mechanism and to a condition resembling hypophysectomy, which required two weeks' dietary therapy for its correction.

Introduction

PROTEIN-BOUND iodine,¹ butanol-extractable iodine,² and total thyroxine (T₄)^{3,4} are very much reduced in the blood of malnourished children. The very low concentration of serum-free-thyroxine (F.T.₄) progressively declines to below the normal range as a result of protracted malnutrition.⁴ This observation prompted us to measure total 3,5,3'-triiodothyronine (T₃) in severe protein-calorie malnutrition (P.C.M.). Serum-thyroid-stimulating-hormone (T.S.H.) concentrations were measured to determine whether the negative feedback exerted by thyroid hormones upon the anterior pituitary remained effective in hypo-proteinæmic states.

Patients and Methods

43 Senegalese children, aged eighteen to thirty months (mean two years) were studied. They had all the features typical of severe P.C.M.—growth and height retardation, muscle wasting, skin lesions, hair discoloration, œdema, and diarrhoea. According to the Wellcome Working Party classification,⁵ 18 of the children were between 80% and 60% of the Boston standard weight-for-age (50th percentile)⁶ and were deemed to be kwashiorkor cases of recent onset with limited height deficit, swollen limbs, and

TABLE I—SERUM-T₃ CONCENTRATIONS IN INFANTS WITH P.C.M.

Group	Day 1	Day 8	Day 15	Day 22
<i>P.C.M. of recent onset:</i>				
Mean serum-T ₃ ±s.d. (ng/dl)	37±14	122±44	212±59	224±73
Range (ng/dl)	13-64	57-214	97-298	113-355
No. of infants	18	17	16	18
Percentage of normal concentration	15.7	51.7	89.8	94.9
Significance	P<0.001	P<0.001	N.S.	N.S.
<i>Protracted P.C.M.:</i>				
Mean serum-T ₃ ±s.d. (ng/dl)	67±45	166±64	226±72	239±59
Range (ng/dl)	5-188	38-295	51-337	122-346
No. of infants	25	24	24	24
Percentage of normal concentration	28.4	70.3	95.7	101.2
Significance	P<0.001	P<0.001	N.S.	N.S.
<i>P.C.M. group as a whole:</i>				
Mean serum-T ₃ ±s.d. (ng/dl)	55±37	148±60	220±67	233±65
Range (ng/dl)
No. of infants	43	41	40	42
Percentage of normal concentration	23.3	62.7	93.2	98.7
Significance	P<0.001	P<0.001	N.S.	N.S.

N.S. = not significant.

heavy liver steatosis. In the remaining 25 children, the percentage of expected weight-for-age was below 60% of the Boston standard,⁶ and they were regarded as being marasmic kwashiorkor cases with moderate oedema and liver injury. The height of the children in this group was significantly less than in the kwashiorkor cases of recent onset. This stunting is an effect of protracted P.C.M.⁷ The children were treated in a metabolic ward by progressive refeeding, as described elsewhere.⁸ Blood-samples were withdrawn on admission (day 1) and at weekly intervals (day 8, day 15, and day 22) until clinical recovery. The control group was composed of 33 healthy Senegalese children of the same age, most of them from families of medical employees.

Serum-T₄ was measured by competitive binding ('Tetrasorb' kits, Abbott). F.T.₄ was estimated by equilibrium dialysis with labelled T₄.⁹ T₃ and T.S.H. concentrations were measured by radioimmunoassay.^{10,11} The statistical significance of the results was assessed by the *t* test.¹²

Results

Controls

In the controls serum-T₃ was 236±41 ng/dl (range 122-328, n=33) and serum-T.S.H. was 8.26±2.67 μU/ml (range 2.63-14.3, n=26). Mean serum-T₄ was 8.4±1.2 μg/dl (n=28) and mean serum-F.T.₄ 2.12±0.33 ng/dl (n=28).

Malnourished Children

Serum-T₃ concentrations were significantly lower than normal in P.C.M. children on admission (P<0.001) and on the eighth day (P<0.001) of the study (table I). Serum-T₃ concentration increased rapidly during the first two weeks of dietary therapy and became normal on and after the fifteenth day of treatment.

There was no significant difference between serum-T₃ concentrations in the two P.C.M. groups, either on day 15 or during subsequent nutritional rehabilitation. The mean serum-T₃ concentration before therapy was 55±37 ng/dl, or 23.3% of normal, in the P.C.M. children as a whole. Furthermore, the drop in serum-T₃ concentration was significantly more pronounced in the group with P.C.M. of recent onset than in the group with protracted P.C.M., at admission (0.001<P<0.01) as well as on day 8 (0.01<P<0.02), despite the wide scatter of T₃ values in the protracted-P.C.M. group.

Mean serum-T.S.H. in the group with P.C.M. of recent onset was within the normal range throughout the study (table II). In contrast, mean serum-T.S.H. in the group with protracted P.C.M. was normal on admission, increased slightly but significantly on day 8 (0.02<P<0.05), increased further on day 15 (P<0.001), and then fell to normal on day 22 (table II).

TABLE II—SERUM-T.S.H. CONCENTRATIONS IN INFANTS WITH P.C.M.

Group	Day 1	Day 8	Day 15	Day 22
<i>P.C.M. of recent onset:</i>				
Mean serum-T ₃ ±s.d. (μU/ml)	10.23±3.68	8.98±2.64	7.76±3.32	8.68±2.85
Range (μU/ml)	4.78-17.48	6.47-13.49	3.12-12.69	5.05-14.27
No. of infants	9	8	6	9
Percentage of normal concentration	123.8	108.7	93.9	105.1
Significance	N.S.	N.S.	N.S.	N.S.
<i>Protracted P.C.M.:</i>				
Mean serum-T ₃ ±s.d. (μU/ml)	10.31±6.34	11.41±6.80	14.32±7.68	8.89±2.15
Range (μU/ml)	2.28-26.9	2.96-31.56	8.65-37.12	5.88-12.33
No. of infants	15	15	15	14
Percentage of normal concentration	124.8	138.1	173.4	107.6
Significance	N.S.	0.02 P<0.05	P<0.001	N.S.
<i>P.C.M. group as a whole:</i>				
Mean serum-T ₃ ±s.d. (μU/ml)	10.28±5.40	10.56±5.75	12.45±7.30	8.81±2.39
Range (μU/ml)
No. of infants	24	23	21	23
Percentage of normal concentration	124.4	127.8	150.7	106.6
Significance	N.S.	N.S.	0.001<P<0.01	N.S.

In the P.C.M. children as a whole, serum-T.S.H. concentration on day 15 was significantly higher than in the controls ($0.001 < P < 0.01$).

In the group with P.C.M. of recent onset (except on day 15 when there was a transitory high positive correlation [$r=0.81$]) there was no significant correlation between serum T.S.H. and T_3 , T_4 , or F.T.₄. Nor was there a significant correlation between serum T.S.H. and T_4 or T_3 in the group with protracted P.C.M.

Discussion

Our results demonstrate that acute infant P.C.M. is characterised by a sharp and significant decrease in serum- T_3 concentration. At admission and on day 8 mean serum- T_3 values were significantly lower than normal in both P.C.M. groups. The drop in serum- T_3 was significantly more pronounced in the group with P.C.M. of recent onset. Serum- T_3 concentrations had returned to normal in both P.C.M. groups after two weeks of appropriate refeeding, and there was no significant difference in serum- T_3 concentration between the two P.C.M. groups on or after the fifteenth day of the survey. The mean serum- T_3 concentration in a control group of healthy euthyroid Senegalese children (236 ± 41 ng/dl) was markedly higher than that in normal White children.^{13,14} The high serum- T_3 concentration in the healthy Senegalese children presumably reflects the exceptionally high serum- T_3 -binding-globulin concentrations which are characteristic of Negro children.¹⁵

Serum- T_3 concentrations were reported to be lower than normal in chronic illness,¹⁶ in hepatic cirrhosis,¹⁷ in obese subjects during severe calorie deprivation,¹⁸ in P.C.M. adult patients,¹⁹ and in anorexia nervosa.²⁰ Our study is the first to show a similar decrease in malnourished children. The fact that the decrease in serum- T_3 concentration was greater than expected in the group with P.C.M. of recent onset may be attributed, at least in part, to lower serum- T_3 binding-protein concentrations, especially of serum-albumin and thyroxine-serum-prealbumin (T.B.P.A.).^{8,15} However, since the fall in circulating T_4 , which is transported by the same serum-carrier-proteins, is less pronounced, other mechanisms may be involved in the exceptional fall in serum- T_3 in the group with P.C.M. of recent onset. In some conditions¹⁶⁻¹⁹ low serum- T_3 concentrations may be produced by decreased peripheral conversion of T_4 to T_3 , rather than by a decline in the secretion-rate of thyroid hormones. Inhibition of conversion of T_4 to T_3 may begin within one or two days of the start of total calorie shortage.¹⁸ In the present study, the amount of defective conversion correlated with the extent of hepatic injury. Serum- T_3 concentrations were more depressed in frank kwashiorkor with heavy liver steatosis than in marasmic P.C.M. with limited fat infiltration. The fact that the liver plays a major part in recovery is demonstrated by the return of T_3 values to normal within two weeks of starting optimum refeeding, whereas the thyroid gland, in terms of other endocrine indices, only returns to normal after six to eight weeks of nutritional rehabilitation.⁴ No negative correlation was found between serum T.S.H. and T_3 in this survey. The transiently high positive regression coefficient

between serum T.S.H. and T_3 on day 15 ($r=0.81$) should be investigated further.

There was no significant difference between serum-T.S.H. concentrations on admission in the children with P.C.M. and the controls (8.26 ± 2.67 μ U/ml). This result accords with previously reported data.¹³ In the group with P.C.M. of recent onset T.S.H. remained within the normal range throughout the entire nutritional study, suggesting that the children remained euthyroid. In children with kwashiorkor of recent onset, central feedback mechanisms are apparently preserved, allowing appropriate adaptation by the thyroid.

In protracted malnutrition such adaptation is clearly irrelevant. Serum-T.S.H. values were widely scattered. Reduced serum-T.S.H. concentrations in P.C.M. have been described elsewhere.^{3,21} Serum-T.S.H. rose to a peak ($P < 0.001$) on day 15, when mean serum- T_3 concentration returned to normal. The lack of a negative correlation between serum T.S.H. and T_3 suggested that the regulatory interplay of T_3 and T.S.H. secretion was defective in cases of severe malnutrition. However, the exact time lag between T_3 and/or T_4 stimulus and T.S.H. response is not known in either normal or pathological conditions. Experimental malnutrition was reported to result in "pseudohypophysectomy", but this was not confirmed in P.C.M. when T.S.H., corticotrophin, and growth-hormone pituitary responses to different stimuli were tested.²²⁻²⁶ Our results indicate that the repair of the feedback mechanism requires two weeks of optimum refeeding.

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Reference continued overleaf

INTERRELATION OF THE COMMON CONGENITAL MALFORMATIONS SOME ÆTIOLOGICAL IMPLICATIONS

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Summary Analysis of congenital defects in a population of 90 921 singleton births revealed a strong interrelation between malformations: for example, 84% of lung defects, 70% of kidney defects, 34% of eye defects, 19% of cleft palate, and 15% of spina bifida coexisted with other defects which could not be designated as subsequently derived structural changes. The strength and intimacy of these interrelations casts doubt on the notion that multiple external factors are involved in the causation of human malformations.

Introduction

SCIENTIFIC inferences may concern events which are retrospective (ætiological) or prospective (predictive) to the process of classification. When malformations are classified so as to allow inferences to be drawn upon ætiology, judgment must be exercised in the selection of an "appropriate" dimension for classification. The failure of epidemiological investigation to identify any significant causal agent in spina bifida is usually explained by saying that the correct causal factor has not yet been selected for investigation—in other words, that the *ætiological* classifications used have been inappropriate. But has enough attention been paid to the propriety of the effect (disease) classification? Should spina bifida and anencephaly be considered separately or together? Those who favour separate investigation argue that combined study of neural-tube defects may mask an association with a factor which is causal for one but not for the other. As a compromise, epidemiologists have tended to study spina bifida and anencephaly both together and separately, but this approach lacks any intrinsic logic. What real justification is there for considering neural-tube defects separately from (say) cleft palate? The only logical explanation (in relation to ætiological inferences)

is that each has a different ætiology; but what evidence is there for this? One argument is that the epidemiology of cleft palate differs substantially from that of neural-tube defect. Given that this is true, should an observation, made after and deriving out of the classification, be accepted as prior justification for that classification, in the absence of independent and convincing evidence that cleft palate and neural-tube defects do in fact have separate ætiologies? A second and more pragmatic view is that their distinct anatomical and pathological features justify their consideration as separate entities. Whilst such an approach may be valuable for making prognostic inferences, past experience suggests that this does not necessarily apply to considerations of ætiology (congenital heart-disease and deafness have the same ætiology in rubella embryopathy). It may be necessary then to consider seriously the notion that, in the sphere of human malformations, classes of proven value for making prognostic clinical judgments may bear little relation to those necessary for appropriate ætiological investigation.

Materials and Methods

This investigation is based on the South Wales Congenital Malformation Study which has been described in detail elsewhere.¹ It covered the years 1964–66 inclusive and involved all births occurring in Monmouthshire, Glamorganshire, and the county boroughs therein (Cardiff, Swansea, and Newport), during this period. Out of a total 90 921 singleton births, 3242 were recorded as having congenital defects by the second anniversary of their birth. An examination of all recorded congenital malformations was carried out which revealed a total of 325 infants with two or more recorded defects (10% of the series). Of these, 232 (7%) were found to have two or more of the defects specified in the accompanying table. Certain categories of defect were excluded from the analysis: limb defects (other than those specified), owing to inadequate description at the time of recording; skin and miscellaneous defects, because of their minor nature; anomalads (a malformation together with its subsequently derived structural changes—e.g., Robin anomalad); and deformations (alteration in shape and/or structure of a previously normally formed part—e.g., torticollis—because they were not strictly malformations but rather primary structural defects arising from a localised error or morphogenesis). Case-finding was restricted to information collected by the second birthday, and not all the subjects came to routine necropsy, with the result that internal malformations such as kidney defect, diaphragmatic hernia, congenital heart-disease, and congenital dislocation of the hip are likely to be under-reported. The results that follow reflect a conservative estimate of the interrelation between the common congenital malformations recorded by the second birthday of a large population, most of whom came to necropsy if they died of a congenital malformation during this period.

Results

The cases included in this investigation all had two or more of the defects specified in the table. Fig. 1 shows the interrelations of the 232 cases included in this study. Each line represents a case possessing the two defects joined by that line. Where more than two defects coexisted, the defect with the highest percentage of associated defects (see table) was used as a base from which several lines were drawn. Since only one possible combination of lines is shown, fig. 1 is a conservative illustration of the extent of interrelation observed in this study.

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