A CLINICAL AND BIOCHEMICAL STUDY OF THE SUBNORMAL CHILD

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The subjects discussed in this paper are the results of an investigation primarily undertaken with a view to determining as far as possible some of the biochemical factors underlying, and predisposing to, the various forms of nephritis in children and adults. In the course of our investigations, it soon became evident that the problem resolved itself into a study of subnormal health or 'debility,' as predisposing to disease in general; or, in other words, into a study of the nature of the soil upon which disease flourishes. In this paper it is proposed to present the results of the investigation in so far as they relate particularly to children. The results of parallel observations on adults are being published elsewhere¹. It is hoped too, that some of the results obtained may form a standard upon which to base further observations on specific diseases as they occur in children, for not a few biochemical data, published as representing the variations peculiar to specific diseases, are in fact already present in that state of subnormal health. This so frequently precedes frank disease that it in part explains the similarity in the findings in diseases which are, in their pathogenesis and clinical nature, widely different.

Selection of cases.—The children investigated were all of the elementary day-school social class, who attended the medical out-patient department of one of us (A.A.O.), at Queen Mary's Hospital, for such minor symptoms as headache, lassitude, constipation, and bilious attacks. The actual symptoms for which advice was sought are given in Table 1. The children were all between the ages of six to twelve years inclusive. Those who had recently suffered from some acute illness, such as tonsillitis or measles, were not included.

The normal control children were selected from those patients who attended the casualty department for such conditions as ringworm, or uninfected cut fingers, and who appeared in every other way to be in perfectly normal health. A certain number of normals was also recruited from among the families of patients.

In this way it was found possible to divide the cases roughly into two groups clinically, the normals, and the subnormals or 'debilitated.' A certain amount of overlapping between the groups inevitably occurred, as it was desired particularly to investigate that borderland state between health and

disease, where the one passes almost imperceptibly into the other, but as will be seen later, subsequent biochemical observations to a large extent confirmed and justified this method of selection.

With few exceptions, a sample of blood for examination was taken between two and three hours after the last meal, the nature and constitution of which was ascertained. Measures were also adopted to ensure that each child was resting quietly for at least an hour before the blood was taken, and of course, in no case was the child aware that this operation was to follow. After considerable experience in obtaining blood from children, it is considered that the technique employed is so free from causing pain, and even but momentary apprehension, that changes in blood chemistry from this cause can be excluded. In a few instances where the element of fright was encountered, the case was excluded from the series.

Methods.—The following methods were used in this investigation :—

(1) Plasma bicarbonate, by the method of Van Slyke, Stillman and Cullen². Titration was carried to a constant end-point of pH=7.4. Phenol red was used as indicator. Results are expressed as molar concentration of bicarbonate.

(2) Plasma chlorides by the method of Claudius³, results being expressed as grammes of NaCl per 100 c.cm.

(3) Ketone bodies in the blood by the method of Van Slyke and Fitz⁴.

(4) Blood sugar (venous blood), by the method of Folin and Wu, results being expressed as milligrammes per 100 c.cm.

Procedure.—The following procedure was adopted, by means of which it is hoped that any personal bias in correlating the biochemical and clinical results, has been reduced to a minimum.

Each child was submitted to a thorough clinical examination by one of us (A.A.O.). This included inspection of the tonsils, etc., and a qualitative examination of the urine for albumen, sugar, and acetone bodies (Rothera and ferric chloride reactions). These results, with the history of the case, and notes on signs or symptoms, were entered up, and a diagnosis of either 'normal,' or 'subnormal' was made. The case was numbered and the child was given a card bearing this number only.

The collaborator (H.G.C.), who had not previously seen the child, then took, without undue compression, a sample of blood under paraffin from a vein in the arm into an oxalated centrifuge tube, which was correspondingly numbered. Estimations were performed within twelve hours of taking the blood, it having been found previously that none of the quantities estimated showed appreciable variations within this period. The blood sugar, however, was estimated immediately after taking the sample of blood.

Comparison of normal and subnormal children.

The main clinical features and chief symptoms of all the children investigated in this series are shown in Table 1. A few of the headings in this table require explanation. Cyclical vomiting ('C.V.') was diagnosed only when there was a clear history of recurrent 'bilious attacks,' preceded by listlessness, and accompanied by headache, vomiting and prostration, lasting 48 hours or more, and necessitating confinement to bed for this period. Debility ('D') was diagnosed in those children who were in subnormal health, but who did not give a clear history of attacks of cyclical vomiting. Children who were in a permanent state of debility, and who also suffered from cyclical vomiting, have been classed under the heading of C.V. only.

The nomenclature adopted in assessing the condition of the tonsils was as follows:—Cases in whom a complete tonsillectomy had been performed at least a year previously, were labelled (a); those in whom there was no history at any time of throat or ear trouble, and whose tonsils appeared to be normal, were labelled (b); and those who gave a history of repeated throat troubles, i.e., tonsillitis, 'sore throats,' cervical adenitis, with or without chronic otorrhœa, and whose tonsils either appeared unduly large, or definitely septic, were labelled (c). No doubt this classification is open to criticism, but it was the best that could be devised, and the number of cases is sufficiently large to make it at least of some value.

An attempt was also made to assess roughly the temperament of each child, that is, whether or not there was an undue tendency to nervousness, excitability, or the reverse. In doing so it was only possible to form an opinion from the behaviour of the child under examination, and from the parent's statements regarding this—neither of them very reliable guides.

Table 1 shows that 108 children were investigated, 38 normals, and 70 subnormals.

Table 2 compares the blood sugar, plasma bicarbonate, and chloride, in groups of normal and subnormal children.

From a consideration of these figures (Table 2), three important facts emerge. First, the plasma bicarbonate is considerably lower in the subnormal than in the normal children. In fact, a definite 'acidosis' is the rule in debilitated children, if the term 'acidosis' is defined as simply a decrease in the plasma bicarbonate, however produced. Such a definition does not necessarily imply any actual change in reaction, or pH, in the direction of increased acidity, in the strict chemical sense of the word. Secondly, this acidosis of debility, is associated with a slight, but definite, increase of the plasma chloride, compared with that of the normals. This point is of interest in view of the experiments of Haldane⁵ and his co-workers, who showed that after ammonium chloride ingestion, the plasma bicarbonate was decreased in exact proportion as the chloride content increased; and also because of the possibility of an accompanying increase in the water content of the body, a subject which has been more fully discussed elsewhere.¹ Thirdly, it is interesting to note that the blood sugar is practically the same in both groups. This is contrary to recent teaching, which asserts that the subnormal child shows a tendency to continued hypoglycæmia—an hypothesis which seems based on insufficient evidence.

One of us (A.A.O.) when working on the subject of cyclical vomiting in children some years ago, showed that this common disorder could generally be prevented or cured by increasing the allowance of sugar in the diet, and it was assumed that there was therefore a shortage of sugar in the blood. The term 'glycopenia,' which unfortunately is still used by some, was coined to describe these children. It is clear, however, from the evidence already presented, that this term is inaccurate, and should no longer be used in this connection. As has been pointed out before⁶, the essential feature of these cases appears to be a shortage of the glycogen stored in the liver, and perhaps

TABLE 1. COMPARISON OF NORMAL AND SUBNORMAL CHILDREN.

Case	Sex	Age	Height	Weight	Diagnosis	Chief symptom	Constipation	Headache	Tonsil history	Disposition
			ft. in.	st. lb.						
1	M	10			N			+	b	Bright
2	F	9			SN	C.V.		+		Dull
3	F	13			SN	Languor		+		Dull
4	M	8			SN	C.V.				Normal
5	F	6½			SN	C.V.		+	c	Normal
6	F	9			N	C.V.				
7	M	8			SN	C.V.				
8	F	7½			SN	Headaches		+		
9	F	7			SN	C.V.				
10	M	5½			SN	C.V.				Dull
11	F	6			SN	C.V.				
12	M	6		2 10½	SN	C.V.				
13	F	6		2 8½	N	Languor		—		Dull
14	M	8			SN	Languor		+		Dull
15	M	8	4 1½	4 0½	N					Normal
16	M	7½			SN	Languor				Dull
17	M	12			N	C.V.				
18	M	12			SN	C.V.		c	c	Normal
19	M	8			SN	Languor				Excitable
20	F	12			SN	C.V.			c	Excitable
22	M	13			SN	C.V.		+		
23	M	6			SN	C.V.				
24	F	12	4 6½	4 8½	N	C.V.		+	b	
25	M	12		7 3	SN		—	+	b	Dreamy
26	M	12		5 1	N	Recurrent abdominal pain.	—	+	b	Dull
27	M	10		5 1½	N	Recurrent abdominal pain.			b	
28	F	8			SN	Joint & limb pains		+	b	
29	M	5		2 6½	SN	C.V.		+	c	
30	F	13	4 4½	8 4½	SN	C.V.		++	a	
31	F	7	3 11	3 3½	N	Threadworms and C.V.			c	
32	F	10		4 0	N	Giddy attacks	+	+	b	Dull
33	F	8½		4 12	SN	C.V.			a	Excitable
34	F	6		1 13	SN	Wasting and C.V.			b	
35	M	11	4 5¼	4 8	SN	Abdominal pain and C.V.		+	a	
36	M	8			N				b	Normal
37	M	5½			SN	C.V.; drowsiness	—		c	Dull but excitable
38	F	8		3 1	SN	C.V. & excitability		+	b	Excitable
39	F	8		3 6	SN	Debility		—	a	Excitable
40	M	7	3 10	2 13½	N	Cough		+	c	Excitable

CLINICAL AND BIOCHEMICAL STUDY OF SUBNORMAL CHILD 153

Habit	Complexion	Remarks	Plasma NaHCO ₃	Plasma NaCl	Blood sugar	Rothera urine	Urinary chloride
Fat & flabby	Pasty	Suffers from C.V.	·0306			—	
Normal	Pasty		·0270			sl. +	
Normal	Good		·0270				
					·107		
Normal			·0280		·09	—	
Normal	Good		·0305		·108	—	
			·0277		·079	—	
			·0278		·093	—	
			·0267		·085	—	
Frail	Pale		·0275		·146	—	
			·0223		·078	—	
			·0288			+	
Normal	Pale	Growing pains	·0308		·089	—	
Normal	Pale		·0302		·125	—	
			·0292		·139	—	
	Pale		·0263		·101	—	
		Suffers from angio-neurotic oedema.	·0302			—	
Normal	Pale		·0290		·114	++	
Thin	Pale	Attended for ? chorea (not confirmed).	·0269		·130	—	
Thin	Pale	Appendicectomy 2 years ago	·0271		·116	—	
					·105		
					·075		
Normal	Good	Sick in trains, etc.	·0290		·083	—	
Fat & flabby	Good	Septic sores on body	·0262		·103	—	
Fat	Good		·0292	·614	·081	—	·985
Normal	Good		·0299		·077	—	
Thin	Pasty		·0287		·099	—	
Thin	Good		·0273		·090	+	
	Pale	Tonsillectomy 8 years before	·0303		·102	—	
			·0135		·016	—	
	Pale		·0290		·081	—	
	Pale	Tonsillectomy 1 year ago	·0281		·092	—	
			·0279			—	
	Pale	Appendicitis simulated. Ton- sillectomy 7 years ago.	·0285		·109	—	
Normal	Good		·0309		·102	—	
Normal	Pale		·0275		·093	+++	
Thin	Pale	Pains in limbs in damp weather	·0316		·079	—	
Thin	Pale	C.V. Tonsillectomy 3 years ago.	·0302			—	
Thin	Fair		·0280			—	

TABLE I—continued.

Case	Sex	Age	Height	Weight	Diagnosis	Chief symptom	Constipation	Headache	Tonsil history	Disposition
			ft. in.	st. lb.						
41	F	7		2 9	SN	Frequent colds		+	c	Normal
42	F	5½		2 13	SN	T's & A's—C.V.	—	+		Excitable but drowsy
43	M	12	4 9½	5 7	N			+		
44	F	9		3 1½	SN	Anorexia			c	Dull
45	F	9	4 4	3 10½	SN	Debility			b	Dull
46	M	8	3 10	3 2½	SN	Asthma	+		a	Dull but excitable.
47	M	8	4 2	4 1	SN	Pains in chest and	+	+	a	Dull
48	F	8	3 10	3 0½	N	Tram-sickness		+	c	Dull
49	M	13	4 4	4 10	SN	Headaches			b	Dull
50	F	10	4 5	4 1	SN	Abdominal pains	+	+	b	Excitable
51	F	5		2 7	SN	Frequent headaches		+	a	Normal
52	F	10		4 3	N	Frequent headaches			a	
53	F	13	4 10	6 0	N	Cough		+	c	Normal
54	M	8	4 1½	3 7½	N	? heart disease	—	—	b	Normal
55	M	5½	3 7¾	3 0½	SN	Languor, anæmia	+	+	c	Normal
56	M	7½	4 0¼	3 10½	SN	Boils and cough	—	+	b	Excitable
57	M	8½	4 1	3 7	SN	Lassitude	+	+	a	Excitable
58	M	8	3 11½	3 4½	SN	C.V.	+	+	b	Excitable
59	M	6¾		3 8	SN	Lassitude	+	+	c	Dull
60	M	9½		4 9½	N		—		a	Normal
61	M	8		2 13½	SN	Asthma	—	—	b	Excitable
62	F	9		4 7	SN	Abdominal pains	+	+	a	Excitable
63	M	10	4 5½	4 13	N	Boils	—	+	a	Excitable
64	F	10	4 4	3 13½	SN	Growing pains	—	+	a	Excitable
65	F	9	4 1¼	3 3	SN	Boils	+	+	c	Excitable
66	M	5½	3 8	3 0	SN	Anorexia	—	—	b	Normal
67	M	11	4 10	6 2	SN	C.V. and boils	—	—	b	Normal
68	M	8	4 3	4 6	SN	C.V.	+	+	b	Excitable
69	F	9		4 9	SN	Anæmia	—	—	a	Phlegmatic
70	M	11	4 3½	4 7	N	C.V.	—	+	b	Normal
71	M	13	5 3½		SN	Listlessness	+	+	a	Normal

CLINICAL AND BIOCHEMICAL STUDY OF SUBNORMAL CHILD 155

Habit	Complexion	Remarks	Plasma NaHCO ₃	Plasma NaCl	Blood sugar	Rothera urine	Urinary chloride
Thin	Pale		-0260			—	
Normal	Pale		-0269			+—	
Thin	Pale	Nervous—afraid of dark	-0321			+—	
	Pale	C.V.	-0248			+—	
	Pale		-0290			—	
Thin	Pale	Tonsillectomy 3½ years before, also previous C.V.	-0280	-594		—	
Thin	Pale		-0275			—	
Normal	Good	Nervous	-0314			—	
	Pale	Pains in feet. Old rheumatic heart.	-0282			+	
Thin	Good	Anorexia	-0287			—	
Normal	Good	Pains in all joints 2 years ago. Tonsillectomy 2 years ago.	-0268	-632		—	
Thin	Good	Nervous. Tonsils out a year ago.	-0312	-608		—	
Normal	Good	Sick in train	-0314	-632		—	-655
Normal	Good	Ac. rheumatism 2 years ago	-0287	-594		—	-702
Normal	Good	Train sickness. ? occasional C.V.	-0289	-638		—	-288
Normal	Pale	Train sickness and C.V.	-0277	-708		—	1·12
Thin	Pale	Train sickness. Tonsillectomy 1 year ago.	-0275	-623		—	1·08
Thin	Good		-0316	-611		—	-614
Normal	Pale		-0283	-608		+	-80
Normal	Good	Tonsillectomy 4 years ago	-0302	-597		—	-535
Normal	Good		-0277	-605		—	-807
Normal	Pale	Is train sick. Tonsillectomy 2 years previously, also suffers from C.V.	-0294	-620		—	-625
Normal	Good	Tonsillectomy 5 years pre- viously, also has cyclical vomiting.	-0296	-587		—	-526
Normal	Good	Suffers from C.V. Tonsillec- tomy 2 years before.	-0268	-605		—	-658
Thin	Pale	Train sick	-0264	-617		—	-646
Normal	Very pale		-0266	-611		—	-714
Normal	Good		-0271	-603		—	-453
Normal	Pale	Acute rheumatism twice last year. Growing pains and C.V. Heart normal	-0284	-620		—	1·14
Normal	Pale	Tonsillectomy 1 year pre- viously.	-0296	-623		—	-49
Normal	Good		-0294	-638		—	-439
Normal	Pale	Formerly C.V. Tonsillectomy 6 years previously	-0283	-594		—	-530

TABLE I—continued.

Case	Sex	Age	Height		Weight		Diagnosis	Chief symptom	Constipation	Headache	Tonsil history	Disposition
			ft.	in.	st.	lb.						
72	F	8	3	9	3 $\frac{1}{4}$	1	N	Headaches	—	+	c	Normal
73	F	10	3	6	4	3 $\frac{1}{4}$	N	Thinness	—	—	a	Excitable
74	F	13	4	2 $\frac{1}{4}$	4	1	SN	Pains in legs	+	—	b	Normal
75	M	9	4	2 $\frac{3}{4}$	4	6	N	C.V.	+	+	c	Normal
76	F	9			4	12	N	Nerves	+	—	c	Excitable & phlegmatic
77	M	12	4	10	5	1	SN	Headaches	—	+	b	Phlegmatic
78	F	7 $\frac{1}{2}$	3	9	3	3	SN	Headaches	—	+	c	Excitable
79	M	7	3	9 $\frac{1}{2}$	2	13 $\frac{1}{2}$	SN	Catarrhs	—	+	a	Normal
80	M	7	4	1 $\frac{1}{2}$	3	9	N	Nerves	—	+	b	Very excitable
81	M	7	3	8	2 $\frac{3}{4}$	13 $\frac{1}{2}$	N	C.V.	—	+	c	Normal
82	M	7	3	5 $\frac{1}{2}$	2	12 $\frac{1}{2}$	N	C.V. & headaches	—	+	b	Nervous
83	F	9 $\frac{1}{2}$	4	1	4	2	SN	C.V. and pains in legs and arms.	+	+	a	Normal
84	F	8	4	1 $\frac{3}{4}$	3	7	SN	Rheumatics	—	+	c	Excitable
85	F	8	3	10 $\frac{3}{4}$	2	13	SN	Abdomen pain and headaches	+	+	c	Excitable
86	M	8	4	3 $\frac{1}{2}$	4	0	SN	Cough and headaches.	—	+	b	Normal
87	F	8	4	2 $\frac{3}{4}$	4	2 $\frac{1}{2}$	N	Headaches	—	+	b	Excitable
88	F	7	4	4 $\frac{1}{2}$	4	8 $\frac{1}{2}$	N	C.V. and ? rheumatic pains	—	+	b	Normal
89	M	8 $\frac{1}{2}$	3	11	3	4	SN	C.V.	—	+	a	Normal
90	M	9	4	3 $\frac{1}{2}$	3	13 $\frac{1}{2}$	SN	Constipation	+	+	c	Phlegmatic
91	F	6			2	12 $\frac{1}{4}$	N	Night terrors	+	+	c	Excitable
92	F	8	4	1 $\frac{3}{4}$	4	0	N	T.T.	—	—	c	Excitable
93	F	11	4	6	4	12 $\frac{1}{4}$	N	Pains in back	—	+	c	Normal
94	F	8	3	11 $\frac{1}{2}$	3	6 $\frac{1}{2}$	N	Headaches and ? rheumatic pains.	—	+	b	Excitable
95	M	7 $\frac{1}{2}$			3	6 $\frac{1}{4}$	SN	Wasting, 'backwardness.'	—	+	c	Normal
96	M	7 $\frac{1}{2}$					SN	Pains in knees	—	—	b	Normal
97	M	6 $\frac{1}{2}$					N	C.V.	—	+	b	Normal
98	M	9	4	1 $\frac{3}{4}$	3	8	SN	Cough	+	+	b	Normal
99	F	7	3	10 $\frac{1}{2}$	3	0	SN	Cough	+	+	c	Excitable
100	F	6 $\frac{1}{2}$	3	5 $\frac{1}{2}$	2	6	SN	Fidgets	+	+	c	Excitable
101	M	9	4	5 $\frac{3}{4}$	4	2	N	Headaches	—	+	c	Normal
102	F	7	3	10	3	6	N	Urticaria papulosa	+	+	b	Excitable

CLINICAL AND BIOCHEMICAL STUDY OF SUBNORMAL CHILD 157

Habit	Complexion	Remarks	Plasma NaHCO ₃	Plasma NaCl	Blood sugar	Rothera urine	Urinary chloride
Normal	Good		-0293	-588		—	
Thin	Pale	Had growing pains. Tonsillec- tomy 5 years ago	-0295	-590		—	
Normal	Good	? subacute rheumatism ; slight systolic bruit apex.	-0270	-608		—	1.14
Normal	Pale	Train sick formerly	-0303	-605		—	1.16
Normal	Good		-0295	-600		—	.32
Thin	Pale	Train sick	-0303	-603		sl. +	1.12
Thin	Pale	Has cyclical vomiting	-0292	-629		sl. +	1.14
Thin	Pale	Tonsillectomy 3½ years pre- viously.	-0291	-588		++	1.08
Normal	Good		-0311	-604		—	-506
Thin	Good		-0292	-620		—	-111
Normal	Good	Extreme nervousness ? rheu- matic pains. Heart normal.	-0263	-611		—	1.18
Normal	Pale	Train sick. Tonsillectomy 1½ years ago. Urticaria papu- losa.	-0288	-614		—	
Thin	Good	Heart ? slightly enlarged, no murmurs.	-0270	-600		+-	-687
Normal	Pale	Train sick	-0308	-603		—	-06
Normal	Good	Wets bed	-0254	-614		—	-995
Normal	Good		-0288	-618		—	-664
Normal	Good	Heart normal	-0294	-603		—	1.14
Very thin	Good	Train sick. Tonsillectomy 3½ years ago.	-0228	-598		—	1.21
Normal	Pale		-0264	-607		++	-658
Normal	Good		-0294	-606		—	-589
Normal	Good		-0299	-603		sl. +	-679
Normal	Good	Train sick	-0306	-608		—	1.05
Normal	Good	Heart normal. Had ? rheu- matic fever 2 years ago.	-0296	-597		—	-326
Normal	Good		-0284	-611		sl. +	-401
Normal	Good		-0278	-591		—	
Normal	Good		-0300	-605		—	-393
Thin	Pale	Train sick. Systolic bruit at apex.	-0278	-576		—	-439
Thin	Pale	C.V.	-0245	-603		—	-907
Thin	Pale		-0257	-617		—	-890
Thin	Good		-0315	-611		—	-962
Normal	Good		-0299	-594		+	-965

TABLE I—*continued.*

Case	Sex	Age	Height	Weight	Diagnosis	Chief symptom	Constipation	Headache	Tonsil history	Disposition
			ft. in.	st. lb.						
103	F	12	4 6	4 7	SN	Anæmia	+	—	b	Phlegmatic
104	F	8			SN	Abdominal pains	—	+	a	Phlegmatic
105	M	6	3 7½	2 8½	SN	Abdominal pains	+	+	b	Excitable
106	M	10	4 4	4 3½	SN		+	—	c	Excitable
109	M	7	4 0½	3 8½	SN	Headaches		+	c	
110	M	6	3 9¼	3 1½	SN	? fainting attacks	+	—	b	Phlegmatic
119	M	8			SN	Asthma		+	a	

elsewhere, and not a deficiency of sugar in the blood. To summarize the findings in these two groups therefore, it may be said that in subnormal, or debilitated children, there is a definite acidosis, with a tendency to high plasma chlorides, and no evidence of hypoglycæmia.

TABLE 2.

COMPARISON OF NORMAL AND SUBNORMAL GROUPS.

Type	Blood sugar (mgrm. %)			NaHCO ₃ (molar)			NaCl (grm. %)		
	No. of	Av.	Range	No. of	Av.	Range	No. of	Av.	Range
Normal	11	95	77—139	38	·0299	·0263—·0321	24	·605	·587—·638
Subnormal	25	100·6	78—146	70	·0276	·0228—·0316	40	·610	·576—·659

Acidosis not due to ketosis.—Owing to the frequency with which acetonuria occurs in sick children, it has generally been assumed that the acidosis so commonly found in them, is due to excess of ketone bodies in the blood. In fact, the terms ketosis, acetonæmia, and acidosis, have long been used synonymously by clinicians. Frew⁷ has shown that something like 60% of children entering hospital for various conditions have acetonuria on admission, and this high incidence has been confirmed by others. But it must be remembered that all these children are sick, and many of them pyrexial. Acetonuria is almost constantly present too throughout the earlier stages of the acute exanthemata, such as scarlet fever, measles and diphtheria, and this is usually accompanied by some degree of acidosis (decreased plasma bicarbonate). As a rule, however, even in the acute exanthemata, the amount of acetone bodies in the blood is not sufficient to account for the

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Habit	Complexion	Remarks	Plasma NaHCO ₃	Plasma NaCl	Blood sugar	Rothera urine	Urinary chloride
Thin	Very pale	Train sick. Tonsillectomy 3 years previously.	·0278	·588		+	·994
Thin	Very pale	Simulating appendicitis	·0263	·614		sl. +	1·32
Thin	Good		·0280	·638		—	
Thin	Pale	Rheumatic fever 15 months ago. Mitral regurgitation.	·0276	·612		—	·396
			·0278	·588		—	1·26
Flabby	Pale		·0274	·601		—	·58
Normal	Good	Tonsillectomy 3 years previously.	·0272	·600		—	

whole of the decrease in the plasma bicarbonate : in other words, the whole of the acidosis is not due to ketone bodies*. Our observations on subnormal children suggest that the acidosis which is so frequently found, is practically never due to an associated ketonæmia. The evidence for this statement is as follows :—

(a) Of the total 108 cases, a positive Rothera reaction was found in the urine at the time of the blood examination in only 17 cases, 1 normal, and 16 subnormals (i.e., 16·5 per cent.). A positive ferric chloride test was present in none of the cases.

(b) Table 3 shows the chemical findings in the cases in whom a positive Rothera reaction was found in the urine. Comparing the figures in Tables 2 and 3 it is seen that in the acetonuric children, the average plasma bicarbonate was even a little higher than the average for the group (i.e., subnormals), namely, 0·0280 M, compared with 0·0276 M. It will also be observed that the blood sugar in the acetonuric and non-acetonuric children is practically the same, namely, 99 mgrm. per cent. in the former, and 100·6 mgrm. per cent. in the latter.

TABLE 3.

CASES SHOWING ROTHERA REACTION IN THE URINE.

Type	Blood sugar (mgrm. %)			NaHCO ₃ (molar)			NaCl (grm. %)		
	No. of cases	Av.	Range	No. of cases	Av.	Range	No. of cases	Av.	Range
Normal	—	—	—	1	·0299	—	1	·594	—
Subnormal	3	99	90—114	16	·0285	·0248—·0303	9	·608	·588—·632

It is clear then that in the debilitated child the presence or absence of acetonuria furnishes no guide to the degree of acidosis.

(c) In a study of a large number of cases of scarlet fever, diphtheria, measles, typhoid, and streptococcal tonsillitis⁸, in which repeated estimations of the plasma bicarbonate were carried out at regular intervals throughout the course of the illness, it was found, as noted above, that estimations of the total acetone bodies in the blood, even in the early and pyrexial stages of the disease during which acetonuria was present, showed that the acidosis was not nearly accounted for by the quantity of these substances present in the blood. Further, it was shown that in 25 per cent. of cases of scarlet fever, a late or delayed acidosis occurred, often as marked in degree as the primary or early acidosis; and that this late form of the condition, which generally occurred between the 15th and the 30th days of the disease, was not accompanied by acetonuria.

(d) In the apyrexial subnormal children with acetonuria in the present series, an attempt was made to estimate the total acetone bodies in the blood of four cases. In none of them was it possible to obtain any evidence of ketonæmia, in fact, no more precipitate was formed than in the 'blank' estimations. On these grounds therefore it is concluded that the acidosis of debility is not due to ketosis.

In this connection, it is of interest to note the difference in response to treatment with sugar, between the apyrexial subnormal child with or without acetonuria, and the child suffering from acute pyrexial disease, such as scarlet fever. In the former, with a normal blood sugar (see above), the giving of extra sugar by mouth usually produces a rapid and striking improvement in the general health⁶; whereas in the latter, where the blood sugar tends if anything to be above normal, not only does the giving of sugar usually fail to produce any improvement in the condition of the child, but it does not hasten the disappearance of acetone bodies from the urine. This suggests that during acute pyrexial disorders, there is inability to utilize the sugar; whereas in debility, although the blood sugar is normal (it is presumably of the first importance to maintain a normal concentration of sugar in the blood), the glycogen reserves of the body are on the verge of exhaustion.

Before leaving the subject of the biochemical variations in the two groups of children investigated, it may be of interest to cite a few of the individual cases, as illustrating some of the points already raised. It must be emphasized that although a decreased plasma bicarbonate is the rule in debilitated children, the degree of acidosis is not necessarily a measure of the unfitness in any given case, though there is a rough parallelism between the two factors. Case 82 looked in every way in the most perfect health, yet he had a plasma bicarbonate of only 0.0263 M. Case 18, on the other hand, looked extremely unwell, had a strong positive Rothera in the urine, and a plasma bicarbonate of 0.0290 M. The relation between the blood sugar and the degree of fitness is of special interest, in view of the current teaching to which reference has already been made. The children who appeared to be most unfit, and were pallid, exhausted, and lacking in energy and in interest in their surroundings,

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were not those with the lowest blood sugars, but, on the contrary, it was quite often found that their blood sugar was relatively high, even above normal. This was particularly noticeable in Cases 10 to 16, 18, 19, 20, 25, and others. Further, repeated estimations of the blood sugar at fortnightly intervals on some of these cases, failed to show any more 'instability' in the blood-sugar level in the one group than in the other. No useful purpose would be served by multiplying instances of these discrepancies, they all go to show that isolated observations of this kind are of little value, and that individual differences are so marked, that it is only in the study and comparison of groups of similar cases, that much can be learned by our present rather crude methods.

Relation of tonsillar disease to debility in children.

Disease of the tonsils and of the upper respiratory tract in general, has so often been considered as one of the chief causes of debility in children, that the removal of tonsils and adenoids is now regarded as almost a necessary preliminary, if not the only treatment required in these cases. It was considered desirable, therefore, to assess as far as possible the relation of tonsillar disease to the clinical and biochemical findings in the present series of cases.

In 94 children, 35 normals and 59 subnormals, the state of the tonsils, and the history of tonsillar disease, including sore throats, cervical adenitis, and chronic otorrhœa, were carefully noted. Table 4 shows the state of the tonsils as found in the healthy and debilitated children. The notation used is that described previously.

TABLE 4.
CONDITION OF TONSILS IN CASES EXAMINED.

	A.	B.	C.
Normal	5	16	14
Subnormal	17	21	20

A study of Table 4 shows that :—

- (1) of 30 normal children, approximately 50 per cent. had tonsillar disease, and 50 per cent. did not.
- (2) of 42 subnormal children, approximately 50 per cent. had tonsillar disease, and 50 per cent. did not.
- (3) of 22 children with previous tonsillectomy, 17 or 77 per cent. were still subnormal, that is, suffering from varying degrees of debility, from one to eight years after tonsillectomy, despite no history of subsequent throat disorders.

The chemical findings in 70 of the children in whom the question of tonsillar disease was studied, are shown in Table 5.

TABLE 5.
COMPARISON OF CASES WITH AND WITHOUT TONSILLAR DISEASE.

Type	Blood sugar (mgrm. %)			NaHCO ₃ (molar)			NaCl (grm. %)		
	No. of cases	Av.	Range	No. of cases	Av.	Range	No. of cases	Av.	Range
(b) Tonsils healthy	8	88	77—103	36	·0287	·0254—·0316	23	·607	·576—·638
(c) Tonsils unhealthy	7	99·7	89—116	34	·0286	·0245—·0315	22	·619	·588—·632

It will be seen that there is no significant difference between those with, and those without, tonsillar disease, as regards the chemical findings in the blood.

Table 6 shows the results of similar observations on the 22 children who had had a previous tonsillectomy. Here again, it will be seen that there is very little difference between subnormal children who have had a previous tonsillectomy, and subnormal children who have not, though it must be admitted that the plasma bicarbonate is a little higher in the former, than in the latter. It is interesting in this connection to recall the evidence regarding the results of tonsillectomy in such specific diseases as acute rheumatism and acute nephritis. It has been shown by many investigators, that this operation is of extremely doubtful value in both diseases, especially as regards recurrences, indicating that this operation does not generally lead to sufficient improvement in general health to protect against recurrence of the disease, once infection has occurred, although in both these diseases the tonsils themselves probably provide the primary portal of entry for the infection.

TABLE 6.
TONSILLECTOMIZED CASES.

Type	Blood sugar (mgrm. %)			NaHCO ₃ (molar)			NaCl (grm. %)		
	No. of cases	Av.	Range	No. of cases	Av.	Range	No. of cases	Av.	Range
Normal	—	—	—	4	·0301	·0312 ·0295	5	·596	·608 ·587
Subnormal	3	101	109 92	18	·0279	·0303 ·0228	13	·610	·632 ·588
Total	3	101	109 92	22	·0290	·0312 ·0228	17	·603	·632 ·587

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Paterson and Gray⁹ showed that in a series of subnormal children, marked improvement in general health, and increase in weight, was found up to 6 months after tonsillectomy, a result which, at first sight, strongly suggests the importance of tonsillar disease as a cause of chronic debility in children. The Board of Education¹⁰, however, found that if a series of subnormal children in whom the tonsils had previously been removed, were followed up for a considerably longer period after operation than six months, the initial improvement noted by Paterson and Gray, was not maintained. Further evidence relating to this problem has been reported by one of us (H.G.C.) elsewhere¹¹.

The balance of evidence would seem to suggest that tonsillar disease is not such an important factor in the production of chronic debility in children as is usually supposed, and that tonsillectomy is an operation which is often performed unnecessarily.

Relation of debility to cyclical vomiting.

In a paper already referred to above⁶, it was pointed out that cyclical vomiting was a disorder met as frequently amongst the children of the hospital classes as amongst those of the well-to-do. This, again, is contrary to the usual teaching. It was also stated that cyclical vomiting occurred in about 30 per cent. of all elementary school children. The evidence for this was based on a history of the symptom-complex described above in 500 consecutive children between the ages of 6 to 12 years, attending hospital for minor disorders. In actual fact, cyclical vomiting, as judged by these standards, occurred in 45 per cent. of the series referred to, but in order to eliminate possibility of error arising from the necessity of asking leading questions in a number of instances, an allowance of 15 per cent. was made. The figure of 30 per cent., therefore, may be taken as a conservative estimate of the frequency of this disorder in the children of the hospital classes. E. C. Warner, working in the Children's Department at Guy's Hospital, informs us in a personal communication that, adopting the same criteria as we had done, he had found that 20 per cent. of a series of 300 children out-patients, between the ages of 3 to 12 years inclusive, suffered from major attacks of cyclical vomiting. As this disorder does not usually appear in its most typical form before six years of age, it is clear that, allowing for this, 30 per cent. is again a fair estimate of the frequency of cyclical vomiting in children of this social class.

In the present series of 108 children, a definite history of major attacks of cyclical vomiting was obtained in 47 cases. Table 7 compares the biochemical findings in 16 children with a history of cyclical vomiting, who had not recently had an attack, and 14 subnormal children who gave no history of this disorder.

These results show that there is no biochemical difference, in respect of the observations made, between these two groups. Of the 39 normal children, 13 to 33 per cent., gave a history of cyclical vomiting, and of the 70 subnormal children, 35 or 50 per cent., suffered from this disorder. These figures, though not very large, suggest that cyclical vomiting is more often found in the unfit,

than in the fit child, and still further emphasizes the clinical fact, hitherto overlooked, of the frequency with which this condition is met in children of the poorer classes.

TABLE 7.

COMPARISON OF CASES SHOWING CYCLICAL VOMITING WITH SUBNORMAL CASES WITHOUT IT.

Type	Blood sugar (mgrm. %)			NaHCO ₃ (molar)			NaCl (grm. %)		
	No. of cases	Av.	Range	No. of cases	Av.	Range	No. of cases	Av.	Range
C.V.	16	99.7	75—146	30	·0277	·0228—·0316	10	·610	·576—·638
G.	14	98.6	77—139	35	·0279	·0254—·0316	17	·601	·588—·623

It is a matter of common observation, referred to by all authorities on the subject, that cyclical vomiting is most apt to occur and to be most intractable, in the highly-strung, excitable child, and to this extent the biochemical results given in Table 7, may be regarded as typical of the nervous child; but as mentioned elsewhere⁶, cyclical vomiting is a disorder which occurs perhaps in its most dramatic form in the child of nervous make-up, but it is by no means entirely confined to such. This is opposed to the view expressed by some that the acidosis and disturbances of carbohydrate and fat metabolism, with which it is said to be associated, constitute a biochemical picture peculiar to the nervous child.

It is at least apparent that cyclical vomiting is a disorder of very frequent occurrence amongst children of all social classes; that children who suffer from it do not differ in respect of the biochemical observations made herein, from those who do not, and that it is not the prerogative of the nervous child.

Observations on the treatment of debility in children.

About seven years ago, one of us (A.A.G.), when collecting cases of cyclical vomiting for investigation in the Children's Department at Guy's Hospital, observed that those children who had been given extract of malt, largely with the object of securing regular attendance at out-patients, ceased to have further attacks of the disorder. This at once suggested that sugar in some form was the needed antidote. This hypothesis was rendered more probable, by the fact that, in an undue proportion of these cases, it was noticed that sugar was being withheld, as far as possible, as the mother had been told that it was 'bad for the teeth,' 'brought the child out in spots,' or, 'was bad for children,' a doctrine which incidentally, is still held, and acted upon, even in some of the best public schools in the country. There is, of course, no adequate scientific evidence for any of these suggestions.

In order to test further the action of sugar in preventing cyclical vomiting, a group of 30 children suffering from this disorder was given extra sugar,

and kept under observation for from one to three years, and as a result, it was found that with very few exceptions, attacks of cyclical vomiting ceased to occur. It became apparent too, that not only was cyclical vomiting easily prevented by this simple and harmless measure, but that a large number of the other common symptoms of debility in children, such as headaches, recurrent abdominal pains, constipation, 'growing pains,' pallor, and undue fatiguability, were also cured, and prevented, and that the giving of extra sugar, in any form, quite frequently resulted in a rapid and marked improvement in the general health, spirits, and appearance of the child. In fact, without any other form of treatment, or alteration in the daily régime, a pale, dispirited, ailing child, would often be converted into a high spirited, healthy, and happy being. This form of treatment was later adopted by Dr. H. C. Cameron^{13, 14}, and he has confirmed the beneficial results obtained. As pointed out elsewhere⁶, cyclical vomiting occurs in three main forms:—the classical cyclical, or periodic vomiting, cyclical diarrhoea, and cyclical pyrexia, each of which may occur singly or together. Quite early in the investigation, it was noticed that there was also a recurrent, or cyclical, 'respiratory' group, the symptoms of which were indistinguishable from those of ordinary bronchial asthma. In view, however, of the well known difficulty of differentiating between some cases of asthma and recurrent bronchitis in young children, it was considered unwise to assert that asthma could be successfully treated by sugar, but it soon became obvious that these cases were, in fact, true examples of bronchial asthma, and that at least in some of them, sugar was an effective prophylactic. Although it has been shown that the most common and constant biochemical feature of debility in children is an 'acidosis,' it is a remarkable fact that, in our experience, the giving of alkalies by mouth does not in any way lead to improvement in the condition, or in any of its numerous and varied symptoms. As far as we have been able to ascertain, also, alkalies are quite without value in the treatment or prevention of cyclical vomiting and asthma in children. There is, however, one point in this connection, which should be borne in mind, before concluding that alkalies are without value in these cases, and that is, the question of increased liability to infection, where some degree of acidosis is present. Cameron¹² asserts that children suffering from acidosis are predisposed thereby to infection. We have long had this possibility in mind, and have endeavoured to obtain evidence upon the question, but at present, it can only be said that no conclusions have been reached. If the type of acidosis referred to here should be shown to predispose to infection, then it is possible that the use of alkalies in these cases may be justified.

Conclusions.

(1) The state of subnormal health in children, usually called 'debility,' is generally associated with some degree of 'acidosis,' defining this as a reduction of the plasma bicarbonate only.

(2) Debility in children is not commonly accompanied by hypoglycæmia, and the term 'glycopenia' is inaccurate, and should not be used to describe these cases.

(3) The acidosis of debility is not generally due to an associated acetonæmia or ketosis.

(4) Ketosis in children is not generally associated with hypoglycæmia.

(5) Tonsillar disease is not the most common cause of debility in children, and tonsillectomy is an operation which is often performed unnecessarily.

(6) Cyclical vomiting is a disorder which occurs with great frequency amongst children of the so-called hospital classes, the incidence in this class being about 30 per cent. of all children between the ages of 6 to 12 years inclusive.

(7) The biochemical picture associated with disturbances of the carbohydrate and fat metabolism, acetonæmia, etc., is not more frequently found in 'nervous,' than in other subnormal children.

(8) There is no specific biochemical picture peculiar to the 'nervous' child.

(9) There is no evidence that alkalis are of value in the treatment of debility in children.

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