Lack of Temperature Control in Infants with Abnormalities of Central Nervous System

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Cross, K. W., Hey, E. N., Kennaïrd, D. L., Lewis, S. R., and Urich, H. (1971). *Archives of Disease in Childhood*, **46**, 437. **Lack of temperature control in infants with abnormalities of central nervous system.** The temperature control of 11 infants with severe abnormalities of the central nervous system has been investigated. 4 were normothermic and 7 poikilothermic. Necropsy of the latter showed that either the hypothalamus was absent or disorganized, or the long tracts through the brainstem were unidentifiable, or in one case interrupted by a cervical myelocele. The lateral horn cells, sympathetic nervous system, and brown fat appeared normal.

Where the normal reflex responses to warm and cool stimuli were absent, direct stimulation of the effector organs was attempted. Noradrenaline both stimulated heat production and constricted the peripheral skin vessels. Surprisingly, local application of pilocarpine or acetyl choline failed to stimulate the sweat glands which appeared normal at necropsy.

Temperature control is a complex mechanism depending on the integrity of the nervous system and its full co-ordination. Much of our knowledge of temperature control is derived from animal experiments. Occasionally loss of temperature control occurs in man as a result of neurological disorders (Davison and Friedman, 1937; Cooper, 1965) and this has allowed some of the underlying mechanisms to be studied.

Congenital malformation of the central nervous system may also be associated with defective temperature control. Cross *et al.* (1966) described the lack of temperature control in an anencephalic infant, and Gubbay (1967) in obstructive hydrocephalus.

We report here observations on temperature control in 11 infants with abnormalities of their central nervous systems. The plan of the investigation has been to test the effect of an adequate stimulus (heat or cold) on the effector organs. Where an effect was lacking we have sought to stimulate the effector organ directly with the appropriate chemical agents. Finally, where reflex effects were absent, it was only possible approximately to localize the defect in the reflex arc by necropsy. Parental permission was obtained for all

investigation either by the clinical staff or the investigators.

Methods

Oxygen consumption, heat storage, evaporative water loss, skin temperature, and heat flow through the skin were measured using the methods developed and described by Hill and Rahimtulla (1965), Hey (1969), and Hey and Katz (1969, 1970). Oxygen consumption was measured with the closed circuit equipment during infusions of saline and noradrenaline in saline. Saline was infused at a rate of 0.5 to 1.5 ml/min into the saphenous or umbilical vein from a motor driven syringe. L-noradrenaline was made up in a proprietary medium ('Levophed' Bayer Products Ltd.) being added when required to give a dose of 0.4 or 0.8 µg/kg min. The indirect heating test of Lewis and Pickering (1931), as modified by Young (1962) to study infants, was undertaken on 5 of these infants. A thermal sweat response was tested using starch paper previously impregnated with vapourized iodine and also with Quinizarin powder (Guttman, 1940). Pilocarpine iontophoresis (Gibson and Cooke, 1959) was also studied on the forearm or thigh in some of these infants.

Results

For clarity the results will be set out in two main groups, depending on the presence or absence of normal temperature control.

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Group I: Normothermic infants with normal hypothalamus and connexions. Four infants will be described in this group: 3 of these infants had hydrocephalus and the fourth an occipital meningoencephalocele. Infants 1 and 4 have died. Infants 2 and 3 are living, after the insertion of a valve, but are mentally retarded. All 4 were female.

Infants 1 and 2 were sibs with hydrocephalus. Infant 1 was born at 32 weeks' gestation weighing 1.2 kg and developed signs of hydrocephalus at 4 weeks of age. A Spitz-Holter valve was inserted at the age of 7 weeks but she subsequently developed staphylococcal septicaemia and died. Her sib (Infant 2) was born at 36 weeks' gestation weighing 1.5 kg, and began to develop signs of hydrocephalus at 2 weeks of age. After the insertion of a valve she is progressing but is moderately retarded.

Infant 3 was born 18 days after the expected date of delivery weighing 2.9 kg. and developed signs of hydrocephalus at 1 week of age. After insertion of a valve she made satisfactory progress but was subsequently found to be grossly mentally retarded.

Infant 4 was born at term weighing 2.5 kg with an occipital meningoencephalocele. She died aged 31 days.

Investigations. Resting oxygen consumption in a neutral thermal environment was normal in all 4 babies, as was the increase in oxygen consumption when the environmental temperature was lowered to 29 °C for 20–30 minutes. When motionless and apparently asleep after sedation (chloral hydrate, 60–80 mg/kg) this increase in heat production was reduced, but was significantly raised as compared with the value obtained in a thermoneutral environment.

All 4 infants sweated normally to thermal stimuli at the time of investigation, and 3 infants who were studied showed the normal changes in thermal circulation index in response to variation in environmental temperature.

Summary of postmortem findings.

Case 1. Internal hydrocephalus of lateral ventricles—with complications arising from sepsis following ventriculo-jugular drainage. Cerebral tissue reduced to 0.5–1 cm in thickness. Other brain structures normal.

Case 4. Asymmetrical herniation of occipital lobes into encephalocele. Diencephalic structures, including hypothalamus, in cranial cavity and normal in structure, apart from partial fusion in midline. Brainstem elongated and kinked, with main nuclear masses and fibre tracts identifiable, situated

wholly within cranial cavity. Cerebellum hypoplastic and extensively scarred, partially herniated into encephalocele.

Group II: Poikilothermic infants with absent hypothalamus, or hypothalamus present but with defective or absent connexions with lateral horn cells. Seven infants will be described in this group, 2 of which were suffering from anencephaly and the remaining 5 from occipital encephaloceles or cervical myelocele. All these infants appeared to possess no thermoregulatory ability and all were found to be hypothermic while in hospital.

Two term female anencephalic infants were studied (Cases 10 and 11). One 3 kg infant was studied when 48 hours old and the second, a 2 kg infant was studied on three separate occasions when between 6 and 60 hours old. Their condition was satisfactory at the time of investigation though both infants were hypothermic on arrival in hospital. There were no signs of respiratory distress or central cyanosis.

Four mature female infants with large occipital encephaloceles (Cases 5–8) and one mature male infant with a cervical meningomyelocele were studied (Case 9).

Investigations. Resting oxygen consumption in a neutral thermal environment was low in all these infants while they were hypothermic but increased progressively as the rectal temperature rose in a warm environment towards a normal level. The rate of a chemical reaction rises exponentially with increasing temperature, the relation being described by the ratio of rates after a 10 °C change in temperature (Q_{10}) (Table I). In infant 5 an exponential relation of this type was observed on

TABLE I
 Q_{10} Obtained on 6 Infants During Rewarming

Diagnosis	Case No.	Q_{10}	r	n	Tr
Anencephalic	10	2.54 ± 0.24	0.97	8	33–37
	11	1.79 ± 0.93	0.93	7	31–37
Encephalocele	5	2.13 ± 0.12	0.98	10	34–38
		2.06 ± 0.19	0.95	9	35–38
		2.05 ± 0.18	0.95	8	35–37
	6	1.55 ± 0.11	0.79	26	33–38
	7	2.14 ± 0.14	0.98	5	31–38
	8	2.05 ± 0.33	0.98	60	34–38

Note: Values for Q_{10} with the estimated error of the mean and correlation ratio (r) for 6 infants with congenital defects of the brain studied in a neutral thermal environment, together with the number of observations on which the estimates are based (n) and the range of rectal temperature studied (Tr) in °C. Infant 5 with an encephalocele was studied on three occasions in the first 9 weeks of life.

3 separate occasions (Fig. 1); the temperature coefficient was similar in each case but absolute values of oxygen consumption were different.

FIG. 1.—Oxygen consumption plotted against rectal temperature of infant No. 5 when the infant was being warmed after being found hypothermic in the ward on three different occasions. ● observations made at 34 hours of age (possibly during fitting activity); ▲ observations at 60 days of age; ▼ observations at 24 days of age while mildly sedated with chloral. The lines are the lines of best fit of $\dot{V}O_2$ upon rectal temperature (see Table II).

No increase in oxygen consumption occurred when body temperature was normal and environmental temperature was lowered to 28–29 °C for a period of 20–40 minutes. The absence of any increase in heat production could have been due to a block in any part of the reflex arc. Responses to skin stimuli were present, so it seemed reasonable to suppose that the afferent side of the reflex arc was functioning, though it was impossible to test this practically. To confirm that the defect in temperature control resulted from a lesion in the nervous system it was necessary to show that the effector organ was normal and capable of responding to direct stimulation. We therefore tested the ability of three babies to increase their heat production by infusing noradrenaline at a rate of 0.8 $\mu\text{g}/\text{kg}/\text{min}$

for 15 to 30 minutes. In infant 5, a catheter was inserted into the umbilical vein but no increase in oxygen consumption was observed after intravenous noradrenaline infusion. Subsequent x-ray angiography showed that the catheter tip had passed into the portal system and along the splenic vein. Therefore in infants 6 and 7, it was decided to insert the catheter through the saphenous vein so that its tip lay in the inferior vena cava. A 50% increase in oxygen consumption was observed in infant 6 (Fig. 2) and a significant increase was also seen in infant 7.

FIG. 2.—The oxygen consumption and rectal temperature of infant No. 6 before, during and after infusion of noradrenaline at 0.8 $\mu\text{g}/\text{kg}/\text{min}$ (indicated by hatching). The mean oxygen consumption together with the standard deviation of the observation is shown for approximately 10-minute periods. Note that the fall of rectal temperature is halted during the infusion.

Noradrenaline infusion (1.6 $\mu\text{g}/\text{kg}/\text{min}$ for 25 minutes) also caused the serum glycerol to rise from 222 to 339 $\mu\text{M}/\text{l}$., the non-esterified fatty acids to rise from 300 to 600 $\mu\text{M}/\text{l}$., and the serum glucose to rise from 63 to 148 $\mu\text{g}/100\text{ ml}$ in infant 7. Exposure to a cool environment (31 °C for 2 hours while naked) on the other hand caused no change in serum glucose, but resulted in the rectal temperature falling to 35 °C while the serum glycerol fell to 92 $\mu\text{M}/\text{l}$ and the fatty acids fell to 180 $\mu\text{M}/\text{l}$. (Dr. C. N. Hales, Department of Biochemistry, Cambridge).

Vasomotor responses to changes in environmental temperature were also studied in 5 infants. The indirect heating test of Lewis and Pickering (1931) was negative and no change in the thermal circulation index could be detected and no peripheral

Lack of Temperature Control in Infants with Abnormalities of Central Nervous System 441

servations on 11 Infants

Poikilothermic						
5	6	7	8	9	10	11
1-65 128	0-3 6	13-20 58	2-6 12	1-2 67	0-3 3	0-2 2
Occipital encephalocele hind-brain malformations; brain-stem in hernial sac				Hydrocephalus Arnold-Chiari malformation; cervical myelocele	Anencephaly	
9 -5 2	-4 — 51	-6 — 26	2 -23 —	19 — —	2 — —	-3 — —
Negative —	Negative Negative	Negative Negative	— Negative	— Negative	Negative —	Negative Negative
Negative —	Negative —	Negative Negative	— Negative	— Negative	— —	Negative —
10.9 11.3	10.5 11.0	8.3 10.5	9.9 11.7	9.9 —	— —	9.3 9.3
2.3 2.5	2.2 2.0	3.6 3.9	— —	— —	2.1 2.1	— —
Negative	Negative	Negative	—	—	—	Negative

mamillary bodies and their connexions. Brain-stem wholly within cranial cavity, but grossly malformed, particularly at upper end, with few identifiable landmarks. Total absence of cerebellum.

Case 9: Gross hydrocephalus. Structure of diencephalon partially obscured by large islands of ectopic grey matter. Arnold-Chiari malformation of hind-brain. Large myelocele in lower cervical and upper thoracic region with interruption of long tracts.

Cases 10 and 11: Anencephaly; no organized structures above level of brainstem.

Discussion

The evidence assembled is consistent with the view that lack of temperature control was associated with developmental defects in the region of the hypothalamus or its connexions. The three infants who presented with raised intracranial pressure, cortical thinning, and dilated ventricles in the neonatal period had normal thermoregulatory function in contrast to the older child reported by Gubbay (1967). The lack of temperature control in the two cases of anencephaly confirms and

amplifies the findings of Cross *et al.* (1966). It seems probable that similar findings would be encountered in some cases of hydranencephaly (Watson, 1944). The prognosis in cases of cranium bifidum varies greatly (Barrow and Simpson, 1966), and it should perhaps be stressed that temperature control usually seems to be normal in infants without microcephaly or extensive herniation of brain tissue even when the sac is large.

Temperature control can be disturbed following intracranial haemorrhage at birth (Mestyan, 1962), but significant haemorrhage was found only in one infant with an encephalocele at necropsy, and this was thought to have been a sudden terminal event. To show conclusively that the lack of temperature control was due to the central nervous defects found at necropsy it would be necessary to show that the afferent and efferent arcs of the various reflexes were intact. It was unfortunately not possible to show that sensory function was unequivocally normal but it was possible to show that most of the effector organs were functional.

Noradrenaline infusion showed that two of the babies with a large occipital encephalocele were capable of increasing their heat production as in

normal babies (Karlberg, Moore, and Oliver, 1962, 1965) while the changes in blood chemistry are consistent with the view that this is due to increased metabolism in brown adipose tissue (Dawkins and Scopes, 1965; Persson and Gentz, 1966). The presumed increase in blood pressure during the same infusion and the fall in heat flow through the skin similarly indicate that the blood vessels were able to constrict on direct stimulation. The absence of any increase in heat production in infant 5 can probably be attributed to the breakdown of the infused noradrenaline during its passage from the portal system through the liver.

Hypothermia is a common accompanying sign in the infants who failed to increase their heat production on cold exposure. In infant 8, a high minimal oxygen consumption was obtained; this high value may have been due to the presence of seizure activity, as both the $\dot{V}O_2$ and seizure activity were substantially lowered following sedation. These infants are able to achieve high levels of basal heat production and consequently are less vulnerable to hypothermia. This may explain why the presence of hypothermia has not been more frequently recorded in these infants.

Sweat function. The absence of any thermal sweat response in five of the infants was in keeping with the lack of other evidence of temperature control. What was quite unexpected was the lack of any response to direct chemical stimulation, as Foster, Hey, and Katz (1969) showed that all normal babies sweat at birth, both to thermal and to chemical stimulation, unless born at least two or three weeks before term. The response to pilocarpine is lost after damage to the post-ganglionic sympathetic nerves, but is normally retained after preganglionic sympathectomy (Hyndman and Wolkin, 1941). The integrity of the postganglionic nerves was unfortunately not tested, but there was no reason to suppose that these nerves were abnormal. Neither was it thought safe to test the response of the glands to direct local heat (Randall, 1947). The sweat glands appeared normal on routine histological examination after death, but few histological changes normally occur in denervated non-functioning glands (Silver, Montagna, and Versaci, 1964), apart from a reduction in cholinesterase.

Investigation of a larger group of babies with defects of central nervous system at birth has since confirmed these findings (Foster, Hey, and O'Connell, 1971) and also shown that, in at least a proportion of infants lacking any sweat response to thermal or chemical stimuli, an axon reflex can

be elicited in the postganglionic sympathetic nerve with acetylcholine (Coon and Rothman, 1940) or faradic stimulation (Lewis and Marvin, 1927). It seems therefore that full functional maturation of sweat glands at birth probably depends on an intact central innervation *in utero*.

Basal metabolic rate. The minimum oxygen consumption of the normal human infant asleep in a neutral thermal environment rises significantly during the first few days after birth. The initial rise is rapid in the term infant, but occurs more gradually in babies weighing under 2 kg. The sharp rise in the first two days of life has been noted in a number of species (Mott, 1963) and its cause has been the subject of speculation. Alexander (1961) considered that it might be related in part at least to the onset of feeding. Cross *et al.* (1966) noting that the minimum oxygen consumption of the anencephalic infant they studied was rather less than that normally found in term infants of the same age and weight, speculated that some of the rise could be due to an increase in central nervous activity in normal infants after birth, as brain tissue is known to have a high oxygen consumption. We have had the chance to study 2 infants with anencephaly and 5 infants with severe encephalocele and little normal cerebral cortex during first three days of life. These infants were not fed during this time though they were given a little water by mouth. Minimum oxygen consumption was nearly 7 ml/kg min (which is within normal limits) in 4 infants on the 3rd day of life, and in 2 infants there was a significant rise in minimal oxygen consumption during first 48 hours after birth. It seems unlikely therefore that either feeding or cerebral function is decisive in influencing the large change in basal metabolism normally observed in the first 3 days of life.

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