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

K. W. CROSS, E. N. HEY, D. L. KENNAIRD, SHEILA R. LEWIS, and H. URICH
From the London Hospital Medical College, London

Cross, K. W., Hey, E. N., Kennaird, 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 myelocoele. 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 (Guttmann, 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.
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 staphlococcal 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. Dienecephalic 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: Polikilothermic 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 myelocoele. 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>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q(_{10}) Obtained on 6 Infants During Rewarming</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case No.</th>
<th><strong>Q(_{10})</strong></th>
<th>(r)</th>
<th>(n)</th>
<th>(T_r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephalic</td>
<td>10</td>
<td>2·54±0·24</td>
<td>0·97</td>
<td>8</td>
<td>33–37</td>
</tr>
<tr>
<td>11</td>
<td>1·79±0·93</td>
<td>0·93</td>
<td>7</td>
<td>31–37</td>
<td></td>
</tr>
<tr>
<td>Encephalocele</td>
<td>5</td>
<td>2·13±0·12</td>
<td>0·98</td>
<td>10</td>
<td>34–38</td>
</tr>
<tr>
<td>6</td>
<td>2·06±0·19</td>
<td>0·95</td>
<td>9</td>
<td>35–38</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1·55±0·11</td>
<td>0·79</td>
<td>26</td>
<td>33–38</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2·05±0·33</td>
<td>0·98</td>
<td>60</td>
<td>34–38</td>
<td></td>
</tr>
</tbody>
</table>

\(Q_{10}\) 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 \((T_r)\) in °C. Infant 5 with an encephalocele was studied on three occasions in the first 9 weeks of life.

**Note:**
Lack of Temperature Control in Infants with Abnormalities of Central Nervous System

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

![Graph](image1)

**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 \( VO_2 \) 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 µg/kg 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.

Noradrenaline infusion (1·6 µg/kg min for 25 minutes) also caused the serum glycerol to rise from 222 to 339 µM/l, the non-esterified fatty acids to rise from 300 to 600 µM/l, and the serum glucose to rise from 63 to 148 µg/100 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 µM/l and the fatty acids fell to 180 µM/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
vasodilatation or increase in hand temperature could be detected when the trunk was warmed and body temperature rose to 38°C. A very significant and sustained drop in heat flow through the hand was however observed in 2 infants during noradrenaline infusion in a warm environment.

Insensible water loss was measured in 5 of these infants and was normal in an environment of 33–34°C, but no increase in evaporative loss occurred in a warm environment (≥36°C) even when the rectal temperature reached 37.8°C. None of these infants sweated anywhere on the body in an environment of 36°C and no sweat secretion could be elicited by pilocarpine iontophoresis in 4 of these infants or by acetylcholine in a further 2.

In infant 8 (occipital encephalocele), it was observed that the values of oxygen consumption were high in a neutral environment when the rectal temperature was within normal limits. This particular infant had frequent seizures so it was decided to sedate the infant with chloral hydrate (50 mg/kg) and to repeat the estimations. There was a significant decrease in oxygen consumption and the frequency of the seizures on sedation. On a further occasion the infant was given intravenous diazepam (0.1 mg/kg) and again a decrease in oxygen consumption and frequency of seizure activity was observed. The oxygen consumption again increased when the drug was no longer active. Infant 5 was also noted to have a number of small seizures and this may be the explanation of the variable values of oxygen consumption obtained (Fig. 1). Table II summarizes the findings in the two groups of babies.

Pathology. All 7 infants died and necropsies were performed.

Cases 5, 7, and 8: Extensive, generally asymmetrical, herniation of cerebral hemispheres into encephalocele. Hypothalamus distorted, often asymetrically, but main landmarks identifiable at least in one hemisphere. Gross malformation of hind-brain with vestigial cerebellum and grossly deformed brainstem displaced into hernal sac. Few identifiable fibre tracts and brainstem nuclei. Constriction of structures lying in hernal neck with secondary vascular lesions or scarring.

Case 6: Extensive herniation of cerebral hemispheres. Hypothalamus somewhat distorted, but all main landmarks identifiable with exception of

---

**Table II**

<table>
<thead>
<tr>
<th>Infant</th>
<th>Normothermic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age when studied (dy)</td>
<td>1-50&lt;br&gt;103</td>
</tr>
<tr>
<td>Age at death (dy)</td>
<td>2-17&lt;br&gt;9</td>
</tr>
<tr>
<td>Pathology</td>
<td>Internal hydrocephalus&lt;br&gt;Occipital encephalocele; brainstem in cranial cavity</td>
</tr>
<tr>
<td>Metabolism</td>
<td>% increase in VO₂ above BMR at 29°C</td>
</tr>
<tr>
<td></td>
<td>% increase with chloral hydrate at 29°C</td>
</tr>
<tr>
<td></td>
<td>% increase in VO₂ to 0.8 µg/kg min I.V. noradrenaline</td>
</tr>
<tr>
<td></td>
<td>Sweat response to: (a) thermal stimuli</td>
</tr>
<tr>
<td></td>
<td>(b) Chemical stimuli</td>
</tr>
<tr>
<td></td>
<td>Total evaporative water loss (g/m² hr)</td>
</tr>
<tr>
<td></td>
<td>Vasomotor control</td>
</tr>
<tr>
<td></td>
<td>Response to indirect heating test</td>
</tr>
</tbody>
</table>

---

Cross, Hey, Kennaird, Lewis, and Urich
Lack of Temperature Control in Infants with Abnormalities of Central Nervous System

Observations on 11 Infants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Temperature</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1-65 128</td>
<td>0-3 6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>13-20 58</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2-6 12</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1-2 67</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0-3 3</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0-2 2</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>51 26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occipital encephalocele; hind-brain malformations; brain-stem in hernial sac</th>
<th>Hydrocephalus Arnold-Chiari malformation; cervical myelocele</th>
<th>Anencephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>10-9</td>
<td>11-3</td>
</tr>
<tr>
<td>-5</td>
<td>10-5</td>
<td>10-5</td>
</tr>
<tr>
<td>2</td>
<td>11-0</td>
<td>11-7</td>
</tr>
</tbody>
</table>

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...
Cross, Hey, Kennaird, Lewis, and Urih

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 $\text{VO}_2$ 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 encephalocoele 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.

We thank Drs. R. H. Dobbs and A. D. M. Jackson who asked us to investigate these patients, and are deeply indebted to our nurse-technicians for conscientious help. Our thanks are also due to Dr. Gary Katz, Dr. Peter Maurice, and Dr. Bridget O'Connell who helped with some observations.

**REFERENCES**


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


Address for reprints and correspondence: Professor K. W. Cross, Department of Physiology, London Hospital Medical College, Turner Street, London E1 2AD.
Lack of temperature control in infants with abnormalities of central nervous system

K. W. Cross, E. N. Hey, D. L. Kennaird, Sheila R. Lewis and H. Urich

Arch Dis Child 1971 46: 437-443
doi: 10.1136/adc.46.248.437

Updated information and services can be found at:
http://adc.bmj.com/content/46/248/437

Email alerting service

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/