Autonomic failure in hydrencephaly

OTTO APPENZELLER, RUSSELL SNYDER, AND MARIO KORNFELD

*From the Departments of Neurology, Medicine, Pediatrics, and Pathology,
University of New Mexico School of Medicine, U.S.A.*

SUMMARY Autonomic functions were studied in three patients with hydrencephalus and five with hydrocephalus. Autonomic failure of central origin was found in the patients with hydrencephalus; whereas, those suffering from hydrocephalus had essentially normal autonomic function. In two patients with hydrencephalus, the hypothalamus was markedly abnormal but the rest of the autonomic nervous system was histologically normal. From this it is concluded that in some patients with mental and motor retardation, autonomic failure may be of cerebral origin but that this is not a feature of patients with hydrocephalus.

The term hydrencephaly was proposed by Crome and Stern (1967) and is used to denote cerebral malformations similar to, but more severe than, those encountered with porencephaly. The larger the porencephalic defect, the more indistinguishable from hydranencephaly the brain becomes. Usually in hydrencephaly the pori are circumscribed holes over which a large part of the pallium has been replaced by a membrane formed by fused leptomeninges and dura. This delicate membrane is usually ruptured at necropsy so that the ventricular system appears to communicate with the subdural space. The rim of cortex which is attached to the membrane is often wedge shaped and the ventricular system is usually dilated.

In the newborn, vasomotor responsiveness to injection of noradrenaline and to changes in environmental temperature increases with age. This has been attributed to maturation of the nervous system (Smith, 1959). After the age of 3 months the initial delay in vasodilatation in the skin of the foot in response to prolonged heating of the limb disappears, and normal adult responsiveness is seen (Bower, 1954). In the hand, however, normal adult responsiveness occurs after 3 days of age (Young, 1962). Other vasomotor reflexes such as the vasoconstriction in response to cold are also delayed in their appearance until the age of 2 months. However, the cold pressor test leads to a normal increase in blood pressure and baroreceptor reflexes are also normally responsive in term and premature infants (Moss, Duffie, and Emmanouilides, 1963). Thermal sweating occurs only after the first week of life and this is often delayed in the premature (Kuno, 1956).

Perspiration from palms and soles which occurs in response to mental stress is not seen until about 1 to 3 months of age. On the other hand, in children aged 1 to 7 years, thermoregulatory sweating is more pronounced on the trunk and chest than in adults under similar thermal conditions (Lipton, Steinschneider, and Richmond, 1965). Studies on neural mechanisms concerned with skin blood-vessel tone have shown that they remain intact in infants with severe motor impairment due to perinatal anoxia and in hydrocephalic infants, but vasomotor activity cannot be demonstrated in the paralysed limbs of infants with meningomyelocele (Young, 1966).

These studies were mostly concerned with one or only a few aspects of autonomic function and a comprehensive picture of vegetative nervous activity related to maturational milestones and the effect of lesions which could be implicated in autonomic dysfunction have not been reported. In the present study autonomic function was tested in three patients with hydrencephaly, in two of whom pathological examination was performed later and compared with the results observed in five patients with severe hydrocephalus.

METHODS

The hydrencephalic patients were hospitalized at the time of the studies. The clinical diagnoses were based on head transillumination, head circumference, and on air encephalograms (Fig. 1). Patients with hydrocephalus were transported to the hospital on the day of the tests from a state institution to which they had been confined for some time. The developmental progress of the patients was compared with that of normals given in the *Develop-*

FIG. 1. Case 2. Air encephalogram brow-up view.

mental Progress of Infants and Young Children (Reports on Public Health and Medical Subjects No. 102, Sheridan, 1960). The pertinent clinical findings are given in Table 1.

Reflex vasodilatation was tested by using a heat cradle containing eight 100 W household light bulbs. The cradle was placed over the chest and upper abdomen and switched on for 10 minutes. Initial central temperature in all subjects, measured in the external auditory meatus, was 36.8°C or higher. Blood flow in digit pulps was measured by heat flow discs before and during heating (Hatfield, 1950). The methods used in other tests of autonomic function and the interpretation of results are summarized in Table 2.

RESULTS

The results are summarized in Table 3. In the three patients with hydrencephaly there was evidence of central failure of autonomic function. No reflex vasodilatation occurred in digits in response to heating of the chest and no fever after the intravenous

administration of pyrogen. Thermoregulatory sweating was absent but sweat secretion could be elicited by pilocarpine iontophoresis and cooling was not associated with shivering in two of the three patients (nos. 2 and 3). On the other hand, peripheral autonomic mechanisms remained intact. The patients had a normal lack of responsiveness of the pupils to the instillation of 2.5% mecholyl into the conjunctival sacs. Pilo-erection could be induced by the intradermal injection of mecholyl in two of the three patients (nos. 1 and 3). Vagal activity tested by the responses to ocular pressure, carotid sinus pressure, or intravenous atropine showed normal function except in patients nos. 2 and 3 in whom some responses could not be observed. Intravenous insulin did not increase gastric acidity in patient no. 2. The triple response of Lewis was normal in all patients.

In the five patients with hydrocephalus, all autonomic functions examined were normal except in patient no. 7 who had no reflex vasodilatation and did not have a febrile response to the intravenous administration of pyrogen. This patient was premature at birth and had a very low birth weight. A significant orthostatic drop in blood pressure occurred in all patients when tilted head-up to 60°.

Necropsies were performed several months after the clinical tests on patients nos. 1 and 2. The pertinent findings were confined to the brain and were similar in both cases (Figs. 2 and 3).

CASE 1

The patient was a female, born 3 December 1967 to an unwed mother who had no prenatal care. At the time of delivery the child was considered to be 7 to 8 months of gestation. Birth weight was 1,700 g. Head circumference was 30 cm. The child was lethargic. No evidence of meaningful vision was noted. Loud noises produced myoclonic jerks. Through a full anterior fontanelle needle punctures were performed. Fluid was obtained and air injected. Radiographs of the skull were then taken which were consistent with cerebral agenesis. The child was

TABLE 1
CLINICAL FEATURES AND DEVELOPMENTAL MILESTONES

Case no.	Sex	Age (yr)	Diagnosis	Head circumference (cm)	Percentile head circumference	Birth weight (g)	Present weight (kg)	Developmental levels (months)			
								posture and large movements	visual and fine movements	hearing and speech	social behaviour
1	F	1½	Hydrencephalus	58	>98	1,860	9.3	1	1	3	3
2	M	3/12	Hydrencephalus	37.5	50	3,230	2.7	1	1	1	1
3	F	7/12	Hydrencephalus	45.2	90	3,100	6.7	1	0	1	1
4	F	16	Hydrocephalus	79	>98	—	36.8	9	9	24	12
5	M	3	Hydrocephalus	52.3	>98	3,800	13.7	15	15	18	18
6	M	1½	Hydrocephalus	48	60	2,800	9.2	6	6	6	9
7	F	15	Hydrocephalus	73.5	>98	810	29	3	0	18	12
8	F	15	Hydrocephalus	58.5	>98	1,800	28.5	6	1	3	3

TABLE 2
INTERPRETATION OF SPECIAL TESTS

Test	Normal responses	Abnormal responses	Conclusions from abnormal responses: dysfunction of	Remarks
Reflex vasodilatation	Vasodilatation in digit pulps	No vasodilatation	Skin receptors; afferents; central structures; efferents; or blood vessels	Sometimes preserved in fingers and absent in toes in patients with partial autonomic failure*
IV pyrogen	Fever	No fever	Central thermoregulatory structures, efferent vasomotor connections	
Thermoregulatory sweating	Sweating	No sweating	Central thermoregulatory structures; efferent sudomotor connections or sweat glands	Usually sweating not entirely abolished. In adults compensatory hyperhidrosis may occur in arcus with preserved sweating
Intradermal mecholyl, observation of hair on skin	Pilo-erection	No pilo-erection	Postganglionic sympathetic nerves	
Instillation of 2.5% mecholyl into conjunctival sac	No change in pupil size	Pupillary constriction	Postganglionic parasympathetic nerves	Evidence of denervation supersensitivity
IV atropine	Cardiac acceleration	No change in heart rate	Impaired vagus nuclei or nerve activity at rest	
Ocular pressure or carotid sinus massage	Cardiac slowing	No change in heart rate	Impaired vagus activity on stimulation	
Pilocarpine iontophoresis	Profuse sweating	No sweating	Abnormal sweat glands	
Intradermal histamine 1:1,000	Triple response of Lewis	No flare	Interruption of afferent pain fibres	Usually preserved in central nervous system lesions which, however, modulate the extent of the flare

*Johnson, Lee, Oppenheimer, and Spalding (1966).

FIG. 2. Case 1. Brain sectioned coronally after fixation showing enormously dilated ventricles.

irritable and had repeated episodes of vomiting and diarrhoea. She passed no motor or social milestones. Intermittent opisthotonic posturing was observed.

When examined at 14 months of age, her weight was 3,050 g, height 52 cm, head circumference 36.5 cm, and the anterior fontanelle measured 3 × 4 cm. She appeared malnourished. Tonic neck reflexes were present. Slow

FIG. 3. Case 2. Brain after fixation: lateral surface.

TABLE 3
RESULTS OF SPECIAL TESTS

	Hydrancephalus Case number			Hydrocephalus Case number				
	1	2	3	4	5	6	7	8
Reflex vasodilatation								
Fingers	No	No	No	—	Yes	Yes	No	Yes
Toes	—	—	No	Yes	Yes	—	No	No
Fever with IV pyrogen* (μ g/kg body weight)	No 0.1	No 0.6	No 0.6	Yes 0.3	Yes 0.4	Yes 0.2	No 0.4	Yes 0.9
Thermoregulatory sweating with central temperature rise of 1°C	No	No	No	Yes	Yes	No	Yes	Yes
Body cooling (external auditory meatus temperature °C)	36.0-35.0	37.0-30.0	38.0-36.0	—	38.2-37.2	36.0-35.0	37.8-36.2	37.0-36.0
Shivering and goose pimples	Yes	No	No	—	Yes	Yes	Yes	Yes
Piloerection with ID Mecholyl	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
2.5% Mecholyl in conjunctival sac	No	No	No	No	No	No	No	No
Cardiac acceleration with IV atropine (0.4 mg)	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Cardiac slowing with ocular pressure	Yes	Yes	No	—	Yes	Yes	Yes	Yes
Cardiac slowing with carotid sinus massage	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Orthostatic hypotension† (mm Hg)	80/P†- 60/P	90/P- 80/P	96/P- 56/P	118/78- 108/60	86/P- 74/P	94/74- 78/60	96/70- Not re- cordable	108/60- 84/48
Pilocarpine iontophoresis (mg sweat)	—	4.5	8.9	—	—	—	—	—
Triple response of Lewis (flare present)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Remarks. Case 2: motor nerve conduction velocities, median 27.5 m/sec, peroneal 27.4 m/sec. No increase in gastric acidity after IV insulin. Case 3: breast development; Cheyne-Stokes respiration. Case 4: shivering observed during pyrogen-induced fever. Case 7: reflex vasodilatation tested on two separate occasions; premature delivery.

*Pseudomonas polysaccharide (Piromen (R)).

†Supine.

‡Upright.

‡P = by palpation.

symmetrical movements of the extremities were noted. A generalized increase in tone was present. The deep tendon reflexes were hyperactive with unsustained clonus. The head transilluminated completely. During the next four months frequent hospitalizations were necessary because of difficulty with feeding. Intermittent opisthotonos continued and was thought to represent seizure activity. Phenobarbitone was administered without change. An electroencephalogram performed at 16 months of age was abnormal for her age with slow wave lateralization to the left side and the appearance of spikes in the left temporal-occipital region. During her hospitalizations the rectal temperature varied between 94°F and 99°F (34.4 to 37.2°C) (Fig. 4).

At the age of 18 months the child was admitted because of difficulty in breathing. She was cyanotic and retraction of intercostal muscles was observed. Chest radiographs revealed bilateral bronchopneumonia. She died four hours after admission.

NECROPSY EXAMINATION *General pathological examination* Acute confluent bilateral bronchopneumonia and

decubitus ulcers over the sacral regions were found. There were no other pathological changes.

Neuropathological examination The brain was perfused *in situ* and not weighed after removal. The falx and dura mater were firmly attached to the convex portions of the cerebral hemispheres. The frontal and temporal lobes were replaced by a thin membrane. A large defect was seen in the basal frontal area extending into the temporal polar area on each side and measuring 3 × 2.5 cm. On the left side the parietal and occipital lobes were preserved. The surface of the right hemisphere showed poorly developed gyri. The right parietal lobe and the posterior portions of the temporal lobe were preserved. The chiasm, tuber cinereum, and mamillary bodies were flattened. The large vessels at the base of the brain were normal. The brain was cut coronally at 0.5 cm intervals. The lateral ventricles were enormously dilated and separated by a mid-sagittally located short membrane (Fig. 2). The corpus callosum was absent. The preserved hemispheric parenchyma was markedly reduced in thickness. In such areas the cortex was clearly demarcated from the thin convolutional white matter. The corpus

FIG. 4. Case 1. Temperature chart showing wide swings in body temperature.

striatum and thalami formed two large protuberances in the floor of the common cavity representing the lateral ventricles. The fornices appeared normal. The striatum, thalami, and hypothalami showed no gross abnormalities. The brain-stem appeared normal. The cerebellum was normal in size and showed no abnormalities on cross sections. The spinal cord was normal.

MICROSCOPIC EXAMINATION Numerous sections of the hemispheres, cerebellum, brain-stem, and spinal cord were examined. They were stained with haematoxylin and eosin and cresyl violet. The membranous part of the cerebral hemispheres consisted of thickened leptomeninges and an underlying band of glial tissue. Large numbers of mononuclear cells and lymphocytes were present in the leptomeninges. Occasional groups of haemosiderin-laden macrophages were also seen.

In many areas the cortex was reduced in thickness but showed distinct lamination, although the neurones were reduced in numbers. Neurones showed swelling, vacuolation of the cytoplasm, absence of Nissl substance, and karyolysis. In some areas of the cortex there were miniature convolutions which were not separated by sulci. The ventricular wall was not lined by ependyma. It was formed by a dense parallel band of glial fibres. A portion of the left parietal lobe consisted of glial tissue in which only irregular groups of degenerated neurones were seen. This tissue contained a number of pseudocysts surrounded by reactive astrocytes.

Skip serial sections through the basal ganglia, hypothalami, and thalami were examined. A thick layer of glial tissue covered the free surfaces of the corpora striata. Occasional precipitates of calcium were found in the deep portion of this layer. Numerous granular excrescences were seen to spring from the walls of the third ventricle, especially from its floor. The larger ones were devoid of ependymal lining. Occasional dense aggregates of glial cells were seen in the anterior hypothalamus beneath the granulations and contained a number of haemosiderin-

laden macrophages (Figs. 5 and 6). Occasionally focal overgrowth of cellular glia compressed the parenchyma. These were demarcated from the latter by a series of tubules formed by the ependyma. In the vicinity of such formations the neurones were decreased in number and showed degenerative changes; however, occasional areas of neuronal degeneration were found independent of nodular glial formations mainly in the posterior hypothalamic nuclei. The cerebellum showed no histological abnormalities. The mesencephalon showed no abnormalities, other than ependymal granulations in the aqueduct of Sylvius. The pons was normal apart from extreme reduction in volume of the long descending tract. The medulla was thin but otherwise normal. The spinal cord contained rudimentary pyramidal tracts and the cells of the intermediolateral columns were normal in number and appearance.

SUMMARY The patient was an 18-month-old female with clinical central autonomic failure and severe mental and motor retardation. Neuropathological examination showed hydrencephaly, widespread abnormalities of the remainder of the cerebral hemispheres including the hypothalamus, and evidence of chronic inflammation. The autonomic neurones and tracts in the brain-stem and spinal cord were histologically normal.

CASE 2

The patient, a male, was born on 11 November 1968 to a 25-year-old gravida 5, para 4, mother. The mother had a previous stillborn term infant. There were no complications with this pregnancy or delivery. Birth weight was 3,232 g. Apgar score at 1 minute was 8 and at 5 minutes was 10. No abnormalities were noted in the delivery room. On examination eight hours after birth the head circumference was 38.5 cm and chest circumference 32 cm. Anterior and posterior fontanelles were large and soft and a 0.5 cm spread of the coronal and sagittal

FIG. 5. *Case 1. Hypothalamus. Granular excrescence in wall of third ventricle with dense glial cells and a few haemosiderin-laden macrophages. Numerous tubules lined with ependymal cells are also shown. Haematoxylin and eosin, $\times 250$.*

sutures was noted. The cry was high pitched. The baby was lethargic. Generalized hypotonia was present. Spontaneous movements were decreased but appeared symmetrical. All deep tendon reflexes were present. Withdrawal occurred from painful stimulation. The pupils reacted to light. There was a normal temporal half of the optic discs bilaterally but no evidence of the discs on the

nasal side. The head transilluminated completely. Needle puncture through the lateral corner of the anterior fontanelle was performed. Three millilitres of slightly xanthochromic fluid were removed and 10 ml of air injected. Radiographs of the skull were then taken which were consistent with hydrencephaly. Examination of the cerebrospinal fluid showed no cells, sugar 36 mg, and

FIG. 6. *Case 1. Anterior hypothalamus showing gliosis and haemosiderin-laden macrophages. Haematoxylin and eosin, $\times 450$.*

protein 70 mg/100 ml. Electroencephalography showed a combination of spike and slow waves with maximum activity in the right central regions. The patient was discharged at 11 days of age. Throughout the hospitalization the child's temperature was in the range of 95°F (35°C).

The patient was readmitted at the age of 8 weeks because of a temperature of 106°F (41°C). No cause for the fever was found, and for 10 days an erratic temperature was recorded with swings from 94.6°F to 103.4°F (34.8 to 39.7°C) (Fig. 7). Repeated skull radiographs were normal.

The third admission was at 10 weeks of age. The child was lethargic with a weak cry and poor sucking. Head circumference was 37.0 cm. Increase in tone was noted. No evidence of meaningful vision was present. Loud noises produced a startle response. Again wide swings in temperature were noted similar to the preceding admission. Motor nerve conduction velocities were: right median nerve 27.4 metre/second, and right peroneal nerve 27.5 metre/second (normal for age).

Final admission was on 15 February 1969 at 3 months of age. There was rapid breathing and cyanosis. Radiographs of the chest revealed early pneumonia. Temperature was 96°F (35.6°C). Twelve hours after admission the child died.

NECROPSY EXAMINATION *General pathological examination* Bilateral bronchopneumonia and patent ductus

arteriosus were present. No other pathological changes were seen.

Neuropathological examination The brain was perfused *in situ* and not weighed after removal. The inner surface of the dura mater was smooth and glistening but showed patchy areas of brownish discolouration and a thin translucent membrane was stripped off its inner surface.

The interhemispheric surfaces were firmly attached to the falx and the basal portions of both temporal lobes were attached to the basal dura. An oval defect in the left hemisphere measuring 22 × 15 mm was found to replace the left temporal pole and posterior portions of the left insula (Fig. 3). The surface of the right hemisphere showed excessive gyrations throughout. The brain-stem and the cerebellum were normal in appearance. Olfactory bulbs and terminal portions of the optic nerves as well as the 3rd to 9th cranial nerves were identified and appeared normal. The floor of the 3rd ventricle was flat and no mammillary bodies were visible. The large vessels at the base of the brain were normal.

Coronal sections of the brain at 0.5 cm intervals showed most of the cerebral hemisphere replaced by a single large cavity; a separation was indicated by the presence of a 5 to 10 mm thick ridge of parenchyma running along the interhemispheric fissure. The corpus callosum was absent. A thin almost translucent membrane closed the cavity posteriorly above the area of the pineal body. The floor

FIG. 7. Case 2. Temperature chart showing wide swings in body temperature.

of this cavity was flattened except for two symmetrical ovoid protuberances measuring 3 to 4 mm in diameter on cross-section. There was no communication between the 3rd and the 4th ventricles. A thin membrane was found separating the upper portion of the aqueduct from the 3rd ventricle. The 4th ventricle was normal in calibre. The brain-stem and cerebellum and spinal cord were normal.

MICROSCOPIC EXAMINATION Numerous sections of the hemispheres, cerebellum, brain-stem, spinal cord, spinal and autonomic ganglia, peripheral nerves, and muscles were examined. They were stained with haematoxylin, eosin, and cresyl violet. The inner surface of the dura mater was covered by a thin membrane consisting of loose connective tissue containing numerous capillaries, and occasional haemosiderin-laden macrophages. The leptomeningeal trabeculae were filled with lymphocytes and macrophages, many of which were haemosiderin-laden. The neurones were markedly reduced in number. Many neuronal nuclei showed degenerative changes and the cytoplasm was occasionally vacuolated. The astrocytic nuclei were more prominent than normal. Ectopic neurones were found in the convolutional white matter. Reactive astrocytes formed a narrow band along the ventricular surface which was devoid of ependymal lining. The thinner parts of the cerebral hemispheres consisted predominantly of astroglial elements and their processes. The cortical blood vessels showed hypertrophy and hyperplasia of their endothelium.

Alternate serial sections through hypothalamus and basal ganglia were examined. The floor of the third ventricle was stretched and thinned (Fig. 8), and its ependymal lining interrupted in several areas frequently forming tubular structures. These were buried under a thick band of fibrillary glia. The individual nuclear

groups of the hypothalamus were not distinguishable because of the deformity of the area. However, the nuclei tuberis were still identifiable. The neurones in the hypothalamus were markedly decreased in numbers and most of the remaining neurones were abnormal in shape and structure. Occasionally the neuropil appeared rarefied and perivascular spaces in such areas were filled with groups of lipid-laden macrophages (Fig. 9). In the caudate nuclei, large numbers of astrocytes and only scattered isolated neurones were seen. Most of the neurones showed heavy precipitation of calcium; occasionally only granular precipitates of calcium were found with no identifiable cell bodies. The putamina showed changes similar to those observed in the caudate nuclei.

The cerebellum was normal.

The mesencephalon showed numerous astrocytes with plump eosinophilic bodies in the collicular and lateral tectal zones. The aqueduct was outlined in its lateral and ventral portions by aggregates of tubules lined by ependyma.

The pons was normal apart from a reduction in volume of the long descending tracts. In the lateral recesses of the floor of the fourth ventricle, granular formations consisting of proliferating ependymal glia were found.

The spinal cord showed narrow lateral columns. They were pale and contained a number of reactive astrocytes. No abnormalities were found in the intermediolateral cell columns (Fig. 10).

The peripheral nerves, stellate ganglion, sympathetic chain, and skeletal muscles were free of histological changes.

SUMMARY The patient was a 3-month-old male with clinical central autonomic failure and severe mental and motor retardation. Neuropathological examination

FIG. 8. Case 2. Floor of third ventricle showing thinness of tissue. The distortion is partly artifactual. Haematoxylin and eosin, $\times 2$.

FIG. 9. Case 2. Hypothalamus showing rarefied neuropil, gliosis, and loss of neurones. Haematoxylin and eosin, $\times 250$.

showed hydrencephaly with widespread abnormalities of the remainder of the cerebral hemispheres including the hypothalamus and aqueduct stenosis. The autonomic neurones and tracts in the brain-stem and spinal cord and the peripheral autonomic ganglia and nerves were histologically normal.

DISCUSSION

The clinical and pathological findings in the first three patients conformed to those previously described in hydrencephaly, which is a recognized cause of mental and motor retardation and is com-

FIG. 10. Case 2. Upper thoracic cord showing a normal complement of neurones in the intermediolateral cell columns. Haematoxylin and eosin, $\times 3$.

patible with survival for several months after birth (Crome and Stern, 1967).

The results of special studies clearly pointed to a central failure of autonomic function in these patients because peripheral autonomic effector mechanisms were shown to be intact in two patients. In case 2, however, almost complete central and peripheral autonomic failure was found during life. The central structures concerned with reflex vasodilatation in the hand or foot are situated above the level of the brain-stem, presumably in the hypothalamus (Appenzeller and Schnieden, 1963). In the patients with hydrencephaly there was no evidence of lesions in either the afferent or efferent structures concerned with this reflex but the hypothalamus was shown to be structurally abnormal in two of the cases. It would appear, therefore, reasonable to suggest that the lack of normal reflex vasodilatation in digits in response to heating the skin elsewhere was due to the lesions in the hypothalamus.

During fever, pyrogen is released from leucocytes and this agent causes the disturbed thermoregulation (Atkins, 1960). For this response to occur an intact efferent sympathetic nervous system is required because fever can be significantly reduced by bilateral sympathectomy (Pinkston, 1935). Numerous studies in animals and man have shown that fever is produced by the activity of structures in the anterior hypothalamus and preoptic regions and that bacterial pyrogens act apparently by releasing pyrogen from leucocytes which migrate into these areas (Cooper, 1966). The absence of fever in response to the intravenous injection of pyrogen in the patients with hydrencephaly is presumably related to the structural abnormalities in the hypothalamus and preoptic areas, although efferent sympathetic dysfunction was not definitely excluded clinically in case 2, even though the intermediolateral cell columns in the spinal cord, the sympathetic ganglia, and peripheral nerves were shown histologically to be intact.

In man, shivering appears when the central body temperature reaches about 36°C; it is maximal at 33°C, and at a central body temperature of 30°C shivering disappears again (Spealman, 1945). Two types of shivering have been recognized: reflex shivering which occurs in response to cold and is dependent on cutaneous receptors, and central shivering which is related to the temperature of the blood (Chatonet and Tanche, 1956). At normal brain temperatures, however, experimental cooling of the hypothalamus in a thermally balanced animal does not cause shivering (Strom, 1950). This suggests that central shivering may normally be subordinate to peripheral receptor induced reflex shivering. In normal neonates sustained shivering in response to cold does not occur, but in adults the metabolic

increase which occurs in response to cold is entirely due to shivering, since it can be abolished by muscular paralysis (Johnson and Spalding, 1963; Johnson, Smith, and Spalding, 1963). Normally when an adult is cooled the skin becomes cold; there is shivering and an increase in metabolic rate and the central temperature is elevated. In this situation shivering is clearly initiated by skin receptors because the rise in central temperature does not inhibit it. In five patients with spinal cord lesions, however, it was shown that shivering occurred in normally innervated muscles above the lesion when the central temperature fell due to cooling of the legs. In these studies the skin above the level of the lesion was kept warm and no patient felt cold. These findings suggest that in man, as in animals, there are central structures capable of inducing shivering in response to a fall in the temperature of the blood (Johnson and Spalding, 1966), but the role of these structures in normal subjects is not fully delineated. In fever, shivering occurs normally. In patients with transverse cord lesions, however, it is confined to muscles innervated from segments above the lesion. Because no shivering is seen in muscles innervated from segments below the lesion, shivering in this situation must be due to the activity of pyrogens acting on central structures (Cooper, Johnson, and Spalding, 1964). Only one of the three patients with hydrencephaly had thermoregulatory shivering, even though the temperature in the external auditory meatus, which is a good approximation of central temperature, fell in all three to levels where normally shivering occurs. It is likely that this abnormality was related to the anatomical changes in the hypothalamus, since, in two of the patients without shivering, peripheral autonomic mechanisms were shown to be intact functionally (cases 2 and 3) and in one histologically also (case 2). The presence of shivering in response to cold in case 1 must be attributed to a reflex phenomenon, since the hypothalamus was shown histologically to be abnormal in this case and there was no shivering in response to the intravenous administration of pyrogen also. It is unlikely that paralysis of limbs was the cause of the lack of shivering in these patients, since shivering is usually first noted and is most pronounced in the facial musculature, and no patient had paralysis of the facial muscles.

Thermoregulatory sweating was absent in all three patients with hydrencephaly. Sweating in response to heating depends on two mechanisms. The first is due to warm blood reaching heat-sensitive structures in the brain and the second is dependent on peripheral receptors which reflexly activate these structures and which then, in turn, initiate postganglionic sympathetic activity and sweat secretion. Under

experimental conditions either of these mechanisms alone, or in combination, can produce sweating. In a hot environment the thermal adaptation of the individual determines the mechanism of sweating. In non-adapted subjects an abrupt rise in environmental temperature causes sweating only after a delay which is related to the rise in central temperature but not to skin temperature. In adapted individuals under similar conditions, there is an immediate onset of sweating which is related to the rise in skin temperature and a further increase in sweating occurs which coincides with a rise in central temperature (Colin and Houdas, 1965). All three patients with hydrencephaly had a rise in central temperature during heating of at least 1°C so that there is good evidence that thermoregulatory sweating could not be initiated in these patients because of a failure of the central mechanism which is dependent on warm blood. In addition, there was functional evidence of intact peripheral mechanisms and pilocarpine iontophoresis produced sweat in two patients with hydrencephaly, showing that sweat gland activity was preserved. The absence of thermoregulatory sweating in these patients, like the failure of reflex vasodilatation, shivering, and the lack of responsiveness to intravenous pyrogen administration was therefore related to the anatomical derangements of the hypothalamus.

A number of other autonomic function studies were directed at the assessment of the functional integrity of peripheral and effector mechanisms in these patients. The responses elicited were, for the most part, normal and strengthened the assumption that autonomic failure in hydrencephaly is the result of hypothalamic dysfunction.

Patients with hydrocephalus were used as controls in this study because they, like our cases with hydrencephaly, were mentally retarded. Moreover, abnormalities in autonomic function were expected to occur because such patients usually have dilated third ventricles. It was thought likely that this dilatation might interfere with the function of the adjacent hypothalamus. Surprisingly, however, the majority of autonomic functions tested were normal. The only exceptions were reflex vasodilatation in toes, which was absent in two, and in one there was, in addition, no response to the intravenous administration of pyrogen (case 7). This patient had an extremely low birth weight and it is possible that other lesions in the brain were present in addition to hydrocephalus, which accounted for the partial autonomic failure.

It seems clear from the results reported here that there is a close relation between normal reflex vasodilatation in digits and responsiveness to intravenous pyrogen and this suggests that the central neural structures which are concerned with these responses

are, if not identical, at least closely associated with each other.

Orthostatic hypotension was present in all patients in this study, and this has been reported in previously normal subjects after prolonged immobilization (Fareeduddin and Abelman, 1969). It is possible, therefore, that the orthostatic drop in blood pressure in our patients was the result of immobilization in bed and consequent cardiovascular deconditioning rather than an expression of a structural lesion of the autonomic nervous system.

Shapiro, Williams, and Plum (1969) described recurrent hypothermia in two patients with radiographic evidence of agenesis of the corpus callosum and attributed this to associated defects in the septal regions. Our patients with pathologically verified absence of the corpus callosum had widespread abnormalities in the hypothalamus including the septal areas. Moreover, a recent description of autonomic failure in cerebral gigantism in a child with an intact corpus callosum but radiographic evidence of hypothalamic lesions (Appenzeller and Snyder, 1969) supports the view that abnormalities in temperature regulation are indeed the result of hypothalamic, rather than callosal, lesions. In many severely mentally retarded children, unexplained abnormalities in temperature regulation manifested by fever or hypothermia are sometimes seen and these may be due to undetected central autonomic failure. If the poikilothermic state in such patients is recognized, close attention to a temperate environment and special protection of their central temperature might be necessary.

We wish to thank the physicians and staff of the Los Lunas State Hospital and the Department of State Hospitals of New Mexico for allowing us to study patients under their care. The excellent technical assistance of Mrs. Cathy Nichols is gratefully acknowledged. Travenol Laboratories generously supplied Piromen.

REFERENCES

- Appenzeller, O., and Schnieden, H. (1963). Neurogenic pathways concerned in reflex vasodilatation in the hand, with especial reference to stimuli affecting the afferent pathway. *Clin. Sci.*, **25**, 413-421.
- Appenzeller, O., and Snyder, R. D. (1969). Autonomic failure with persistent fever in cerebral gigantism. *J. Neurol. Neurosurg. Psychiat.*, **32**, 123-128.
- Atkins, E. (1960). Pathogenesis of fever. *Physiol. Rev.*, **40**, 580-646.
- Bower, B. D. (1954). Pink disease: the autonomic disorder and its treatment with ganglion-blocking agents. *Quart. J. Med.*, **23**, 215-230.
- Chatonnet, J., and Tanche, M. (1956). Dissociation du frisson 'central' et du frisson 'réflexe', chez le chien à moelle détruite. *J. Physiol. (Paris)*, **48**, 439-442.
- Colin, J., and Houdas, Y. (1965). Initiation of sweating in

- man after abrupt rise in environmental temperature. *J. appl. Physiol.*, **20**, 984-990.
- Cooper, K. E. (1966). Temperature regulation and the hypothalamus. *Brit. med. Bull.*, **22**, 238-242.
- Cooper, K. E., Johnson, R. H., and Spalding, J. M. K. (1964). Thermoregulatory reactions following intravenous pyrogen in a subject with complete transection of the cervical cord. *J. Physiol. (Lond.)*, **171**, 55P-56P.
- Crome, L., and Stern, J. (1967). *The Pathology of Mental Retardation*. Churchill: London.
- Fareeduddin, K., and Abelman, H. (1969). Impaired orthostatic tolerance after bed rest in patients with myocardial infarction. *New Engl. J. Med.*, **280**, 345-350.
- Hatfield, H. S. (1950). A heat-flow meter. *J. Physiol. (Lond.)*, **111**, 10P-11P.
- Johnson, R. H., Smith, A. C., and Spalding, J. M. (1963). Oxygen consumption of paralysed men exposed to cold. *J. Physiol. (Lond.)*, **169**, 584-591.
- Johnson, R. H., and Spalding, J. M. (1966). The role of a central temperature receptor in shivering in man. *J. Physiol. (Lond.)*, **184**, 733-740.
- Johnson, R. H., and Spalding, J. M. (1963). Whole body metabolism of a paralysed man during surface cooling. *J. Physiol. (Lond.)*, **166**, 24P-25P.
- Kuno, Y. (1956). *Human Perspiration*. Thomas: Springfield, Ill.
- Lipton, E. L., Steinschneider, A., and Richmond, J. B. (1965). The autonomic nervous system in early life. *New Engl. J. Med.*, **273**, 147-153.
- Moss, A. J., Duffie, E. R., Jr., and Emmanouilides, G. Blood pressure and vasomotor reflexes in the newborn infants. *Pediatrics*, **32**, 175-179.
- Pinkston, J. O. (1935). Experimental fever in sympathectomized animals. *Amer. J. Physiol.*, **111**, 539-550.
- Shapiro, William R., Williams, G. H., and Plum, F. (1969). Spontaneous recurrent hypothermia accompanying agenesis of the corpus callosum. *Brain*, **92**, 423-436.
- Smith, C. A. (1959). *The Physiology of the Newborn Infant*. 3rd Edn. Thomas: Springfield, Ill.
- Spealman, C. R. (1945). A characteristic of human temperature regulation. *Proc. Soc. exp. Biol. Med. (N.Y.)*, **60**, 11-12.
- Ström, G. (1950). Effect of hypothalamic cooling on cutaneous blood flow in the unanesthetized dog. *Acta physiol. scand.*, **21**, 271-277.
- Young, I. M. (1962). Vasomotor tone in the skin blood vessels of the newborn infant. *Clin. Sci.*, **22**, 325-332.
- Young, I. M. (1966). Responses of the systemic circulation of the new-born infant. *Brit. med. Bull.*, **22**, 70-72.

The June 1970 Issue

THE JUNE 1970 ISSUE CONTAINS THE FOLLOWING PAPERS

Early recognition of heterozygotes for the gene for dystrophin myotonia SARAH BUNDEY, C. O. CARTER, and J. F. SOOTHILL

Calcium uptake and bioelectrical activity of denervated and myotonic muscle H. RADU, I. GÖDRI, E. ALBU, A. RADU, and R. ROBU

Biochemical studies in Nevin-Jones syndrome K. VALMIKINATHAN and J. N. CUMINGS

Spontaneous arteriovenous malformations in the cervical area J. GREENBERG

The role of diffusion barriers in determining the excitability of peripheral nerve K. N. SENEVIRATNE and O. A. PEIRIS

Mapping of motor units in experimentally reinnervated rat muscle ERIC KUGELBERG, LARS EDSTRÖM, and MICHELE ABBRUZZESE

Relapsing corticosteroid-dependent polyneuritis W. B. MATTHEWS, D. A. HOWELL, and R. C. HUGHES

The central nervous system in motor neurone disease BETTY BROWNELL, D. R. OPPENHEIMER, and J. TREVOR HUGHES

A critical review of evidence concerning long-loop reflexes excited by muscle afferents in man M. MICHAEL GASSEL

Primary neurogenic orthostatic hypotension R. C. HUGHES, N. E. F. CARLIDGE and P. MILLAC

Late complications of hemispherectomy: report of a case relieved by surgery NINAN T. MATHEW, JACOB ABRAHAM, and JACOB CHANDY

Seronegative dementia paralytica: report of a case L. CH'EN, B. M. HATHAWAY and C. W. ISRAEL

Epileptic seizures resulting from acute cerebral anoxia D. MADISON and E. NIEDERMEYER

Cerebrospinal fluid pressure K. C. BRADLEY

Necrosis of muscle with carcinoma: myositis or myopathy? H. URICH and MARCIA WILKINSON

Unilateral electroconvulsive therapy and cerebral dominance: effect of right- and left-sided electrode placement on verbal memory J. J. FLEMING, D. J. de L. HORNE and P. N. NOTT

Book Reviews

Copies are still available from the PUBLISHING MANAGER,

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, WC1H 9JR, price 21s.