MEDICAL PRACTICE

Clinical Topics

Rett's syndrome in the west of Scotland

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Abstract

Nineteen girls with characteristic features of Rett's syndrome, including normal initial development, regression at about 12 months of age, repetitive hand movements, and severe mental handicap were studied. This represents an estimated incidence of one in 30 000 live births (one in 15 000 girls) in the west of Scotland. Although the children were often initially considered to be autistic, they did not conform to this diagnosis as they made good personal contact within the limits of their mental development. The developmental regression was sometimes falsely attributed to vaccination.

Each child showed striking involuntary movements and abnormality of tone, varying from hypotonia, which was found only in the youngest, to rigidity, which was common in older girls; this permitted classification into three clinical subtypes. The abnormalities were highly suggestive of an extrapyramidal disorder, and this has implications for further research and possible treatment.

Introduction

In 1966 Rett described 22 mentally handicapped children, all of them girls, who had a history of regression in development and displayed striking repetitive movements of their hands.[1,2] He considered them to be autistic and increasingly spastic and proposed diffuse cerebral atrophy as the underlying cause. The syndrome has continued to be described,[3-5] but Rett's original findings of hyperammonaemia have not been substantiated. We report the first study of this important disorder in an English speaking population. Its purpose is to draw attention to this not uncommon cause of mental handicap in girls and to give a detailed description of its characteristic presentation, features, and progression together with a fresh assessment of their importance.

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Methods

In 1982 we decided to look for cases of Rett's syndrome in our area, estimate the incidence, and search for features that might assist diagnosis and classification. For this purpose we chose diagnostic criteria common to cases that had been described previously. These criteria were: normal pregnancy, birth, and development to 6 months; partial or complete loss of speech, use of hands, and locomotion without identifiable cause between 7 and 24 months; repetitive hand movements; postural difficulty; occipitofrontal circumference in the normal range at birth subsequently crossing the centiles to, or remaining at, the second centile; and severe mental handicap at follow up.

The Fraser of Allander Unit is the referral centre for paediatric neurology in the west of Scotland, which has roughly 40 000 births every year. Over 12 years (1972-84) there were 5400 referrals to the unit, of which 42 had been seen with an undiagnosed neurological disorder beginning at 7-24 months of age. The case records were reviewed and clinical observations made of all those children whose history did not rule out a diagnosis of Rett's syndrome.

Nineteen children were identified as fulfilling all of our criteria for Rett's syndrome. All were girls. Figure 1 shows the distribution of cases relative to the population of children. Assuming complete ascertainment, this indicated an incidence of one in 30 000 births. Ages ranged from 3 to 15 years and were spread evenly through that range.

Each girl was admitted for a 36 hour inpatient assessment. The procedures used were as follows: full history, examination, and video filming; estimations of blood gas tensions, concentrations of urea, electrolytes (including copper and zinc), and fasting ammonia, and activities of creatine phosphokinase, aldolase, and leucocyte enzymes; and high resolution prometaphase banding of X chromosomes. Urine tests were performed to estimate excretion of amino acids, glycosaminoglycans, oligosaccharides, organic acids, hydroxymethylmandelic acid, and 3-methoxy 4-hydroxy-

phenylglycol. Waking and sleeping electroencephalography and radiography were also performed, and in some cases computed tomography, nerve conduction studies, and electromyography.

Results

The table gives the chief clinical observations. Family histories spanning three generations showed no other cases of Rett's syndrome. At the birth of the children with Rett's syndrome mean maternal age was 25 (range 16-40) and paternal age 27 (21-40). There were 17 male and 18 female siblings and nine miscarriages. There was no consanguinity. The mother and grandmother of one child were considered to be schizophrenic.

At birth mean gestation was 40 weeks (38-42) and mean birth weight 3200 g (2100-4000) and occipitofrontal circumferences were within or close to the normal range (mean 34 cm (32-36)). Only one child required resuscitation, with Apgar score of four at one minute and seven at five minutes (case 19).

All children were immunised against diphtheria, tetanus, and poliomyelitis and all but one against pertussis. Two had a febrile reaction, but none had a seizure. There was no consistent relation between the time of immunisation and onset of regression, but seven families considered immunisation against pertussis to be responsible for their child's condition.

General health was usually good up to the time of regression. One girl (case 11) had chickenpox, measles, and whooping cough shortly before onset; another (case 2) had a febrile illness with serology positive for Coxsackie virus B4 at 21 months; and a third (case 4) had oral ulcers at 12 months.

The history of onset of Rett's syndrome was most clearly apparent in the pattern of learning and regression (table). Achievement of early milestones was fairly normal, whereas more sophisticated skills were acquired late and poorly performed. Every child showed regression of locomotion, manipulation, and speech (mean age 16 months, range 10-24), but the more complicated skills were lost completely. Mental age at follow up was at about the 6-12 month level. Figure 2 shows the highly characteristic trend of development schematically.

At the onset of regression screaming attacks were common. One child had two brief generalised seizures, but in no other case was there any sign of systemic illness. At about this time onset of repetitive hand movements and loss of communication led to 12 of the girls being described as autistic. After acute regression there was little change. The children became more placid and their lower limbs increasingly stiff. Wasting and scoliosis were progressive. Six children had generalised seizures, all of which were controlled by standard anticonvulsant treatment.

All 19 girls were strikingly similar in appearance (fig 3). They had pretty

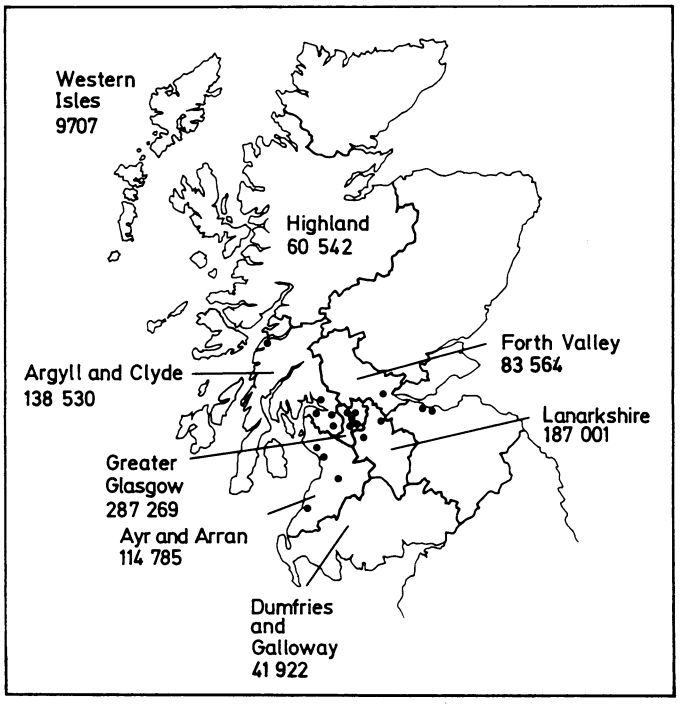

FIG 1—Map showing origin of cases of Rett's syndrome (•) and giving population figures for under 19 year olds in 1982 (figures from Department of Health and Social Security).

Data on 19 patients with Rett's syndrome

	Type I				Type II: Not wasted						Type II: Wasted			Type III					
Case No:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age examined (years)	3	3	4	4	6	6	8	9	10	10	8	13	15	8	9	9	12	12	13
Age at regression (months)	12	12	18	12	15	13	18	18	17	18	18	22	15	18	18	11	10	18	24
Occipitofrontal circumference centile:																			
Birth-6 months	50	50-98	2-50	50-98	<50	2%	90%			50-98					98%	50-98			2%
1-2 years	2-50	50		50	50		50	50	10-50	50%	98%	>50	2-10	<2%		50	2-50	2-10	
At examination	<2	10-50	2%	2%	<2	<2%	2-50	<2%	2-10	<2%	50%	2%	<2%	<2%	2%	2-50	<2%	<2%	<2%
Developmental gain/loss:																			
Responsive smile (weeks)*	6/	4/	7/	6/	8/	6/	7/	8/	7/	7/	6/	5/	6/	6/	6/	6/	6/	6/	6/
Able to sit alone (months)*	8/12	7/11	6/	15/	6/	7/	7/	6/	10/	6/	6/	7/	7/	13/	9/18	7/	9/36	6/	8/
Able to walk alone (months)*			20/48		18/	14/	12/	18/	18/	17/	30/	16/	36/	15/30	13/18				
Able to pick up objects (months)*	4/	5/	9/18	9/	7/	9/	8/23	11/	10/	10/	9/	4/	5/	7/	9/18	8/10	12/36	6/	6/24
Able to drink unaided from mug (months)*	9/12	10/11	12/18		12/15	10/	9/18		10/17	10/18		12/22	12/15					18/24	18/24
Able to say da, ma, ba (months)*	9/12	9/12	10/12	8/12	8/15	10/13	9/22	12/18	10/17	12/19	10/18	10/22	12/15	9/18	8/18	6/9	12/24	9/18	
Able to speak own words (months)*	10/12	10/12		12/24	12/20	12/24	12/22	12/18	12/17	12/19	10/18	15/22	12/15	12/18	12/18	8/9	12/15	12/18	
Maximum No of words	1	12	0	1	10	4	10	1	7	5	1	6	2	6	1	5	2	8	0
Neurological findings:																			
Scoliosis	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Wasting	Yes	Yes	No	No	Slight	Slight	Slight	No	No	Slight	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Muscle tone	↓	↓	†	↓	Slight ↑ †	†	↑	↑	Slight†	Slight ↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Reflexes:																			
Brachioradialis	+	+	+	+	++	+	+	+	+	+	+	+	+	+	++	+	+	++	++
Patellar	+	+	++	+	++	+	++	+	++	+	+	+	+	+	++	++	+	++	++
Tendocalcaneus	+	+	++	+	++	+	++	+	++	++	+	+	+	+	++	++	+	++	++
Plantars	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	††	↓↓	↓↓	↓↓
Adductor spasm	No	No	No	No	No	No	No	No	No	No	Slight	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Dislocated hips	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No
Tight tendo Achillis	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Generalised fits	No	No	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No
Atypical fits	Yes	?	No	?	?	No	?	?	No	Yes	?	?	No	No	No	No	No	No	No
Panic attacks	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hyperventilation	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Involuntary movement:																			
Jerking	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Writhing	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

*Age when skill acquired/age when skill lost (if lost completely).
†Equivocal.

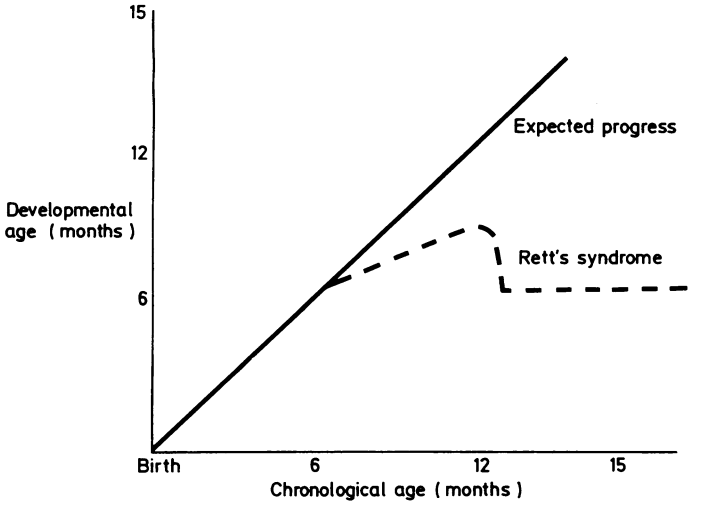

FIG 2—Diagrammatic representation of developmental progress in Rett's syndrome.

faces with fine features, healthy skin and hair, and appropriate colouring and looked at the examiner's face intently, although the expression remained rather blank. The mouth sometimes underwent slow involuntary movements. Close contact was clearly enjoyed. Hand movements were rhythmic, each hand keeping its own distinctive posture and movement, often with fingers adducted and partly extended. The hands were kept at chest or chin height, and the child rarely watched them. The youngest girls were inclined to pull their hair, while the others usually kept their hands at or near the midline, patting or lightly clapping them, banging the mouth, or wringing and squeezing intertwined fingers. Interruption of these activities improved the child's concentration. The girls were clearly interested in a nearby object, but if they could reach it at all it was only after considerable and often agitated delay and typically in a sudden dash.

Difficulty with balance was universal and gait often broad based. Gradients and stairs could not be negotiated. Initially two girls could run in a precipitate fashion, but this ability was later lost. Apparent panic with intense hyperventilation was provoked by strange situations but also occurred spontaneously. Laughter was common and often unprovoked. Air swallowing occurred in two cases.

On formal examination the only abnormalities were in the nervous system. Occipitofrontal circumferences are shown in figure 4 and the table. Vision, eye movements, hearing, and sensation seemed to be normal. Balance was poor, and unbalancing produced panic, although there was some attempt at self righting. The table gives the important neurological observations, which reflect a natural division of the cases into three clinical subtypes according to the disorder of tone and movement. The average age was 4 years in subtype I, 9 years in subtype II (ambulant), and 11 years in subtype III (non-ambulant) (fig 3). Briskness of tendon reflexes, tightness of tendo Achillis and hip adductors, scoliosis, and wasting tended to increase from subtypes I to III. Plantar responses were never extensor. Superficial abdominal reflexes were present. Muscle tone was invariably abnormal, progressing from hypotonia in subtype I to rigidity in subtype III.

Involuntary movements were always present and were of three kinds: the rhythmic hand movements described above; jerky or choreiform movements of the trunk and limbs, which were most pronounced in subtype I; and sinuous movements or dystonia, which were present in all subtypes to a varying extent. Involuntary movements diminished as rigidity increased in subtype III.

Early records, our own serial observations, and evidence from parents who had watched video film of younger affected children suggest that these subtypes may reflect stages in progression of the disorder and to some extent degrees of severity. The sequence type I to II to III, however, did not occur in every case, and the prominence of each type of involuntary movement varied considerably between the children.

Special investigations were not in general contributory. Biochemical screening yielded negative results, as did chromosome studies. Computed tomography of the brain was normal in five children and compatible with mild generalised atrophy in three. Electroencephalograms were of most value, with the characteristic changes noted by Hagberg *et al.*[3] Records were obtained in all but one girl and all were abnormal after 6 years of age. Common appearances were bursts of slow waves (four), two per second spike and wave with changes accentuated in sleep (five), and featureless recordings (two). Sleep organisation was poor with rapid eye movement sleep apparently increased at the expense of stage II sleep.

Discussion

We identified 19 girls with Rett's syndrome and are satisfied that this is a distinct clinical entity. This is the first report of the disorder in the United Kingdom. Our incidence of one in 30 000 live births was derived from the diagnostic outpatient index of the single major referral centre for paediatric neurology in the west of Scotland and birth figures for the area from the Department of Health and Social Security. Some children born in the area who developed the disease may not have been referred or may have been sent elsewhere, and so our figure is possibly an underestimate. It is clear that Rett's syndrome is not excessively rare. Any school for the severely or profoundly handicapped should expect to have at least one case, and a regional referral centre should expect to see one new case each year. The most recent report from Sweden supports our figure.[6] The age at regression in Rett's syndrome directs suspicion to vaccination, but we did not find evidence that this either initiates or aggravates the disability.

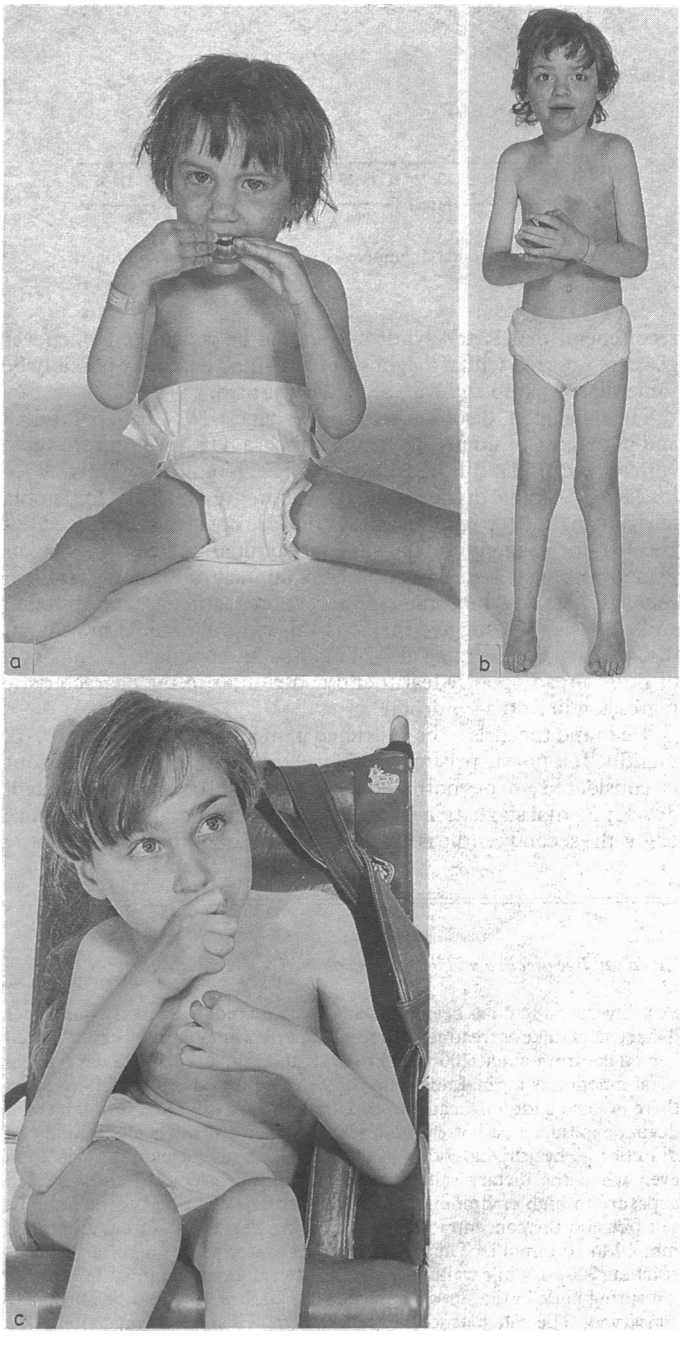

FIG 3—Examples of patients with Rett's syndrome. (*a*) subtype I; (*b*) subtype II; (*c*) subtype III.

In describing these girls the use of the term autism is misleading and, we believe, incorrect. It implies a loss of interest in personal contact, which we did not find. The girls continued to meet the eye and to relate in a friendly fashion within the severe restrictions of their mental and physical handicaps. Areas of excellence were absent. Hand movements actively interfered with voluntary movement, and interruption of them was beneficial; they were unlike the flapping eye level activity of the classically autistic child. As 12 of our patients were initially described as autistic, however, we would

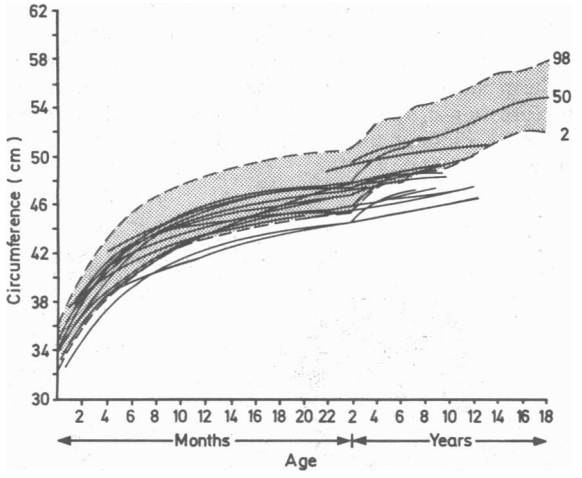

FIG 4—Occipitofrontal circumference in 19 cases of Rett's syndrome.

recommend that Rett's syndrome should be considered whenever girls are referred with a diagnosis of autism. There may possibly be some shared pathology with secondary autism.

The movement disorder is strongly suggestive of extrapyramidal and not, at least initially, pyramidal disease. On this point we agree with the recently published observations of Nomura *et al*.[5] Evidence for extrapyramidal disease is the typical progression from hypotonia to rigidity; the deep tendon reflexes that are not at first increased but become increasingly brisk while abdominal reflexes and flexor plantar responses are retained; the involuntary movements reminiscent at times of parkinsonian tremor, chorea, athetosis, or dystonia; and akinesia. We suggest that it is this extrapyramidal movement disorder which, emerging at 7-24 months, interrupts the acquisition of skills already poorly learnt and contributes to the characteristic regression in Rett's syndrome.

We found the girls to be restricted in mental development to 6-12 months. It is not surprising, therefore, that their learning behaviour is considered to be normal below this age or that subsequent developmental stagnation occurs. An occipitofrontal circumference below the second centile is not an essential part of the clinical picture in early childhood, but there is a tendency for the centile lines to be crossed after 4 months. This may reflect gradual, perhaps secondary, loss of cortical cells; degree of disability and occipitofrontal circumference, however, did not correlate. It is instructive to note the considerable motor and sensory cortical functions that are retained and the lack of computed tomographic evidence of appreciable cortical atrophy.

We have described three subtypes—the first with hypotonia, the second with variably increased tone but retained ambulation, and the third with rigidity and inability to walk—as an aid to clinical recognition. These subdivisions are not inflexible and do not necessarily reflect chronological progression. The wasting, which was most striking in the girls suffering from rigidity (subtype III), is presumed to be of central origin as there is no firm evidence of denervation or myopathy.

As regards the cause of Rett's syndrome, we agree with Hagberg *et al* that the initial defect is probably a mutation of a dominant gene on the X chromosome,[3] occurring only in the affected case and lethal to the male. This explains the absence of a family history and the equal numbers of male and female siblings of girls with Rett's syndrome. It implies no automatic increased risk to families of patients. The genetic defect must be presumed to lead by means of a single protein fault and structural or biochemical defect to abnormal neurological function. A search for the defective gene is required.

We have no doubt that abnormality should be sought in the basal ganglia and in the neurotransmitter systems. Interestingly, Rett described a case with remarkably little melanin content in areas of the substantia nigra.[2]

Pharmacological alleviation of the movement disorder may prove possible. So far we have tried laevodopa on a limited scale without success. Further clinical studies will further elucidate the clinical course and range of the disease and should permit better understanding of the movement and learning disorder.

We thank all those who helped with this study, in particular Dr Ruth Day for allowing us to include patients under her care, and the department of medical illustration, Yorkhill hospitals, for preparing the figures for publication.

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Can a salt free diet in a middle aged woman cause muscular spasms?

Possibly the patient has been advised to practise moderate restriction of her dietary salt intake as treatment for mild hypertension. She may have reduced her intake from about 200 mmol to around 80 mmol (4·7 g) a day.[1] If her renal function is normal this is unlikely to lead to sodium depletion unless there is some additional cause of sodium loss—for example, through sweat during exposure to a hot environment or in urine if she is also taking oral diuretics. A healthy individual need not necessarily develop salt depletion even when the dietary salt is restricted during prolonged and repeated exposure to high environmental temperatures. The urine becomes almost salt free and the concentration of sodium in sweat can fall from around 50 mmol/l to 10 mmol/l.[2] Thus although sweat rates will be high in the heat, reaching 900 g/h while walking in the sun at an air temperature of 38°C or 700 g/h sitting nude in the sun at the same temperature,[3] salt may be effectively conserved. The salt balance, however, is then somewhat precarious; the duration of exposure to heat is critical. The addition of an oral diuretic will certainly lead to salt depletion. Adolph and his colleagues[3] described the symptoms of this form of salt depletion/clinical "dehydration" in detail. Heat exhaustion is characterised by thirst and vague discomfort, the heat becomes noticeably more oppressive, the victim will be restless and sleepy, she will show an inclination to sit or lie down because to stand will produce dizziness, and she may describe muscle fatigue and tingling in the limbs. She will be found to have postural hypotension as well as other signs of shrinkage of the extracellular fluid volume. Muscular spasms do occur with sodium depletion though somewhat less frequently than the other symptoms. These muscular cramps are attributed to the dilution of body fluids rather than to the sodium loss itself. This is similar to the mechanism imputed for the muscular spasms of chronic renal failure when the dilutional hyponatraemia rather than the sodium loss seems important.—P H FENTEM, professor of physiology, Nottingham.

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