When comparing the birth weights of children in different knock-knee grades it was found that the mean birth weight was slightly higher in those with increased amounts of knock-knee. There does not seem to be any association between the age at which the child started to walk and the development of knock-knee. No relationship was found between the duration of breast-feeding and the development of knock-knee. The percentage of children taking vitamin supplements was similar for each grade of knock-knee. The number of days spent in bed through illness showed no relationship to the development of knock-knee.

Mothers were usually extremely vague about habitual sleeping or sitting postures. Many children sleep in a prone-kneeling position when young, and this did not seem to be especially common in those children who had knock-knees. Other information about posture was too unreliable or too scanty to be useful.

Roughly 1% of children seen in these infant welfare clinics had been advised to wear wedged shoes at some time. About 4% had been taught foot and leg exercises (this figure is high because a physiotherapist was attached to one of the clinics). An additional 2% had attended hospital solely for observation. Only one child was seen who had worn night splints for knock-knees. He was aged 59 months and had 4 in. (10 cm.) of knock-knee. In the past he had worn night splints for six months and had been given exercises at hospital for a similar period. Neither of these treatments had been effective, and he was still under hospital observation.

Conclusions

Knock-knee is commonest among children aged 3 to 3½ years. At this age 22% of children were found to have a knock-knee of 2 in. (5 cm.) or more. Only 1 to 2% of children aged 7 years and over have an equivalent amount of knock-knee.

The mean weight of children with knock-knee is greater than the mean weight of comparable children without knock-knee.

The development of knock-knee is not associated with any of the following factors: valgus feet; flatfoot; age at which the child started to walk; duration of breast feeding; quantity of vitamin supplements taken during the first 18 months; illness as judged by the number of days spent in bed.

Knock-knee is very common among toddlers, but fortunately it usually improves without treatment. Apart from operative procedures, no effective treatment for knock-knee is known.

Knock-knee in children under 7 years of age can probably be safely ignored unless it is excessive or unless an underlying cause, such as epiphyseal damage from a fracture or renal rickets, is present.

An underlying cause for knock-knee should be sought if: (1) the knock-knee is excessive—over 3½ in. (9 cm.); (2) the knock-knee is of unequal amount in the two legs; (3) the child is short for its age: this might rarely be due to an epiphyseal dysplasia or to an endocrine disorder; (4) there is a family history of severe knock-knee or other bony deformity; this could be due to a metabolic disorder such as Fanconi's syndrome.

Toddlers' knock-knee can be allowed to join the growing group of developmental deviations which seldom need treatment, such as the infant's tight foreskin (Gairdner, 1949) and the baby's umbilical hernia (Woods, 1953).

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ENCEPHALOPATHY DURING SALICYLATE TREATMENT OF ACUTE RHEUMATISM

BY

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Salicylates are still widely used in the treatment of acute rheumatism, often in toxic doses. Some patients have an idiosyncrasy to salicylates and develop anaphylactic or allergic symptoms which are sometimes fatal. Other well-known toxic effects (Gross and Greenberg, 1948; Goodman and Gilman, 1956) include "salicylism" (tinnitus and deafness, nausea and vomiting, sweating and vasodilatation, etc.), haemorrhages due to hypoprothrombinaemia, capillary damage, or thrombocytopenia (Rappoport *et al.*, 1945; Troll and Menten, 1945), and respiratory alkalosis associated with low pCO₂, high pH, and later an elevated bicarbonate level in the plasma (Guest *et al.*, 1945; Rappoport and Guest, 1945; Boyle *et al.*, 1947; Farber *et al.*, 1949; Reid *et al.*, 1950; Singer, 1954).

Salicylates may also produce cerebral excitation (Gross and Greenberg, 1948; Goodman and Gilman, 1956), with delirium, hallucinations, disorientation, restlessness, excitability, and irritability; later there may be depression leading to coma with respiratory failure and cardiovascular collapse, sometimes with terminal asphyxial convulsions. Ryder *et al.* (1945) describe a fatal case with symptoms partly attributable to a severe respiratory alkalosis, in which necropsy revealed a toxic encephalopathy with nerve-cell degeneration and haemorrhages.

The case reported here was treated with orthodox doses of sodium salicylate and developed an encephalopathy, from which the patient nearly died.

Case Report

A labourer aged 20 was admitted to hospital on February 25, 1954, under Dr. Kenneth Harris. He had had scarlet fever and rheumatic fever at the age of 12. He had not been feeling well for a fortnight, and for the past week had had pain, swelling, and stiffness of both knees and ankles. He was febrile (temperature 101.4° F.: 38.6° C.), and his pulse was dicrotic (100 a minute). He was flushed and looked ill. Both knees and ankles were swollen and

extremely tender, and there was a small effusion in the right knee-joint; movements of these joints and of the hips were limited by pain. The heart was moderately enlarged, with a thrusting impulse 11 cm. from the midline in the left fifth intercostal space. At the apex there was a loud systolic murmur and thrill, faint third heart sound, and soft, short, variable mid-diastolic murmur; a moderately accentuated pulmonary second sound was heard, but no basal murmur. The other systems were normal. The urine contained no sugar or albumin.

Blood count: Hb, 84% (Haldane); white cells, 10,600 per c.mm. (normal differential); E.S.R., 54 mm. in one hour. Throat swab: no *Streptococcus haemolyticus* grown. Anti-streptolysin O titre, 500 units per ml. Chest radiograph showed moderate cardiac enlargement. E.C.G.: P-R interval 0.24 second; left axis deviation. A diagnosis was made of recurrent acute rheumatism with carditis in a case of chronic rheumatic heart disease with mitral incompetence.

Treatment was started on admission with sodium salicylate (10 g. a day) without bicarbonate. The fever and arthritis subsided in 48 hours. On March 3 the plasma salicylate level was 26.5 mg. per 100 ml. Next day the fever recurred (temperature 100.2° F.: 37.9° C.) and he complained of precordial pain. A widespread pericardial friction rub was heard. The E.S.R. was 58 mm. in one hour. On March 5 the dose of sodium salicylate was increased to 12 g. a day; the chest pain, fever, and pericardial friction rub rapidly disappeared. On the 10th the plasma salicylate level was 26 mg. per 100 ml. On March 14 his respirations were noticed to be very deep. Next day his condition was unchanged on awakening; hyperpnoea was still present. At 10.45 a.m., almost immediately after an uneventful venepuncture, he groaned and became unconscious, with extensor spasm of arms, legs, and back. At this time, pulse and heart sounds were undetectable, respirations had ceased, and he became cyanosed. The pulse returned abruptly after approximately one minute. He was given intravenous nikethamide, and oxygen by B.L.B. mask. He started to breathe again, irregularly at first, and then very deeply and noisily.

At this stage his limbs were flaccid and he had very weak reflexes and absent plantar responses. He then started to have frequent tonic extensor spasms of all four limbs, accompanied by trismus and opisthotonos; between the spasms there was general muscular flaccidity. They continued for over an hour.

Intravenous calcium gluconate (10 ml. 10%) and mephensin (1 g.) were without effect, as was 7 ml. of intramuscular paraldehyde. Anaesthesia was then induced by Dr. R. Molloy with thiopentone (0.5 g.) and gallamine triethiodide (8 mg.), and the tonic spasms ceased immediately. Controlled respiration was maintained by the anaesthetist. Lumbar puncture was performed; the C.S.F. pressure was more than 300 mm.; the fluid was clear and colourless, and the chemical and cytological findings were normal. The temperature was 100.2° F. (37.9° C.). At 12.30 p.m. the plasma salicylate level was 50 mg. per 100 ml., plasma CO₂ content 18.1 mEq/l., plasma chloride 111 mEq/l., prothrombin concentration 31%. The E.C.G. was normal (P-R interval, 0.18 second).

He gradually recovered consciousness and had no further spasms. An intravenous drip was started and 750 ml. of 5% sodium bicarbonate solution and 570 ml. of M/6 sodium lactate were administered. On March 16 he was conscious and alert, and hyperpnoea was less marked. Sodium bicarbonate was given freely by mouth. The plasma salicylate was 23.5 mg. per 100 ml., the plasma CO₂ content 27 mEq/l., the plasma chloride 105 mEq/l., the prothrombin concentration 51%. Clinical examination revealed no abnormality in the central nervous system. A lumbar puncture on March 19 showed the C.S.F. to be under normal pressure.

The patient was subsequently treated with corticotrophin, and ultimately, after a prolonged course with recurrent fever, chest pain, pericardial effusion, and erythema marginatum, all evidence of rheumatic activity disappeared. Cortico-

trophin therapy was supplemented with small doses of calcium aspirin; the plasma salicylate never rose above 11 mg. per 100 ml. and there were no ill effects.

Discussion

Central nervous symptoms occurring in the course of acute rheumatism treated by salicylates may be due to the disease or to the treatment, and in many of the reported cases it is difficult to be certain which was responsible. Cerebral manifestations of acute rheumatism at the present time appear to be exceedingly rare, and standard textbooks scarcely mention them, but it seems that they are usually associated with rheumatic hyperpyrexia. Southey *et al.* (1882), writing shortly after the introduction of salicylates, which were given to only a few of their cases, discuss in detail the features of hyperpyrexial acute rheumatism. Delirium was almost always present and sometimes preceded the onset of hyperpyrexia. Among other nervous symptoms noted were restlessness, insomnia, coma, tonic spasms, risus sardonius, convulsions, etc.; but these occurred in relatively few cases, and clearly were not essential or even common features of this complication of acute rheumatism. Cruickshank (1951) reported a case of acute rheumatism in which the rectal temperature rose to 110° F. (43.3° C.), and the sequence of events included rhythmic twitching of the limbs, generalized clonic movements, intermittent tonic spasms with arching of the back, and coma with flaccid limbs and areflexia between spasms; the patient recovered but was left with temporary cerebellar signs. This patient had been treated with 16 g. of sodium salicylate daily (with alkali) for three days, and on the fourth morning complained of buzzing in the ears and a black cloud in front of the eyes. It is at least possible that the encephalopathy was due to sodium salicylate.

Though our patient had some features—namely, coma, and tonic extensor spasms with opisthotonos—in common with the descriptions quoted, he had no hyperpyrexia (temperature 100.2° F.: 37.9° C.), and the episode of encephalopathy was short-lived. After recovery from the general anaesthetic, about six hours after the onset of the encephalopathy, he had no further spasms or any other evidence of central nervous excitation. Though cardiac arrest continued for approximately one minute, the clinical picture was not that of a Stokes-Adams attack.

It seems almost certain, therefore, that the episode was one of salicylate poisoning. This is supported by the fact that it was preceded by marked hyperpnoea, and that recovery was associated with a fall in the plasma salicylate level from 50 to 23.5 mg. per 100 ml.

It seems likely that the nervous symptoms and signs in this case were due to a direct cerebral and spinal excitation. The alkalosis was only moderate (plasma CO₂ content 18.1 mEq/l.), though unfortunately no pH measurements were made. Petechial haemorrhages have been observed in the brains of fatal cases of salicylate poisoning; these may be due to a direct action on the capillary endothelium or the hypoprothrombinaemia. In this case the "prothrombin" concentration (by the one-stage method) was reduced to only 31%, and the rapid clinical recovery is perhaps against a haemorrhagic cause. The raised C.S.F. pressure suggests that cerebral oedema may have been present.

Large doses of salicylates are commonly recommended in the treatment of acute rheumatism, and plasma salicylate levels of 35 mg. per 100 ml. or more are advocated (Coburn, 1943; Taran and Jacobs, 1945). Illingworth and his colleagues (Illingworth *et al.*, 1954; Holt *et al.*, 1954) aimed at serum salicylate levels between 30 and 40 mg. per 100 ml.; though this appears to be effective, these authors express uncertainty whether such high dosage is essential. Unless it is shown that cortisone or corticotrophin alone produce better results, it is likely that salicylates will continue to be used for the treatment of acute rheumatism and that large doses will be given. Holt (1954) and Reid (1948) have discussed some of the difficulties involved in maintaining

steady blood levels, and it appears to be inevitable that in some patients the plasma salicylate level will rise dangerously; weekly estimations are no guarantee that this will not occur.

Previous reports state, and experience with this case confirms, that marked hyperpnoea should be taken as a warning of impending dangerous toxic reactions; it should be an indication for a reduction in dose. The plasma level is not an absolute guide, as it is evident that the toxic level varies greatly from patient to patient. Graham and Parker (1948) have found that severe drowsiness and excitement commonly appear at levels of 35 to 55 mg. per 100 ml. Intravenous salicylate administration to patients with carbon dioxide retention and respiratory acidosis has been shown (Wégria *et al.*, 1955) to reduce the arterial $p\text{CO}_2$, and has been suggested as a possible method of treatment of such cases; the use of salicylate-induced hyperpnoea in this way would seem to be dangerous, as the blood levels which may be required or involuntarily achieved to produce a therapeutic effect differ little from those which in some subjects are dangerously toxic.

In treatment of established salicylate encephalopathy, general anaesthesia, with the use of a relaxant and controlled respiration, may be necessary, and was effective in the above case in arresting the tonic spasms; elimination of salicylate in the urine may be encouraged by the administration of intravenous sodium bicarbonate. Bicarbonate was formerly recommended to combat the supposed acidosis, but its main action is to promote renal excretion of salicylate (Parker, 1948; Reid, 1948). It may, however, cause a further rise in pH (Rapoport and Guest, 1945); but, theoretically, inhalation of high CO_2 gas mixtures might be expected to correct the metabolic disturbance. A high rate of urine formation should be maintained by an adequate fluid intake (either intravenous or oral).

Summary

A case of acute rheumatism, complicated by encephalopathy attributed to sodium salicylate therapy in ordinary dosage, and associated with a plasma salicylate level of 50 mg. per 100 ml., is described.

Hyperpnoea should be taken as a warning sign of impending dangerous toxic effects of salicylate therapy.

Encephalopathy occurring in these circumstances can be treated successfully by general anaesthesia, with the use of a relaxant and controlled respiration, intravenous administration of sodium bicarbonate, and the maintenance of a high fluid intake.

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AN EVALUATION OF THE MICROSPECTROGRAPHIC DIAGNOSIS OF APLASTIC ANAEMIA

BY

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Our attention has recently been drawn to a paper by Kobayashi and Watanabe (1955) describing differences in the spectroscopic absorption curves of the haemoglobin in individual erythrocytes of leukaemia and aplastic anaemia. They suggest that their technique may be of some help in the differential diagnosis of these two conditions. We have in this laboratory some experience of cytospectrophotometry and its attendant errors, and we consider that the absorption curves published by them show enough inaccuracies to invalidate their conclusions. As the medical treatment of these two conditions may be diametrically opposite, we felt that it was essential to publish, as soon as possible, preliminary results confirming our doubts about the value of this method of diagnosis.

Absorption Curves of Red Cells

Fig. 1 shows the absorption curves of normal red cells redrawn from the paper by Kobayashi and Watanabe. A close examination of these curves reveals considerable inaccuracies. We have regularly plotted absorption spectra (4,000–7,000 Å) from small areas of individual red cells, both normal and abnormal, from various mammalian species (man, rat, guinea-pig, camel), and have always obtained curves having their maxima at identical wavelengths (4,150 Å, 5,420 Å, and 5,750 Å) (Keohane and Metcalf, 1956). These agree with the figures obtained by us and by many others for solutions of haemoglobin (Sidwell *et al.*, 1938; Jope, 1949). The differences in the chemistry of haemoglobins of different species are differences in the globin part of the molecule, and do not affect the visible absorption spectrum, which is entirely due to the haem radical.

Many early workers in this field found it difficult to obtain the 4,150 Å (Soret) absorption with intact erythrocytes (Adams, 1938; Keilin and Hartree, 1941), and others obtained inaccurate maxima for the 5,420 Å and 5,750 Å absorption (Cordier and Coudier, 1950). These errors have been shown to be due to scatter in the apparatus (Jope, 1949; Keohane and Metcalf, 1956). Elimination of this scatter corrects the error and improves the consistency of the curves. As the wavelengths of the absorption maxima of haemoglobin are constant it can be assumed that the peaks demonstrated above 4,500 Å in Fig. 1 are simply fluctuations due to experimental error and give a measure of the accuracy of the method. Other workers have failed to demonstrate the α and β (5,420 and 5,750 Å) absorption of intracellular haemoglobin (Jope, 1949; Metcalf, 1951). This is not surprising, as the percentage absorption of light at this wavelength is of the same order as the accuracy of photographic photometry ($\sim 10\%$). We have adopted a photometric technique in order to be able to obtain the α and β absorption maxima consistently and accurately in individual cells (Keohane and Metcalf, 1956).

The type II curve of Kobayashi and Watanabe (Fig. 2) shows decreased absorption in the Soret region but considerable absorption in the 4,500–5,000 Å region, a wavelength band in which haemoglobin should have no absorption. This spurious absorption is easily produced by using