subnormal nutrition can constitute a serious handicap to the educational advancement of a child. A further inference from the data is that the mental activity of girls is even more closely related to their general physical state than is that of boys.

It may be contended that these deductions are not valid, inasmuch as parents of low intelligence not only beget children with a poor mental capacity but, in addition, cannot accord these children proper and sufficient care, with the result that malnutrition arises. In this way, it could be argued, the children who are mentally slow and who also suffer from malnutrition can be accounted for. Though this sequence is undoubtedly of not infrequent occurrence, yet only a comparatively small proportion of the cases in any one area could be accounted for on this basis. Moreover, the investigations of Corry Mann (already cited) are particularly significant in this connexion, in that he found that the boys in the group receiving supplementary milk, whose nutritional condition was thereby raised above that of the other groups, were more high-spirited and active. The same observation has been made in school dining centres provided for children with defective nutrition. The inference is that the malnourished child who has been labelled "slow" may, as a result of corrected dietetics and improved nutrition, attain to an ability to use his mental powers equivalent to that enjoyed by his better-nourished school-mate.

It is evident that further light on this aspect of the nutrition of children will be of value particularly to those interested in educational advancement.

Summary

The nutrition grades of 355 bright and 357 slow children were investigated. Of the bright children 28.2% were graded Nutrition A and 5.6% graded Nutrition C. Only 6.7% of the slow children were Grade A, while 22.1% were graded Nutrition C. The 3 instances of Grade D children were found in the slow group.

Of this group 583 members were arranged according to sex. Of the bright boys 26% were graded A and 7.4% were graded C, the corresponding figures for the girls being 30% and 4% respectively. In the case of the boys who were regarded as slow, 7% were Nutrition A and 18.6% were Nutrition C, whereas 5.3% of the girls in the slow category were Nutrition A and 26.6% were Nutrition C.

I am indebted to Dr. John Stokoe, whose keen interest in matters connected with nutrition was a stimulus to inquiry.

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pigmentation of the skin of the neck and of both upper eyelids. The prominence of her eyes was associated with conspicuous lid retraction on both sides—retraction so great that her eyes closed incompletely during sleep. The left cornea had a small abrasion. The thyroid was firm, both lobes and the isthmus being easily palpable and definitely enlarged. There was no retrosternal dullness. The outstretched hands showed a fine tremor; regular tachycardia of 100 to 110 persisted during the day and declined little at night. The cardiovascular system showed no abnormality apart from the tachycardia, and the other main systems seemed to be normal. The tongue was dry, brick-red, and fissured, but not sore. Her red blood cells numbered 4,800,000 and her haemoglobin was 81%. On admission the hands were persistently cold and blue—an unusual feature in thyrotoxicosis. The nails were brittle, conspicuously spoon-shaped, longitudinally striated, and cracked. She said that they had been in this state for about six months. The skin surrounding the nail, and especially at its base, was dry and scaly, and was encroaching upon the actual nail itself in an irregular manner. The free margin of the nail bed, instead of showing the normal clear-cut line of demarcation, was irregular.

Her stay in hospital was prolonged owing to the development of various complications. Soon after admission an acute respiratory infection was treated successfully with sulphathiazole. At that time the patient was having 30 minims of Lugol's iodine daily, and at the end of the course, which coincided with the end of the respiratory infection, her pulse rate during the day was 80 to 90 and at night 80, with definite diminution of other thyrotoxic signs. During July she developed a large bed-sore and a suppurative parotitis, from which she recovered. Despite these infections her general health improved steadily, and it was noticed at the time that the condition of her nails was altering and that growth was now occurring normally, the scoop being pushed onwards (Fig. 3). The skin around the nails had become more normal and the pulp was more rounded. There was no further cracking of the nails. By August she had gained a stone in weight; her red blood cell count was 5,010,000 and Hb 98%. Her basal metabolic rate was + 61%.

During September she developed another acute respiratory infection, which was treated with sulphathiazole, and also a severe conjunctivitis with corneal ulceration after a short course of thiourea. Nevertheless her general condition continued to improve steadily and her weight was increasing. Her pulse rate was in the region of 80 to 90 both day and night; her basal metabolic rate was + 48%. On Oct. 1 her red cells were 4,690,000 and Hb 84%—values similar to those on admission. The normal growth of her nails continued, and as they grew they soon became perfectly formed and clear-cut at their margins, brittleness being lost (Fig. 4). She had gained nearly 2 stone more in weight.

Recovery of Nail Growth in Case I

The nails in Fig. 2 seem shorter than in Fig. 4. This apparent shortening was due to the skin clinging to the base of the nail and being carried onward with it. The extent of this skin encroachment could be ascertained by measuring from the V-shaped crease of skin to the nearest part of the exposed nail in Fig. 4 and transferring this measurement to Fig. 2. This is shown in the outlines of Fig. 1: the nail is at least as high up the finger as the dotted line of the right-hand tracing. It is important to fix this, the growing root of the nail, as accurately as possible if we are to ascertain the time at which growth

FIG. 1.—Case I. Outline of middle finger on June 21 (right) and July 19 (left), showing the relative position of the proximal edge of the scoop, the root of the nail, and a V-shaped crease in the skin over the distal interphalangeal joint. Used to estimate the date at which formation of deformed nail ceased. Drawings made from Figs. 2 and 3.

changed from normal to abnormal. The position of the proximal margin of the scoop can be fixed relative to a given skin crease in Figs. 2 and 3 and, through this, to each other. In this middle finger it moved onwards by 5 mm. in four weeks; and the rate at which the scoop grew onward in the index finger was the same. In Fig. 2 the growing root of the nail lies about 9 mm. above the proximal margin of the scoop. It

KOILONYCHIA AND ITS RECOVERY IN CASES OF THYROTOXICOSIS

BY

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So much emphasis has in recent years been thrown upon the relation of koilonychia to the anaemias, and especially to hypochromic anaemia, that it may be of value to record two cases and to comment that in neither was there any reason for supposing iron metabolism to be at fault.

Case I

Mrs. A., aged 69, was admitted to hospital on May 11, 1943, complaining of nervousness, palpitations, abdominal colic, and loss of weight of two years' duration, and of general tiredness and staring eyes for three months. On examination she was found to be emaciated, nervous, and very excitable. She had diffuse brown

would seem, therefore, that the arrest of abnormal growth must have occurred about seven weeks before Fig. 2 was taken—a date about April 1, or six weeks before the patient entered hospital. It may have been a little more or less. Special inquiry showed that the patient was continuously at home with her family between June, 1942, and May, 1943, and that during

FIG. 2.—Case I, June 21. Fingers 2, 3, and 4 of right hand, showing spoon-shaped nails. Note broken skin near root of nail—dry, and attached to nail and drawn onward by its growth.

FIG. 3.—Case I, July 19. The same fingers, showing growth of well-formed new nail; the scooped nail is growing off.

FIG. 4.—Case I, Nov. 15. The same fingers, with well-formed nails.

that period, though ailing, she refused to see a doctor and took no medicine of any kind. No iron was given to her during her stay in hospital. It seems very difficult in these circumstances to associate the koilonychia with an iron deficiency, clearing up, as it would be necessary to suppose, during the end of the period of her home life. Moreover, her blood counts gave no encouragement to this idea.

The case serves to stress the importance of noticing in cases of koilonychia, when first seen, how close to the root of the nail the scoop comes, and the rate of nail growth, in attempting to correlate the scoop with clinical events. The factors bringing about faulty growth are not necessarily present when the deformity is first seen; they may have ceased to operate many weeks previously.

Case II

Mrs. B., aged 59, was admitted to hospital on Jan. 25, 1944, showing symptoms and signs of severe thyrotoxicosis. She complained of extreme nervousness for three years, and palpitations, staring eyes, and loss of weight for six months. On examination she was found to be thin, flushed, sweating, and very nervous. Her prominent eyes showed marked lid-retraction, up to 5 mm. of the sclerotic being exposed above the pupil and 3 mm. below. The lids failed to shut during sleep. The thyroid showed a definite, firm, even, pulsatile enlargement of the whole gland. The heart was slightly enlarged, and presented a regular tachycardia which decreased during sleep, a soft systolic apical murmur, and an accentuated aortic second sound. Her pulse was conspicuously water-hammer in character, and there was capillary pulsation. The blood pressure was 200/100 mm. Hg. A fine tremor shook the extended hands and all reflexes were brisk. The tongue was smooth, fissured, and bright red, but not sore; there were sordes at the corners of the mouth.

The finger-nails were deformed and had been spoon-shaped, thin, and brittle for about three months. The nails affected were those of both forefingers and, to a lesser extent, the right middle finger; the remaining nails were thin, brittle, and longitudinally striated, but showed no scoop. The skin at the base of the nail was dry and adherent for 2 or 3 mm., producing apparent shortening of the nail, as in the last case. The free nail margin was broken, and was irregular in thickness. The obvious concavity of the nail of the index finger extended up to the adherent skin.

Her basal metabolic rate two days after admission was +138 and her blood count showed 5 million red cells and 6,000 white cells, which remained constant throughout her two months' stay in hospital. Weekly haemoglobin estimations showed a variation between 90 and 98%. A fractional test meal showed a normal acid curve.

For the first fortnight in hospital the patient was treated with rest in bed only. During this period her pulse rate subsided from 110 to 90 a minute with a slight general improvement. Thiourea 1 g. three times a day was begun early in February. Five days later she developed severe conjunctivitis, which subsided in eleven days after the change to thiouracil 0.2 g. five times a day. Apart from this complication her general improvement continued steadily. This was shown by her calm behaviour and lack of apprehension, a fall in the pulse rate, and a conspicuous decrease in the exophthalmos and lid-retraction. Her basal metabolic rate decreased in five estimations steadily down to +15 and her weight increased by nearly a stone in two months. Her finger-nails gradually became normal; the brittleness disappeared, they became thicker and more unyielding, the dry skin at the base of the nail receded, and the scoop gradually grew off.

The dose of thiouracil was reduced, the patient being discharged on April 1, 1944, on 0.2 g. daily.

Recovery of Nail Growth in Case II

In this case the nail of the index finger was at first concave over almost its whole surface. Some weeks elapsed before, as the nails began to grow properly, the upper margin of scoop could be defined clearly. It was marked by staining it with a line of nitric acid, and its rate of onward movement was determined relative to the distal edge of the nail bed. On March 11 the distance was 8 mm., on the 25th it was 6 mm., on April 13 it was 4 mm., and on May 11 the line had just grown off. Thus the growth was regular, and at a rate of about 1 mm. a week. Now, the distance of the nitric acid mark from the root of the nail on March 20 was 6 mm.; and thus it may be calculated that normal growth began weeks earlier—namely, about a week after admission, a little more or less. Close inquiries showed that the patient had used nothing in her household duties, such as washing soda, that could be held to account for the condition of her nails on admission. She had taken no iron before admission, and was given none while in hospital.

Discussion

Discussion must be short because our observations on these two cases still leave the cause of koilonychia obscure. A brief inquiry into past records is enough to show that the spoon-shaped nail occurs under distinct circumstances, that it may be

hereditary or acquired, temporary or permanent, and that it has been described in conjunction with various factors, local and general, thought to be of possible significance. Among other conditions we find thyrotoxicosis named more than once (Heller, 1927; Rossegger, 1936); curiously, thyroid deficiency has also been blamed (Schönstein, 1929). Reference may be made to the useful general accounts of Heller (1927), Cipollaro (1930), and Rossegger (1936).

The other chief point we desire to stress is that, in temporary koilonychia, attempts to associate the nail change with any particular factor should take into account the abruptness with which the nail growth may lose its abnormality, while the change in the nail, which has been the result of earlier abnormal growth, may continue to be shown for many weeks or perhaps months. Thus it is clear that the presence of a concave surface does not mean that the process responsible for it is still active; indeed, when the concavity is at the distal end of the nail it is probable that the cause has been for a long time in abeyance—a fact to which Toegel (1937) draws attention in his case which followed brief exposure of the nails to benzene.

Our thanks are due to Sir Thomas Lewis for his assistance with these cases, and to Prof. H. P. Himsworth and Dr. Kenneth Harris, of University College Hospital, for permission to use the case reports.

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HISTOLOGICAL EFFECT OF INJECTION OF MEPACRINE (ATEBRIN) DIHYDROCHLORIDE*

BY

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Recently a note was published (Hawking, 1943) concerning the histological effects produced by the intramuscular or subcutaneous injection of mepacrine methanesulphonate (atebrin musonate). However, the preparation most commonly issued for injection in the Army is the dihydrochloride (atabrine dihydrochloride). An investigation has therefore been made to see whether the effect of the dihydrochloride is significantly different from that of the methanesulphonate, and the opportunity has been taken to compare both of these preparations with quinine dihydrochloride, which is the preparation of quinine most commonly recommended for injection.

A 4% solution of quinine dihydrochloride has a reaction of pH 3.08. A 10% solution of mepacrine methanesulphonate has a reaction of pH 4.0; and one of 5%, pH 4.24; a 3.3% solution of mepacrine dihydrochloride has a reaction of pH 4.40. All these reactions were measured at 17° C. There is consequently no substantial difference in the acidities of the two solutions of mepacrine, and both are somewhat less acid than that of quinine dihydrochloride. The chief physical disadvantage of mepacrine dihydrochloride lies in its lower solubility. The methanesulphonate is soluble in water up to 33%, but the dihydrochloride only up to about 3.3% at 17° C. To obtain a 10% solution the mixture must be cautiously warmed to about 50° C. (decomposition occurs on boiling), and then the solution is cooled to 37° C. and injected without delay.

Technique

Mepacrine dihydrochloride (atabrine dihydrochloride, Winthrop), 43 mg. in 0.5 c.cm. of warm water, or mepacrine methanesulphonate (May and Baker), in equivalent amount (50 mg.), was injected intramuscularly into the thigh or loin of rabbits; some injections were also made subcutaneously on the abdomen. Similar injections of quinine dihydrochloride (Howards), 20 mg. in 0.5 c.cm., were given to other rabbits: in the previous work it had been found that the toxic action of 20 mg. of quinine was approximately equal to that of 50 mg.

of mepacrine. The animals were killed at suitable intervals (1 to 10 days); the sites of injection were fixed in formalin and studied by the usual histological technique. Altogether mepacrine dihydrochloride was injected into 11 sites intramuscularly and 4 sites subcutaneously, and mepacrine methanesulphonate into 4 sites intramuscularly. Quinine dihydrochloride was injected into 7 sites intramuscularly and 3 sites subcutaneously.

A parallel series of observations were made with rats: 4.3 mg. of mepacrine dihydrochloride in 0.3 c.cm. of water was injected intramuscularly into the thigh and subcutaneously on the abdomen, respectively, in 8 sites of each type; 5 mg. of mepacrine methanesulphonate was injected intramuscularly and subcutaneously into 3 sites of each type; and quinine dihydrochloride 10 mg. in 0.3 c.cm. of water was similarly injected into 8 sites of each kind. The dose of quinine was twice that of the mepacrine, since the therapeutic dose of quinine (0.6 g.) is usually at least twice that of mepacrine (0.3 g.).

Experimental Results

Naked-eye Appearances.—When mepacrine dihydrochloride was injected into the lumbar muscles of rabbits a fusiform lesion was produced about 4 cm. in the long axis of the muscle, by 2 by 1 cm. The lesion, on section, was dark red surrounded by a narrow yellow or whitish zone (leucocytes). In the thigh the connective tissues along the sciatic nerve were usually swollen, and often there were haemorrhagic patches in the adjacent muscles, but the appearances were less regular than those in the loin. The thigh is much less suitable than the loin for observing the effects of intramuscular injection, since so many fascial planes are present that the injected material is deposited chiefly in the connective-tissue spaces between the muscles rather than inside the muscles. In the thigh of rats there was occasionally some yellowness and oedema of the connective tissue around the chief vessels and nerves, and in one animal killed after seven days there was contracture of the muscles; but on the whole the macroscopical changes were inconspicuous. The lesions produced by mepacrine methanesulphonate were indistinguishable from those described above, and so were those produced by quinine dihydrochloride (apart from the absence of any yellow staining).

When mepacrine dihydrochloride or methanesulphonate was injected subcutaneously it caused great thickening of the skin, extending 4 to 9 cm. and due to yellow gelatinous oedema of the deep connective tissue; later a hard necrotic scab was formed. With quinine dihydrochloride the swelling was less marked and there was no yellowness.

Since mepacrine is strongly fluorescent some of the animals were examined under ultra-violet light; diffuse yellow fluorescence was seen in the tissues around the site of injection, especially subcutaneously, but the distribution could not be definitely mapped out by this method.

Microscopical Appearances.—When mepacrine dihydrochloride was injected into the compact muscles of the loin an area of coagulative necrosis with haemorrhage was produced, as described above. A short distance inside the margin of this area there was a zone of disintegrated leucocytes (seen macroscopically as a yellow band), but the necrosis extended outside this zone, and the demarcation between necrotic and living muscle was initially indistinct. After some days there was a second cellular reaction at the demarcation line, and in 10 days a definite layer of granulation tissue was formed in which were embedded shrunken muscle fibres, a few giant cells, and new collagen. In the looser tissues of the thigh the main reaction occurred in the intermuscular connective tissue, which was initially greatly distended with fluid and infiltrated with polymorphs and mononuclears. Haemorrhages and collections of albuminous exudate were also present, and most of the tissue appeared necrotic. The superficial layers of the adjacent muscles were necrotic to a variable depth and the connective tissue inside the muscle often contained fluid and leucocytes; haemorrhage was sometimes present. After from 3 to 7 days some of the necrotic muscle fibres became calcified, and the necrotic areas were separated from the healthy tissue by a zone of young granulation tissue containing many mononuclear cells. In the thighs of rats the appearances were similar. The lesions caused by mepacrine dihydrochloride were indistinguishable

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