

## Original Articles.

### OSTEOMALACIA: ITS EARLY RECOGNITION, MODERN PREVENTION, AND TREATMENT: (A THREE YEARS' "FOLLOW UP" OF 69 PRIVATE CASES).

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IN view of the fact that throughout the Northern quadrant of India from Peshawar to Calcutta in a thousand townships there are young girls, married women and old ladies suffering from the active disease or some sequelæ of its chronic form, it behoves us to review the clinical aspects of osteomalacia with a view to its modern prevention and treatment. For whereas a few years ago we looked upon this disease as a painful and hopelessly crippling condition, and did not recognise its variegated types, to-day we should be able to diagnose the many diverse clinical forms and definitely state that the disease can be cured or arrested if the proper treatment be carried out.

In order to make the rationale of the modern treatment understood, certain primary facts must be stated, viz:—

1. Any variations from the normal in the blood calcium and phosphorus of osteomalacics depend directly upon the severity of the disease and its duration. The normal percentage of calcium in the blood per 100 c.c. is 10.5 to 11 mgm. and of phosphorus 4 to 5 mgm.

2. Osteomalacia may occur at puberty and resemble late rickets; it may occur in those who have never been pregnant; or occur for the first time in women during or after the menopause. In our experience, the most usual time has been either during lactation or during the third or fourth pregnancy.

3. The menstrual flow in all our non-pregnant patients has been uniformly scanty and irregular.

4. Improving the diet alone in Indian patients has no marked effect on the disease, nor has any benefit been derived from giving any of the derivatives of calcium alone, but if cod-liver oil is added to the diet or given intravenously, there is immediate relief of symptoms:—the hobbling, waddling, groaning cripple in a few weeks walking, sitting or rising without pain.

5. If from poverty or other cause it is not possible to rectify the calcium deficiency in the diet, and yet cod-liver oil is given, exactly the same benefits will accrue. Therefore there must be some element in cod-liver oil which activates the retention of calcium in the system, or which enables the calcium to be utilised, *in the presence of sunlight.*

6. Osteomalacia is a deficiency disease and is to be placed in the same category as rickets; the deficiency principally is in the fat-soluble vitamins A and D, or the calcium activator content of the diet.

7. There is no pathological evidence whatever that the ovaries are in any way connected with the aetiology of osteomalacia. It is difficult to understand how this erroneous idea started and is still held by a few die-hards. Presumably it gained acceptance because castration not only prevented further pregnancy, but also stopped all menstruation with its consequent monthly drain of menstrual calcium.

8. Radiographs have been taken in a great number of our cases. In some, all that was seen was decalcification or blurring of outline. In others there was the typical bony deformity of the pelvis, sternum, vertebræ or long bones. In one Sikh from Burma and in one Bengali there was the anterior beaked pelvis like the prow of a boat. In a great many there was such crumpling of the pelvis as to make the true conjugate or outlet transverse but two inches or less. In Bengal the funnel pelvis is peculiarly common, not only among Indians but also among Anglo-Indians. The greater frequency of this deformity to-day, not only in India but also in Europe, suggests that its causation may be due to mild osteomalacia or food deficiency errors at puberty, for we have observed that in all these cases there is a history of delayed or irregular onset of the menstrual cycle, probably dependent on deficient calcium activation and vitamin shortage, for the vitamins are to the endocrines what the endocrines are to the economy.

#### *Symptoms.*

*We particularly wish to stress the point that just as rickets is a deficiency disease with multiple clinical types, so is osteomalacia.*

In our series of cases such symptoms as tetany, or hyper-irritability of the muscles with exaggerated knee jerks, and in some cases actual paralysis of the extremities were very common.

In other cases still the symptoms were mainly gastric or intestinal, with great distension and inability to digest food. In some of these the anæmia was very great, and girdle pains a marked feature, resembling the gastric crises of locomotor ataxy.

In most cases worms are present, and it would seem as if in addition to a vitamin A and D deficiency, there was a vitamin B shortage as well.

In some tetany and anæmia were practically the only symptoms in the early stages of the disease; later, the patients having been treated for hysteria by their medical attendants, or having developed girdle and shoulder pains, or having complained of pain in rising and sitting, a further opinion was usually sought.

In other cases we found that the patient, being old and past the menopause, had been treated with iodides and salicylates for months

on the plea of rheumatoid arthritis. Many of these were so crippled that they could not stand or walk and had been anchored to one corner of a room for months.

In some there was almost complete paralysis below the waist line after child-birth, and because they had no pain whatever, the diagnosis had been an organic cord lesion. We have seen these patients walking about within a month of efficient treatment. Others only complained of numbness or pain in the extremities, and in some this numbness was associated with a sensation of ants creeping over the skin, particularly in the waist line and lateral parts of the thigh. In two cases this formication symptom was in the shoulder girdle with only stiffness but no pain, suggesting a mild neuritis or vasomotor disturbance.

In a few, face-ache or tooth-ache with neuralgia was the main complaint, beside the anæmia.

Finally, it is *all-important to remember that the typical bony changes such as the triradiate pelvis of the advanced case are by no means a necessity.*

We have seen patients at puberty and after abortion or full term labour where the signs and symptoms were *entirely muscular, nervous, or tetanoid* and in whom all symptoms subsided after correct treatment. An interesting feature of this type of case is that the disease may occur mildly with such like nervous, muscular or tetanoid symptoms and give rise to no obstetric difficulties whatever, and then suddenly in a subsequent conception become acute, with crumpling of the bones and complete immobility, necessitating Cæsarean section or an extraordinarily difficult craniotomy.

One of the tragedies of osteomalacia is or has been that the obstetrician has not realised that the foetus suffers with the mother, and fails to get enough calcium when the mother's blood (starved of its fat-soluble vitamins) is deficient in this mineral. The consequence is that the foetus when born is skinny and its long bones are poor in ostein and chondrin, whilst the epiphyseal zone of calcification is irregular. The tragedy lies in the fact that if the attendants after a normal delivery, or surgeons after a Cæsarean section do not realise this, the infant may rapidly go down hill and die from calcium and vitamin starvation.

It behoves all attendants to remember that both mother and child after delivery require adequate and correct vitamin feeding, for it is a slur upon the surgeon if a Cæsarean baby should die early through ignorance of this fact and negligence of the benefits of sunlight, for sunlight is the essential factor in the cod-liver oil treatment.

Moreover all babies born of osteomalacic mothers later tend to develop rickets. We have seen a great number of these children with typical rachitic phenomena between the years of 1 and 8. Therefore the parents should be warned of the necessity of proper feeding and

sunlight for their children. There is a deplorable tendency to-day in Bengal to give patent milk preparations to all children whom their mothers cannot nourish. Such feeding is a mistake. Fresh cow's or goat's milk is always procurable, and cod-liver oil can be added in the form of one teaspoonful of the 50 per cent. "Collosol" emulsion of Crookes' twice a day.

#### *Ætiology.*

Mellanby, whose work on diet and disease with special reference to teeth, lungs and pre-natal feeding is so well known, postulates that in the prevention of rickets, and we may say also of osteomalacia, three factors are necessary:—

- (a) A sufficient supply of salts and suitable proteins and carbohydrates.
- (b) A sufficiency of the necessary vitamins.
- (c) An activator for calcium metabolism, this factor being bound up with the question of sunlight and movement.

In Calcutta and the plains of India there are periods of the year when vegetables and fresh milk are expensive or unprocurable, and there are localities where the *pardah nashin* restrictions are very rigid.

The Marwari women of Calcutta are peculiarly prone to osteomalacia, and two-thirds of our cases have been seen among this community. The diet of Marwaris consists of wheaten bread, dal, ghee and milk (boiled), cooked vegetables and oil. Their customs do not permit them to touch meat, fish or eggs. They live in tenements or are herded together in large houses in the most crowded parts of the city, and their women rarely go out or have the opportunity of reaching the flat-topped roofs, the result being that although they may arrive from Rajputana strong and healthy, they quickly deteriorate, and owing to the factors A, B, C being defective or diminished, they very readily begin to suffer from one or more of the diverse symptoms of osteomalacia with anæmia.

It may be that the first generation escape, but their children, born and bred in Calcutta, frequently suffer at puberty or after marriage from this disease or rickets. It is no uncommon experience to find female members of long resident Marwari families who have been treated for anæmia with iron and arsenic, for hysteria with bromides and valerian, and for rheumatism with iodides and salicylates, when the whole symptom-complex is merely the result of a food and sunlight deficiency.

Amongst the Mohammedans, owing to their strict *pardah nashin* habits, sunlight and movement deficiencies are perhaps more common factors than food defects alone. Stapleton, writing of the United Provinces, and Vaughan of Kashmir, both emphasise the factors of overcrowding, and the *pardah nashin* as being determining causes of this very frequently seen disease, and are of the opinion that though cod-liver oil is essential, cod-liver oil without

sunlight is of very little use. Our experience amply bears this out.

Cod-liver oil may be separated into saponifiable and unsaponifiable fractions; the anti-rachitic properties are found to be in the unsaponifiable fractions only. This fraction consists principally of cholesterol and phytosterol; if these two substances are irradiated they become anti-rachitic. Rats and dogs fed on irradiated cholesterol develop normally, while those fed with the same substance which has not been exposed to the ultra-violet rays develop rickets.

The skin of animals has much cholesterol, only the brain having more; and since the ultra-violet rays of the sun penetrate only a short distance into the skin, it is to be presumed that these rays activate the cholesterol which exists in the skin, and this is then taken up by the bloodstream and distributed, fresh inactivated cholesterol being brought to the surface in its place. From this it would seem that the skin should perhaps be considered an organ instead of merely a covering.

These biochemical facts are confirmed in the case of rickets and osteomalacia, for the commonest seasons in the tropics to meet with these diseases are the winter months and the rains, when the sun is obscured or people tend to stay indoors in order to keep warm or dry, the consequence being that sufficient cholesterol is not activated by the solar rays, and hence from a vitamine deficiency osteomalacia develops.

#### Treatment.

The treatment of all disease should primarily be preventive, therefore, seeing that osteomalacia results from dietetic and hygienic errors, there should be no difficulty in eliminating it from the book of India. But it is exceedingly difficult to break through the prejudices of caste and custom. Until sunlight can penetrate verandahs, houses are airy, exercise is possible, and roofs are available for the women folk of all classes of Indian society, and particularly the Marwari community, the disease will not be eradicated. Therefore it should be the aim of City Fathers to see that suitable houses are built, and that the *pardah nashin* inhabitants of a town have the facilities of *pardah nashin* recreation grounds. Where these things are not possible, press, or public health propaganda should clearly demonstrate the folly and danger of lack of sunlight for the women and children of the household, and at the same time adequate provision should be made for an unadulterated milk and food supply.

Improvement Trusts may vastly benefit a town, but in Calcutta dense over-crowding in certain areas must perpetuate the disease, for tens of thousands of women and infant children rarely see the sun except for a brief period at midday when it may shine down into a damp courtyard crowded with cattle and their offal. How often does one not see in narrow alley ways and crowded thoroughfares the sun exclud-

ed by closed shutters, or see dirty sacking over the verandahs to prevent the inhabitants from being observed.

The central well or courtyard system of building may be a cool one, but in crowded cities with fifty to one hundred women and children living in one house, if they cannot all use the roof or freely take exercise thereon, ideal conditions exist for the onset of one of the many symptoms of osteomalacia.

It should be remembered that osteomalacia is not a disease of the very poor who have to earn their living and therefore have few *pardah nashin* restrictions, but is a disease of the middle classes, proud of this custom, who have not the wealth or desire to go out and about and cannot get away to their own country from time to time.

It is difficult to alter the dietetic habits of a thousand years, and we have already remarked on the fact that these people under no circumstance will eat eggs or fish. Moreover they rarely eat any raw vegetables or fruit, the idea of such being unwholesome having quite naturally originated in a country where cholera is endemic.

Everything eaten is boiled may be for an hour or more. Milk is boiled and the vegetable (mustard) oil used in cooking is boiled. In better class families the rice is husked by machinery, and the bran which is thus produced, so rich in phosphates, is given to the cattle. In Calcutta the cows of the wealthier classes are rarely driven out to graze, but are dry fed in dark stables under the living rooms, the result being that the milk supply is vitamine-deficient and the quality of the ghee, a household necessity, extremely poor.

For those who are unable to keep their own cattle it is a matter of vital importance that the ghee supply to a city should be pure and unadulterated.

To the writer it has seemed as if many of the bowel, blood and bone diseases of the women in Bengal can be attributed to an impure ghee supply, or to ghee prepared from the milk of stall and dry fed cattle, for during the hot months cattle which graze on parched *maidans* or stubble grass give milk which is 50 per cent. short of vitamins A and D. Such milk is conducive to rickets in the child or osteomalacia in the mothers who live in the over-crowded parts of a city.

It may be that education, propaganda and time will alter affairs, but these are matters which vitally concern ward councillors and municipalities to-day.

#### Drugs.

In 1925 and 1926 we began giving calcium in lactate or phosphate form by the mouth, but during the last two years, having got very little result from these, we have substituted injections on alternate days of 2 c.c. of "Collosol" calcium (Crookes). In this form the calcium apparently is taken up by the blood, for

our experience is in agreement with Professor Dixon's that calcium is inert and not absorbed when given by the mouth. At one time we gave parathyroid gland in one-twelfth of a grain dose twice a day, but results were negative.

Cod-liver oil combined with sun baths on the roof or verandah, or in the open field is the essential drug treatment. We order one ounce twice a day, taken alone or in milk. From caste or taste prejudices, at times it is refused, but when once its beneficial results can be demonstrated by the example of another patient of the same community, it will usually be taken. It is the fishy smell and taste which prejudice Marwaris against it.

Ostelin and "Collosol" cod-liver oil have not been nearly so successful as the raw drug.

During the last year if prejudice to cod-liver oil has been very great, or we have thought, despite statements to the contrary, that the drug had not been taken because the symptoms were not alleviated, we have been obtaining astoundingly good results with intravenous injections of sodium morrhuate made up in ampoule form by Smith Stanistreet and Co. We give two injections a week, beginning at 1 c.c. and gradually working up to 6 c.c. These injections are painless and symptomless, they do not offend caste prejudices, and are remarkable in the way they cause subsidence of the muscular and bony pains of the disease. The general health rapidly improves and we have seen patients huddled, crippled and groaning in the corner of a room, or even paralysed, walking about cheerfully within a month.

Intravenous sodium morrhuate is most particularly useful in pregnant patients with acute symptoms of osteomalacia. We have used it in a great number of cases with signal success.

Early in 1926 in addition to the above measures we began giving irradiated cholesterol, prepared according to the technique of Parsons by submitting pure B. D. H. cholesterol in thin layers on a Petri dish to the rays of a quartz mercury vapour lamp for one hour at a foot distance. Two drachms of the irradiated drug are then dissolved in four ounces of liquid paraffin and a dosage of 2 drachms of the liquid is ordered twice a day in addition to the cod-liver oil. We found it was not wise to irradiate more than one week's supply at a time because the drug quickly deteriorates or loses its potency in the tropics.

The effect of irradiated cholesterol is most marked upon the bony symptoms. We have had cases that were refractory or slow in responding to cod-liver oil, in whom improvement has been immediate when this preparation has been given. It is worthy of record that uneducated patients themselves have told us that the white medicine (paraffin) gave them great relief, and the records of 37 patients to whom it was given bear this out.

It should be stated that whether irradiated cholesterol synthesises the anti-rachitic factor

vitamine D, or mobilises the reserves of vitamine A has not yet been determined.

This year in an endeavour to diminish the cost of the above treatment, we have tried Radiostol, but patients have not benefited; presumably the quality of this preparation changes during transit from Europe.

In the tropics with its abundant sunlight, it is rarely necessary to have recourse to ultra-violet radiation by carbon arc lamps, but in a few cases where the pains or the bony lesions have been very marked, we have submitted patients to direct ultra-violet ray treatment with benefit. Babies born of osteomalacic mothers, either naturally or after Cæsarean section, have done very well under ultra-violet rays in the hands of an expert in a few difficult cases.

The essential medical treatment therefore of osteomalacia may be summed up as an improved diet, fresh air, sunlight, cod-liver oil or intravenous sodium morrhuate, and irradiated cholesterol, with or without injections of collosol calcium.

Sometimes it is a good plan to give for a few days santonin or carbon tetrachloride (tetraform) with the object of eliminating possible intestinal parasites before commencing the essential treatment.

We have no intention of discussing the operative measures for osteomalacia, for when once its early diagnosis, prevention and treatment are generally recognised, the necessity for craniotomy or Cæsarean section will become exceptional, for the disease in its early stages can be aborted and cured. Moreover, then we shall rarely see those un-get-at-able and inoperable cases of vesico-vaginal fistulæ which at present in rural India are one of the most terrible sequelæ of this disease.

To give an idea of how common osteomalacia is in Bengal, it may be of interest to state that during the last 30 months out of 2,870 maternity cases which have passed through the labour room of the Eden Hospital, it has been necessary to perform 26 craniotomies and 15 Cæsarean sections for osteomalacic conditions *alone*.

Of the Cæsarean sections 8 were Hindus, 1 was a Mahommedan, 2 were Anglo-Indians, 3 were Marwaris and 1 was a European. Of the craniotomies 18 were Hindus, 5 were Marwaris, 2 were Mohammedans and 1 was an Anglo-Indian. Alas! all these craniotomies could have been obviated were the benefits of ante-natal care and supervision generally understood and practised.

I have to express a great debt of gratitude to Drs. N. L. Barman, G. N. Roy, S. N. Das and Dhaur for the pains they have taken to follow up and so energetically treat and cure so many of these patients, seen in consultation with them.

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### A NEW ORGANIC AROMATIC COMPOUND OF BISMUTH SUITABLE FOR INTRAVENOUS INJECTION IN THE TREATMENT OF FRAMBÆSIA.

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BISMUTH compounds were used as cicatricising agents in cutaneous lesions as far back as the 17th century, and in 1780 they were used internally for the treatment of gastro-intestinal affections. Balzer (1889) carried out a series of experiments on dogs to test the toxicity of bismuth compounds with a view to their employment against syphilis, but he found them so toxic that he had to abandon their use. Robert and Sauton (1916) tried bismuth preparations in the treatment of spirochaetosis of fowls and found them to be very efficacious. The experiments conducted by these investigators were confirmed by Sazarec and Levaditi (1921) who showed that in experimental syphilis of rabbits bismuth compounds had a well marked curative action. They also tried compounds of bismuth against syphilis in man and found that they produced rapid cicatricisation of the lesions of this disease. Since these facts have come to light a number of compounds of bismuth have been put on the market because the cost of treatment with bismuth preparations is much cheaper than with the organic arsenicals. The older preparations of bismuth recognised by the *British Pharmacopæia* such as bismuth subnitrate, bismuth carbonate and subcarbonate, etc., were not suitable for injection and could only be given by the mouth. As only very minute quantities of bismuth are absorbed from the alimentary canal their action was chiefly local on the mucous membrane. During the last decade efforts have been made to prepare a number of new compounds which could be given by the intramuscular or by the intravenous route. Of these tartro-bismuthate of sodium and potassium known by the trade name of "Trepol" was one of the very early preparations which

was put on the market; it is sold in the form of an emulsion in oil and in solution in water. Colloidal suspension of bismuth hydroxide, bismuth oxychloride in suspension in camphor water (bischloral), basic salicylate of bismuth which is soluble in water and is recommended for intravenous use, sodium trioxo-bismuthate which is an aromatic compound containing 50 per cent. of bismuth, and colloidal metallic bismuth are some of the other preparations which are in use. The disadvantage of most of these preparations is that they are not satisfactory for intravenous administration, and even for intramuscular injections most of the compounds that we have tried produced much pain and discomfort to the patient. The insoluble compounds, though not so painful as the soluble ones, are not absorbed quickly and regularly, so there is danger of cumulative poisoning from their use. When given intravenously the bismuth compounds produce agglutination and hæmolysis of the red blood corpuscles and may give rise to emboli and severe reactions. Even such compounds as soluble tartro-bismuthate or colloidal preparations which do not produce hæmolysis and agglutination, produce severe reactions following intravenous injections. Magnus (1924) reported cases of sudden death after intravenous injections of bismuth compounds with symptoms of colloidal shock.

It was for these reasons that we endeavoured to get a compound which could be given intravenously with safety. This was attained through the efforts of Dr. B. C. Ghose, D.Sc., in-charge of the Chemical Department of the Union Drug Company of Calcutta to whom the entire credit of preparation of this compound is due. He succeeded in preparing a soluble organic compound of bismuth which is freely soluble in water and which can be given intravenously without producing any untoward effects. This compound is an organic aromatic compound of bismuth and is practically the bismuth analogue of urea-stibamine. Chemically it may be described as a sodium salt of para-amino-phenyl-bismic acid in combination with urea, and has been given the trade name of "Bisnene." This compound has been given the following formula by its author:  $\text{NH}_2\text{—CO—NH—C}_6\text{H}_4\text{BiO—(OH)ONO}$ . Analysis shows that it contains 50.1 per cent. of bismuth and this is an important fact, as the curative properties of these compounds are proportional to their bismuth content.

#### Preparation of "Bisnene" and its Toxicity.

The first stage in the preparation of the compounds is the acetyl para-amino-phenyl-bismic acid, obtained by a modification of the well-known Bart's reaction for the preparation of the corresponding antimony compound. The acetyl compound is hydrolysed with caustic soda solution and the para-amino-phenyl-bismic acid condensed with urea. The salt thus obtained is dissolved in water, and made alkaline with