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CHAPTER I.

INTRODUCTION.

It has long been a commonly held view that the bones become rarefied in old age and that this rarefaction or osteoporosis is a physiological process. Generalised osteoporosis, however, occurs in a considerable number of patients long before senility. In the pre-senile group many factors have been held responsible for the thinning of bones and it seems possible that they may also account for this condition in old age. Black et alii (17) indeed state that senile osteoporosis is a pathological process and that only a small number of cases are severe in degree.

Before considering the aetiology of osteoporosis in the old, it is worth reviewing briefly some of the factors which may produce this condition in younger age-groups. Rarefaction of individual bones is well-known and may result from disuse (1a) or injury (2a), (2b) to a limb. Other common causes are inflammatory conditions of neighbouring joints, e.g. gonococcal arthritis, rheumatoid arthritis, osteomyelitis and Kummel's disease. Experimentally osteoporosis can be produced in the skeleton on one limb by active immobilisation, by maintenance of non-union of a fracture in the proximal bone or by interference with the vascular supply (Harris 1b). Clinically the condition can be studied in disuse, non-union of a fracture, vascular lesion such as thrombosis, and interference with inner-

vation. Harris is of opinion that irrespective of the cause of atrophy the response of the bone is similar and can be estimated either radiographically or histologically. It is obvious that disuse whether due to natural inertia or to the group of so-called rheumatic conditions is much commoner in the old than in the young. Accordingly in discussing the aetiology of senile osteoporosis it will be necessary to consider the possibility of the condition being due to local osteoporosis involving many parts of the skeleton, "multiple local osteoporosis".

Generalised osteoporosis may result from many causes and it will suffice to tabulate these.

1. Dietary.

(1) Reduced intake of calcium and/or vitamin D e.g. rickets, (4a) osteomalacia (4b).

(2) Failure of absorption of calcium e.g. bowel disease such as coeliac disease, sprue, idiopathic steatorrhoea etc. (5) (7a); prolonged biliary drainage (5); achlorhydria; insufficiently acid intestinal pH; insufficient amounts of phosphatase in the intestinal secretions. (7b).

(3) Failure to utilise calcium e.g. Renal dwarfism (9).

II Trophic.

(1) Nerve lesions e.g. Lesion of the brachial plexus producing atrophy of the bones of the hand (1a); Hemiplegia in adults producing brittleness of the bones in the paralysed limbs. (10).

(2) Vasomotor disturbance e.g. Post-traumatic osteoporosis (5).

(3) Vascular disease (3).

(4) Blood disorders e.g. multiple myeloma, sickle cell anaemia, Cooley's anaemia, acholuric jaundice (11a).

(5) Disuse (12).

(6) Infections e.g. rheumatoid arthritis, gonococcal arthritis. (2a) (2c).

(7) Tumours e.g. Secondary carcinoma, lymphadenoma (2d)

(8) Acidotic states e.g. administration of ammonium chloride, acid poisoning (5)(12).

(9) Senescence (1c).

III Endocrine.

(1) Hyperparathyroidism (13) (14)

(2) Hyper-thyroidism (13) (12)

(3) Pituitary basophilism (5) (15)

(4) Suprarenal disease (5)

(5) Post - menopausal disorders (16)

IV Congenital disease.

(1) Osteogenesis imperfecta (2e)

(2) Bone cysts.

V Idiopathic group

(1) Paget's disease of bone i.e. Osteitis Deformans (4d).

Is generalised senile osteoporosis simply a manifestation of the degenerative changes in bone, the natural accompaniment of old age? This question has obviously to be considered first of all. Generalised osteoporosis occurs in a considerable number of patients long before the 'senile' age group is reached and the aetiology of the osteoporosis in these cases presents the same difficulties as the investigation of the origin of senile osteoporosis. That one is dealing with the same condition is very probable as there is no evidence to suggest otherwise, and this leads one to conclude that senile osteoporosis is probably not a physiological manifestation. Black et alii (17) state that senile osteoporosis is a pathological process as only a small number of cases are of a severe degree.

Attention has been drawn to the subject of senile osteoporosis by Schmorl (18) who studied the anatomy of the condition, and later by Meulengracht and Meyer (19) who suggested that the main factor in the origin of the condition was longstanding calcium deficiency. This attractive hypothesis has received considerable support from Leitch (20), Owen (21) and Owen et alii (22). If this view is correct, senile osteoporosis should be included under the disorders of calcium metabolism, and the possibility must be considered of calcium metabolism in middle and old age differing from that of younger adults. Is osteoporosis in the older age groups, due to failure to absorb and utilise calcium? Wishart (23) states that "when the need arises the adult's absorption can

rise to the 70% level associated with infancy and it has been repeatedly shown that individuals, at or past middle age, who have become osteoporotic, will recover under adequate treatment." Douglas Robertson (24), after careful investigation in which he compared the calcium metabolism of 12 adults, ages ranging from 19-39 years, with 12 adults, ages ranging from 40-60 years, states that the calcium metabolism of middle age is no different from that of young adults. He points out, also, that overdosage of calcium cannot occur as the healthy body rejects in the faeces whatever calcium it does not require.

Owen and Owen et alii have demonstrated that older male subjects, including patients in the senile age group, are capable of storing the calcium and phosphorus of diets containing more of these elements than the amounts they had been habitually ingesting. Owen et alii have also shown that patients of ages ranging from 69 to 79 years, with senile osteoporosis are capable of such storage. Their work indicated in addition that osteoporotic patients can adapt themselves to a low intake of calcium and may be in equilibrium in adequately nourished subjects. Owen et alii support Meulengracht's hypothesis on the grounds that it is likely that osteoporosis would develop during a prolonged period of calcium deprivation before the equilibrium noted above was reached. Before this view can be accepted a further question must be answered. Is the storage of calcium and phosphorus which takes place as indicated above, merely a temporary one, so that the positive balance may disappear after

a short interval? Adams, Boothby and Snell (25) studied a case - a woman aged 65 years suffering from senile osteoporosis, - for 19 weeks and demonstrated a retention of 29.3g calcium and 13.3 phosphorus on treatment with calcium salts alone and also with calcium salts plus vitamin D. This suggests that such patients might remain in positive balance over a prolonged period. All the above evidence suggests that calcium metabolism in the older age-groups is similar to that of younger adults and is strongly in favour of senile osteoporosis being the result, not merely of senescent atrophy, but of a deficient intake or absorption of calcium. There would seem to be little doubt, at any rate, that patients over 40 years of age and even over 65 years of age, are capable of retaining considerable amounts of calcium and phosphorus if they have been previously ingesting relatively small amounts of these elements over a prolonged period. If senile osteoporosis is the result of a deficiency as is suggested then one would expect to be able to demonstrate (a) that treatment with a high calcium intake over a long period would produce a positive calcium balance over a long period and (b) that the condition would respond to such prolonged treatment and allow of radiological proof of cure. These two points were selected for investigation. Black et al. (17) carried out an investigation on senile osteoporosis of the spinal column in patients treated over several months with calcium, phosphorus and vitamin D. In 18 cases in which follow up x-rays were available, the average period between

x-rays being 29 months, no change sufficient to class as recalcification and not to variation in x-ray technique, was demonstrable. This finding appears to conflict with the above results and points out the necessity for further investigation.

Hyperparathyroidism (13), hyperthyroidism (14), and pituitary basophilism (15) have also been found to produce generalised osteoporosis at all ages. It is very unlikely, however, that dysfunction of these endocrine glands is responsible for osseous rarefaction in the old. Statements are often made as to atrophy of the ductless glands in later life but there is no clinical or biochemical evidence that this takes place to a significant degree. Certainly the serum calcium fails to reveal any abnormality suggesting overactivity of the paraphyroids nor do the blood cholesterol values suggest any abnormality of the thyroid secretion. If anything, the clinical picture of old age is one of hypo- rather than hyper-thyroidism but the blood cholesterol is not raised and the basal metabolic rate, as estimated by the Sanborn-Benedict apparatus, falls within normal limits in elderly patients. Albright et alii (16), however, as a result of a study of 42 osteoporotic patients between 45 and 65 years of age, came to the conclusion that the menopause may be a potent factor in the production of the osteoporosis and recommended the use of stilboestrol as a therapeutic agent. Black et alii found that senile osteoporosis was four times

commoner in females than in males. The possibility of some dysfunction of the sexual hormones as a causative factor must therefore be considered. That disuse may play an important part cannot be ignored while the well-known increasing incidence of vascular disorder with age is also suggestive.

Of the list of possible causes of generalised osteoporosis, therefore, the following emerge for investigation as most likely to be concerned in the production of generalised senile osteoporosis:-

A. Dietary.

B. Disuse.

C. Vascular Disease.

D. Endocrine disorders.

These, then, were the causes chosen for investigation. The incidence of generalised osteoporosis in patients over 40 years of age was determined, this age being selected in order to provide a suitable lower limit which would include the years of the menopause in the female. The age of 65 years has been taken as a suitable point to divide arbitrarily middle age from the senile age-group. Estimations of the serum calcium, phosphorus and phosphatase were carried out and the results in "normals" and "osteoporotics" were contrasted. The symptomatology of generalised osteoporosis was considered. A series of x-rays of spines taken over a period of 3 years, 1939-41 inclusive, were examined with reference to osteoporosis of the vertebrae and the incidence of osteoporosis of the spine in the various years was compared.

This part of the investigation also proved of interest with regard to the symptomatology of osteoporosis of the spine. Specimens of ribs were obtained at post-mortem examination in a few normal and osteoporotic cases and the calcium and phosphorus contents were estimated and contrasted. Calcium retention experiments were undertaken in a small series of cases to determine if "senile" patients could be put into positive balance and if this state would remain over a fairly prolonged period. The effect of treatment with calcium and vitamin D, over a long period of time was judged by means of x-ray examinations performed at monthly intervals, and by repeated estimations of the blood chemistry.

An attempt has been made to estimate the potency of the disuse factor by studying the effect of prolonged disuse in a series of patients suffering from the after effects of epidemic encephalitis, and also by trying to estimate the effect of this factor in the series of cases under investigation.

The blood pressure was recorded in each case and the presence or otherwise of arteriosclerosis was also noted in order to estimate the effect of vascular disease. The effect of stilboestrol therapy on the serum calcium, phosphorus and phosphatase in senile osteoporosis was investigated in a small series of patients.

DIAGNOSIS, SYMPTOMATOLOGY AND PATHOLOGY

CHAPTER II

This chapter is devoted to a consideration of the symptomatology and pathology of senile osteoporosis. It may be stated at once that neither clinical manifestations not changes in blood chemistry suffice to detect the condition. Accordingly the method of diagnosis is first described and this is followed by a discussion on symptoms and signs, a consideration of the changes in blood chemistry and finally an account of a few observations on the composition of bones obtained at autopsy.

It should, however, be stated here that prior to any investigation a clinical examination was made of each patient in order to exclude individuals suffering from conditions such as gross joint disease (rheumatoid arthritis, osteoarthritis etc.) which of itself might be responsible for an osteoporatic condition of the bones. The Wassermann reaction was also performed in order to eliminate syphilis as a cause of any of the bony lesions which might be detected.

A. Diagnosis.

There is little doubt as will be seen later from a consideration of signs and symptoms that the x-ray is the only method at present available for the diagnosis of osteoporosis.

X-RAY EXAMINATION - METHOD

All cases were investigated as follows:- Films were taken of (1) Right half of pelvis including right hip joint and proximal half of right femur.

(2) Left shoulder joint and proximal two thirds of left humerus.

(3) Right hand.

(4) Left foot.

(5) The left knee joint i.e. lower end of left femur and upper end of left tibia and fibula.

(6) In some cases a film of the lumbar vertebrae was also taken.

As can be seen from this selection a considerable part of the skeleton was examined in each case and any condition such as multiple arthritis would be revealed at once as one hip, one shoulder, one knee, one wrist and one ankle joint were available for examination for every patient. The routine technique of the X-ray Department was adopted. This ensured that the films from different patients could be compared with a degree of accuracy sufficient for the purpose of diagnosis.

CRITERIA OF OSTEOPOROSIS

The diagnosis of osteoporosis in any one bone was based on a consideration of the following two points.

(1) Absorption of the transverse trabeculae. This is probably the earliest sign to be detected on the x-ray film. In the severer degrees of osteoporosis absorption of the longitudinal trabeculae is also seen (1a)

(2) A diminution in the density of the shadow thrown by the bone when compared with a series of films taken of normal bones from healthy well-nourished subjects. When these subjects are carefully chosen with reference to their health and nutrition no difference can be detected in the x-ray densities

among the various age-groups.

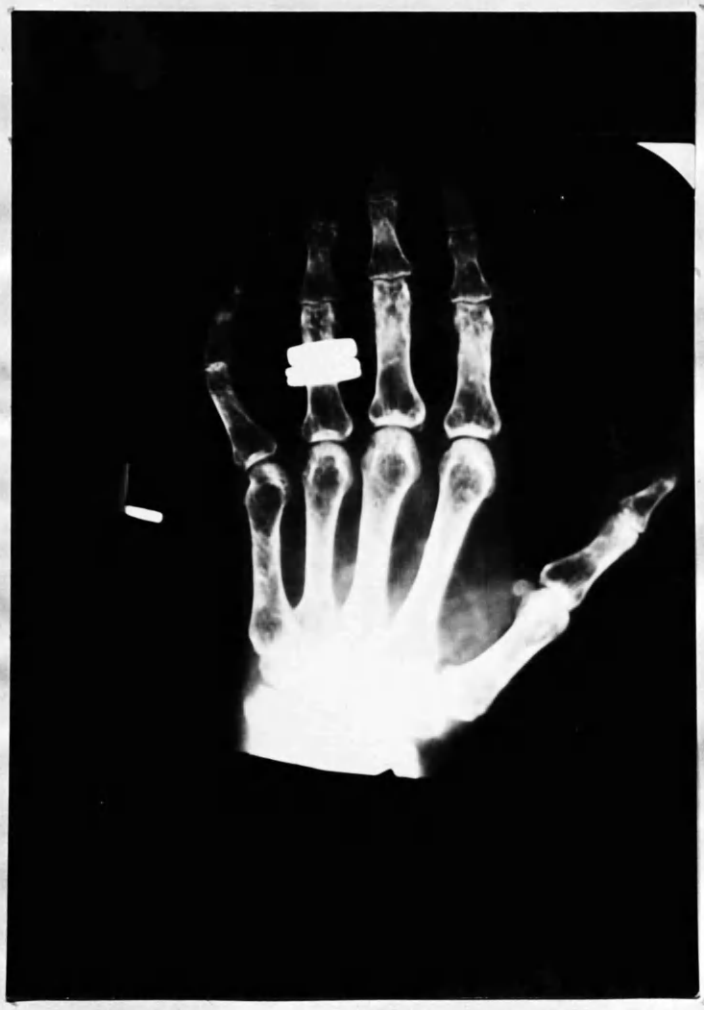
It is more difficult to determine the point at which osteoporosis should be considered "general". A generalised osteoporosis must of necessity begin in one region. Almost inevitably it is more prominent in one region than in others. Accordingly there must be considerable difference of opinion in the diagnosis of early cases unless standards are defined and rigidly adhered to. For the present investigation it was decided that osteoporosis is generalised if it were shown to be present in no fewer than three of the sites detailed in the description of the method of examination. This standard which is a fairly severe one must obviously exclude slight or commencing osteoporosis but it has the advantage that the diagnosis is not in doubt as far as positive findings are concerned.

Commonest Site of Osteoporosis - It is of interest at this point to consider which parts of the skeleton are most commonly affected by rarefaction. Black et alii (17) investigated 23 cases of senile osteoporosis, taking x-ray films of upper and lower extremities as well as of the spine and came to the conclusion that the vertebrae showed osteoporosis in the greatest degree. Todd, (3) however, states that demineralization of the skeletion with advancing years is found first in the bones of the extremities - foot and then hand and later in the innominates, vertebrae, sternum, ribs, lower and upper tibia and fibula and then lower end of femur. In an investigation into osteoporosis occuring in the

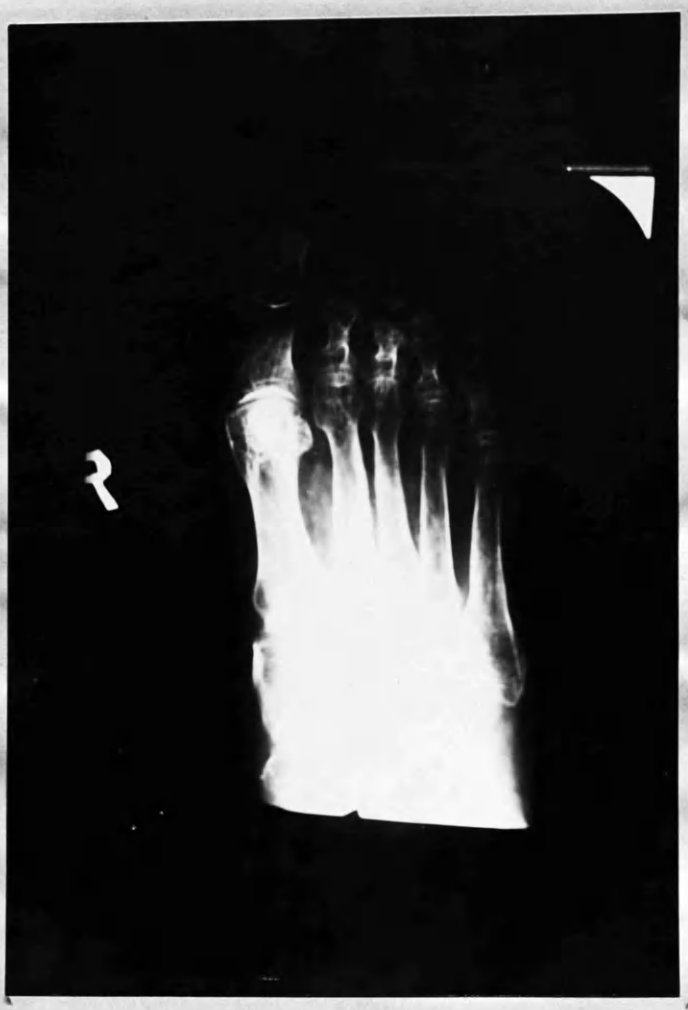
menopausal periods of life Albright et al. (16) state that it has predilection for the spine and pelvis and that long bones are only involved in more severe cases, the skull not being involved at all. The findings in the present investigation were that osteoporosis is most marked usually in the feet, hands and spine and that probably the bones are affected in that order. It is possibly more difficult technically to obtain as good films of the vertebrae as of the bones of the feet and hands which perhaps may have some bearing on this matter. The following photographs provide examples of osteoporosis in the bones of the hand and foot:- Mrs.J. 73 years. These may be contrasted with normal ones:- J.T. 76 years.

The x-ray appearance of the vertebrae is of importance in the diagnosis of senile osteoporosis. The anatomical changes in the vertebrae have been described by Schmorl (18) who found that the cortical bone is thinner than normal and that the marrow spaces and medullary cavity are enlarged. In severe cases there is collapse of the bodies of the vertebrae and expansion of the nucleus pulposus and intervertebral disk producing the "fish-tail" vertebra. The x-ray appearance corresponds with these findings. There is diffuse osteoporosis: ballooning of the discs and compression fractures may also be found. (2d)(26) It is very difficult to obtain photographs which demonstrate these points since much of the detail apparent in the film is lost by reproduction. Photographs have been inserted in an attempt to illustrate some of the findings. While these changes are seen typically in senile

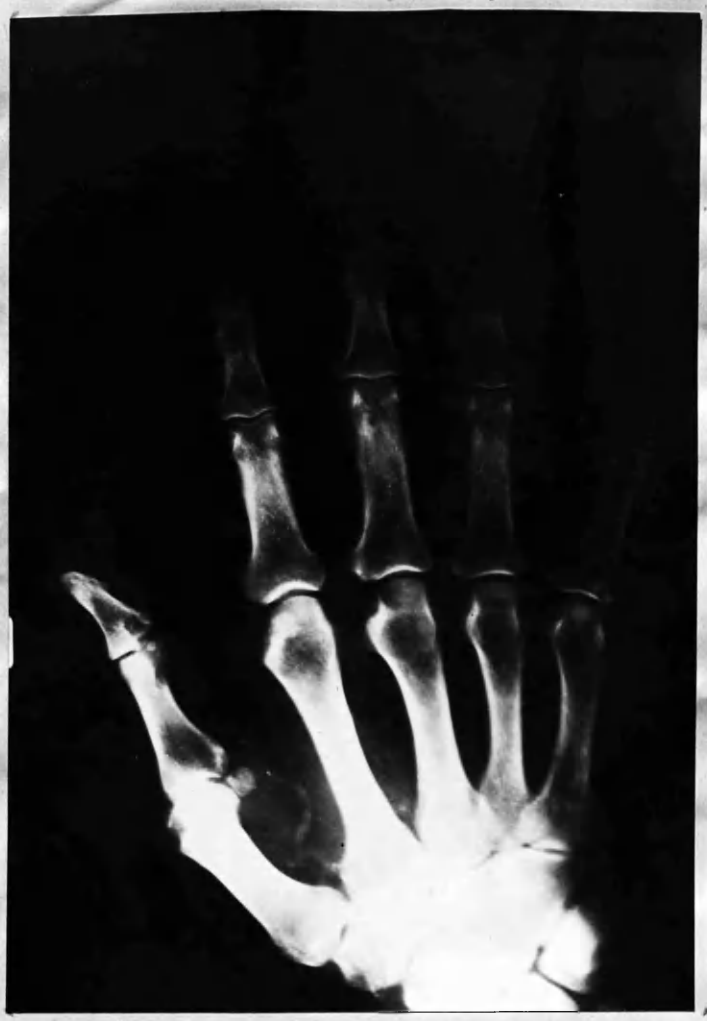
Mrs J. 43 yrs. X-Ray of left hand.



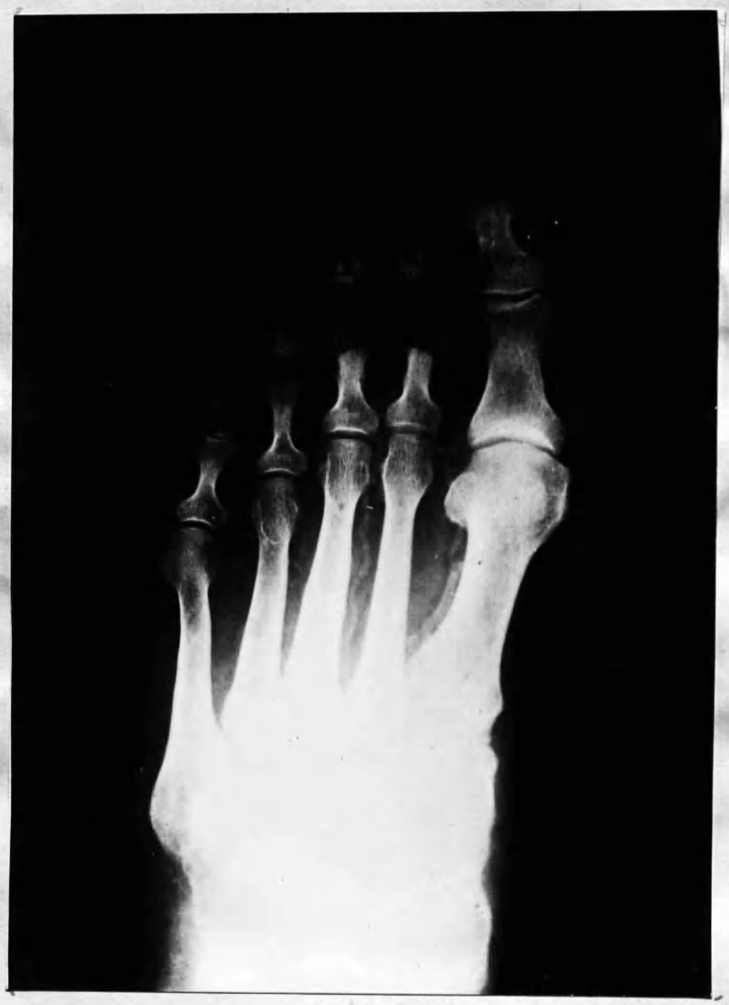
Mrs. J. 43 yrs. X-Ray of right foot.



J.T. X-Ray of left hand.



J.T. X-Ray of foot.



osteoporosis they may occur in such diseases as osteomalacia, osteitis deformans and osteitis fibrosa cystica (27) but these conditions are easily differentiated by other features. Senile kyphosis may be present. This condition was investigated by Beadle (28) who described a necrosis of the anterior portion of the annulus fibrosus resulting in the approximation of the bones and bony ankylosis anteriorly with resulting kyphosis. These conditions are revealed when the spine is x-rayed.

2.Symptoms and Signs.

Symptoms.

Symptomatology which might reasonably be due to osteoporotic bones is not very common. Characteristically, the part which is involved is the back especially the lower thoracic and lumbar regions. Complaints are made of vague aches and pains in the back and perhaps in the abdomen and thighs. The pain, however, may become very acute. Stiffness and weakness of the back may also be found and if the symptoms are severe the patient may be unable to walk. Black et al. (17) found in senile osteoporosis, that a dull ache and weakness may be present for years before mild trauma such as lifting or bending caused a sudden snap or an acute pain in the back caused by collapse of a vertebra. From the date of the injury the "back pain" was worse. They also state that referred pains may occur in the limbs and neck. In menopausal osteoporosis Albright et el. (16) state that

the commonest clinical picture associated with a vertebral lesion is a history of a minor fall about 10 years after the menopause resulting in pain in the back. Cases of senile osteoporosis were eliminated from this series by excluding all patients over 65 years. Thus, similar syndromes have been shown in the senile group and in the menopausal group. The incidence of symptoms in the present series of osteoporotic patients over 40 years of age is shown thus:-

Age Group	With Symptoms	Without Symptoms
Below 70	1	8
70-79	7	13
80-89	2	6

The majority of patients suffering from generalised osteoporosis, therefore, do not evince symptoms. Six of the patients who complained of pain in the back had a very deformed spinal column or actual fractures of the vertebrae which could account for the pain. Examples of this are shown by the photographs of patients who suffered considerable pain in the back. Further study of this aspect of the investigation was undertaken as follows. All x-rays of spines, in patients 40 years of age and over, which had been taken in Stobhill Hospital during the years 1939-41 inclusive, and which were still available for inspection, were re-examined for the presence or absence of osteoporosis. X-rays showing decalcification due to such causes as secondary neoplasms were, of course, discarded. The osteoporosis cases revealed the following incidence of symptoms:-

Table 1.

Age Group	OSTEOPOROSIS OF SPINE					
	1939		1940		1941	
	With Symptoms	Without Symptoms	With Symptoms	Without Symptoms	With Symptoms	Without Symptoms
40-49	1	-	5	-	-	3
50-59	1	1	4	2	6	2
60-69	6	2	7	1	9	3
70-79	5	1	3	-	5	-
80-89	1	-	2	-	-	-
90-99	1	-	-	-	-	-
TOTAL	15	4	21	3	20	8

The combined results for the 3 years 1939-41 are therefore:-

Table 2.

OSTEOPOROSIS OF SPINE (1939-41)		
Age Group	With Symptoms	Without Symptoms
40-49	6	3
50-59	11	5
60-69	22	6
70-79	13	1
80-89	3	-
90-99	1	-
TOTAL	56	15

These results differ from the findings of the series discussed above but it should be remembered that in the majority of cases, the spine is x-rayed because symptoms are present. A truer picture is therefore obtained by calculating the incidence of osteoporosis in patients exhibiting symptoms thus:-

Table 3.

PATIENTS WITH SYMPTOMS

Age Group	1939		1940		1941	
	O	N	O	N	O	N
40-49	1	21	5	19	-	13
50-59	1	16	4	7	6	13
60-69	6	13	7	6	9	6
70-79	5	1	3	3	5	4
80-89	1	2	2	1	-	-
90-99	1	-	-	-	-	-
TOTAL	15	53	21	36	20	36

The combined results for these 3 years are shown below:-

Table 4.

Age Group	1939-41		
	O	N	
40-49	6	53	
50-59	11	36	
60-69	22	25	
70-79	13	8	
80-89	3	3	
90-99	1	-	
TOTAL	56	125	31%

These findings demonstrate that of the cases x-rayed because of symptoms, those with osteoporosis comprise only 31%. Therefore symptoms may be produced by many other conditions apart from ostoporosis, for example, fibrositis, neuritis, arthritis etc. Accordingly even in osteoporotic patients, the sumptoms may arise from factors quite apart from the osteoporosis. The records of patients with spinal osteoporosis who exhibited symptoms were reviewed with this in mind and the following results obtained.

PATIENTS WITH SPINAL OSTEOPOROSIS

Table 5.

AND SYMPTOMS

Year	No. of cases with adequate cause for symptoms apart from osteoporosis of its complications	No. of cases in which symptoms are probably due to Osteoporosis or its complications
1939	6	9 (60%)
1940	9	12 (57%)
1941	10	10 (50%)
TOTAL	25	31 (55)%)

This shows that only 55 % of patients with spinal osteoporosis and symptoms could definitely be considered as cases in which the cause of the symptoms was probably Osteoporosis or a complication of the Osteoporosis. This is seen in perspective when one states that in only 31 out of 181 patients i.e. 17% was the cause of the symptoms probably the osteoporosis per se or a complication of the osteoporosis. The true incidence of symptoms in the osteoporotic cases in this series is therefore 31 out of 71 or 44% This result is still much higher than that found in the series of cases of generalised osteoporosis which is 27%. One considers that the latter is the more accurate result as there was no selection of cases, whereas in the spine series the majority of the cases were x-rayed because of symptoms.

SIGNS

The physical signs consist of tenderness and perhaps spasm in the erectores spinae. In cases in which there is collapse of one or more vertebrae the spine is seen to be shortened, throwing the skin of the back into transverse folds, while the lower ribs approximate to the iliac crests. The abdomen also may show transverse folds of redundant skin due to the shortening of the spine. Deformities of the spine such as kyphosis and scoliosis may be found. Senile kyphosis is much more common than scoliosis. The x-ray findings are osteoporosis, "fish-tail" vertebrae and ballooning of the intervertebral discs, as has already been described. True compression fractures may be found as the result of trivial

injuries, owing to the osteoporosis. These physical signs have been noted also by Ghormley et al. (16) in "menopausal" osteoporosis. Albright el al. also state that herniation of the nucleus pulposus through the end plate of the vertebra may occur.

It is of interest to consider the cause of pain in osteoporotic individuals. It is obvious from the figures which have been given that many subjects have generalised osteoporosis without complaint and indeed that it is only the minority who exhibit symptoms. Prima facie, therefore, it would appear that osteoporosis per se is not likely to give rise to pain. Black et alii., however, are of the opinion that the dull back-ache is due to osteoporosis directly and that the sharp pains which are sometimes experienced result from ballooning of the intervertebral disks and compression of the vertebral bodies. They go on to state that in many patients ballooned disks and compressed vertebrae may be detected without related pain. It is of course true that severity of the deformity is likely to be an important determining factor while the psychological reactions of patients to discomfort vary enormously. Unfortunately it has not been found possible to measure either factor with any degree of accuracy. As regards backache it is worth mentioning that the back is almost always the only region about which complaint is made. It would seem natural if osteoporosis itself produced symptoms, that pains in other regions of the body would be more commonly encountered. As has already been

mentioned six of the ten osteoporotic patients with pain in the back had either deformity of the vertebrae or compression fractures. Of the 56 osteoporotic patients from the general hospital series who complained of pain 20 had some complication to which might rationally be attributed the discomfort. This leaves a considerable residue of patients in whom the pain would seem to be attributed to the osteoporosis directly. It has to be remembered, however, that a considerable number of individuals over the age of 50 in the West of Scotland suffer from fibrositis or allied condition which is well known to cause pain. So much is this the case that in every one of the series which was examined it was possible to detect painful areas on pressure. Whether or not the pains and aches of the osteoporotic patient result from fibrositis or rarefaction of the bones is a question which cannot be decided in an area where fibrositis is so prevalent. It is hardly fair to adduce examples from younger age groups but it is worthy of mention that coeliac disease and uncomplicated rickets are two conditions in which rarefaction of the bones may be very marked without any pain or discomfort.

COMPLICATIONS.

(a) Fractures:-

The commonest site of fractures resulting from osteoporosis, is the spine. A true compression fracture may be seen, and the part usually affected is the lower thoracic and lumbar region.

The other common fracture is intracapsular fracture of the neck of the femur. Mrs. McI. 77 years provides an example of this. The generalised nature of the osteoporosis was adequately demonstrated by films of other regions. The incidence of fractures in the series of patients with generalised osteoporosis was 22%. In the series of x-rays of spines in patients 40 years of age and over, the incidence in the osteoporotic cases was found to be:-

Table 6.

Year.	Total No.	No. with fractures.
1939	19	6 (32%)
1940	24	7 (29%)
1941	28	4 (17%)
TOTAL	71	17 (24%)

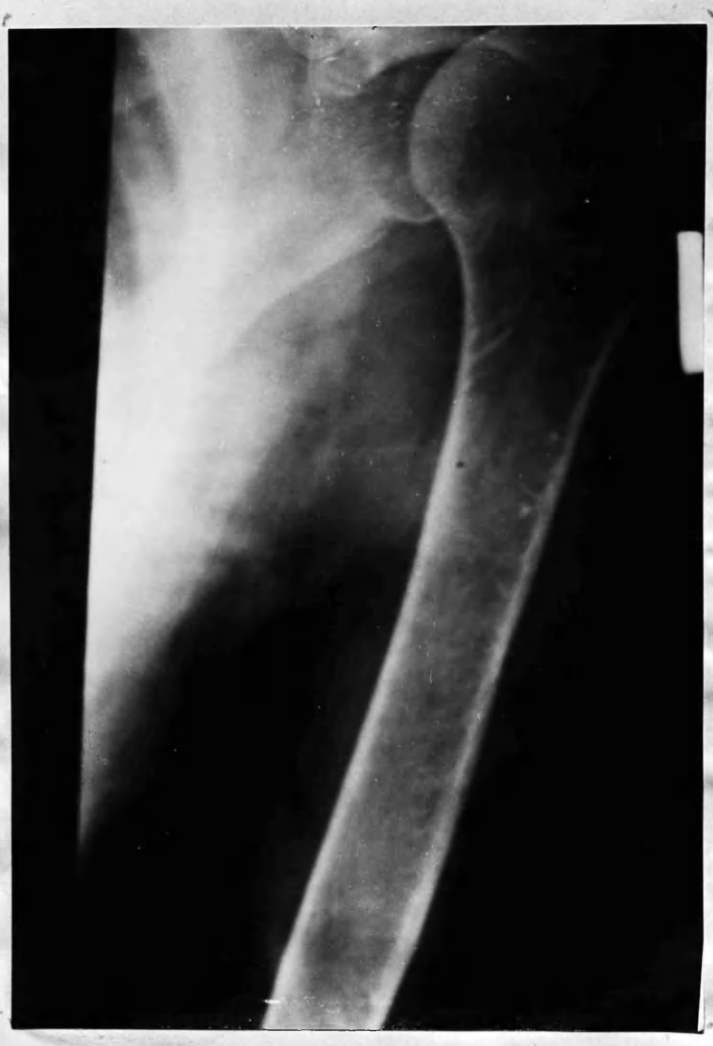
The results in this series, therefore, are similar to the previous one.

Ghormley et al. (26) in a large series of patients with senile osteoporosis, found an incidence of 8%. They also demonstrated that the commonest cause of pathological fracture, apart from metastases from a primary breast cancer, is senile osteoporosis. Osteoporosis from any cause can, of course, produce pathological fractures e.g. osteogenesis imperfecta (26) pituitary basophilism (15) etc. Spontaneous vertebral fractures have been noted in rabbits fed on a diet deficient in calcium by Light et al. (29) who suggest that it is possible that a similar condition could occur in man. While this may be feasible, the well known fallacy of direct comparison of experimental evidence and human pathology, should be remembered.

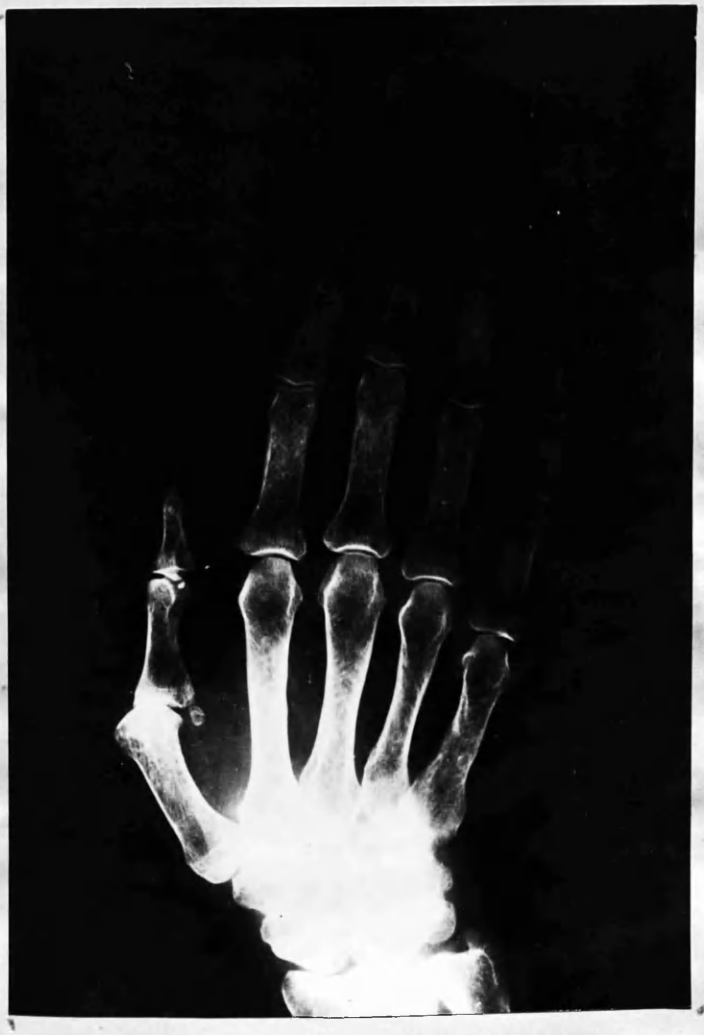
(b) DEFORMITIES

Senile kyphosis is the common deformity but sometimes a

Mrs. M°I. 44yrs. X-Ray of shoulder.



Mrs. M^c I. 44 yrs. X-Ray of hand.



scoliosis may be found. If the deformities are marked a fair degree of hypertrophic osteoarthritis of the spine may be seen.

It is interesting to note that very similar symptoms, signs and complications may be observed in osteomalacia. (30)(31)(32). There are certain differences however. According to Maxwell (30) scoliosis is more common than kyphosis in osteomalacia. The reverse of this holds good in senile osteoporosis as has been noted above. Maxwell also points out that pelvic deformities and deformities of the long bones occur in osteomalacia. He is unable to decide whether bending or fracture of the long bones is more common. Deformities of the pelvis and long bones are not seen in senile osteoporosis as far as one is aware, Maxwell has recorded a case of osteomalacia in which pain was an early symptom and he believes that pain in the back is an early indication of deficiency of calcium and vitamin D (33).

CONCLUSIONS

Symptoms and signs of generalised osteoporosis may be found especially in severe cases. They consist usually of back-ache, stiffness and weakness, tenderness and spasm of the erectores spinae.

The typical x-ray appearance of the spine is diffuse osteoporosis, "fish-tail" vertebrae and ballooning of the intervertebral discs. If collapse of one or more vertebrae is present a shortening of the spine may be detected clinically.

It is suggested that the symptoms associated with

generalised osteoporosis may be in large measure due to complications such as fractures or deformities.

There is a close similarity in the clinical pictures of osteoporosis and osteomalacia but certain differences can be detected. The resemblance, however, is sufficiently striking to suggest the possibility of similar aetiologies.

The value of symptoms and signs in the diagnosis of generalised osteoporosis is slight but clinical manifestations may be of importance in directing attention to a possible involvement of the skeleton. It is obvious that x-ray examination is the valuable diagnostic method.

3. BLOOD CHEMISTRY

The biochemical estimations which are of interest in the study of diseases of bone are the serum calcium, serum or plasma inorganic phosphorus and serum or plasma 'alkaline' phosphatase. In all the estimations performed in this investigation serum was used. In some conditions there are considerable departures from normal: thus in hyperparathyroidism characteristic findings are high serum calcium, low serum inorganic phosphorus and high serum phosphatase, while in osteitis deformans the serum calcium and phosphorus are normal and the phosphatase raised. (7c)(34).

According to Gutman et al (35) in generalised osteoporosis the phosphatase is slightly increased in the young and middle-aged but not in the old. Bodansky and Jaffe (36), too, state that there is no rise in phosphatase in senile osteoporosis.

Experimentally, decalcification produced by calcium deficiency was found to cause a rise in the serum phosphatase (37). Similarly in the osteoporosis associated with the defective calcium absorption in non-tropical sprue a slight rise has been noted (36) while a raised phosphatase may accompany the demineralisation associated with hyperthyroidism (36)(38).

Morris et al. (9) point out that where the bone cells are not very active there may be mineral depletion and grossly inadequate mineral supply but no increase in the serum phosphatase: thus, in coeliac disease and renal dwarfism there may be marked osteoporosis with a low phosphatase.

Estimations of the serum calcium, inorganic phosphorus and phosphatase were performed in 60 patients over the age of 40 years in whom the presence or absence of generalised osteoporosis had been recorded. Unfortunately a reagent used in some of the phosphorus estimations was faulty and the estimations of phosphorus in 22 cases have had to be discarded owing to this.

The methods employed were as follows:-

Serum Calcium - The Clark-Collip modification of the Kramer-Tisdall method (39)

Serum inorganic phosphorus - Youngburgs method (39)

Serum phosphatase - Method of King et al. (40)

The results are shown in the following table:-

Table 4.

Sex	Initials	Age yrs	X-Ray	Serum Calcium mgm%	Serum Phosphorus mgm%	Serum Phosphatase units
F.	E.McJ.	59	N	9.3	2.29	9.7
F.	Mrs.B.	62	O	9	2.06	9.2
F.	Mrs.H.	54	O	9	2.73	4.95
F.	Mrs.N.	85	O	8.9	3.2	11.78
F.	Mrs.W.	72	O	8.8	4.13	9.45
F.	J.P.	75	O	10.25	4.03	5.4
F.	Mrs.F.	75	O	12.5	3.03	14.3
F.	Mrs.D.	79	O	9	3.55	10.15
M.	A.P.	82	O	10.5	3.75	8.15
F.	Mrs.R.	66	O	10.45	3.13	4.95
F.	Mrs.J.P.	66	O	10.13	3.43	13.95
M.	J.G.	70	N	11.75	3.68	7.65
F.	M.B.	48	N	9.15	3.15	4.05
M.	J.T.	76	N	9.63	2.68	8.2
F.	Miss B.	49	N	9.85	3.53	6.5
F.	A.A.	89	O	10.4	3.78	9
F.	Mrs Kor W.	78	N	10.2	3.73	6.6
F.	Mrs.L.	72	N	9.88	3.68	5.3
F.	Mrs.M.	82	N	9.63	3.08	9.4
F.	Mrs.F.	81	N	9.7	3.25	6.2
F.	Mrs.K.	88	O	9.45	2.53	19.1
F.	Mrs.McI.	77	O	10	2.45	7
F.	Mrs.C.	64	N	10.68	3.35	6.3
F.	Mrs.C.	77	O	9.55	3.75	7.9
F,	Mrs.J.	77	O	10.5	4.9	12.15

Note O = generalised osteoporosis. N = Normal.

Sex	Initials	Age yrs	X-Ray	Serum Calcium mgm%	Serum Phosphorus mgm%	Serum Phosphatase units
F.	M.F.	77	O	10.38	5.85	7.8
F.	Mrs.R.	75	N	10	4.15	5.9
F.	Mrs.McC.	74	O	9.63	3.83	7.9
F.	Mrs.N.	73	O	10.35	3.45	7.5
M.	W.McM.	71	O	10.5	4.5	14
M.	W.B.	65	N	9.25	3.5	5.4
M.	F.B.	74	O	10.13	3.75	4.3
M.	J.McC.	65	N	10.5	3.45	7.5
M.	O.McC.	68	O	10	3.1	11.6
M.	H.L.	64	N	10.13	3.35	10.7
M.	J.McG.	66	N	10.13	3.48	7.7
F.	Mrs.A.J.	73	O	10.75	3.5	5.7
F.	Mrs.McK.	82	O	9.9	3.5	7.7
F.	Mrs.W.S.	55	N	10.58	-	3.
M.	R.S.	68	O	10.1	-	3.6
M.	W.B.	59	N	10.6	-	1.8
F.	Mrs.C.	57	O	9.5	-	8.3
F.	Mrs.S.	80	N	9.2	-	13.7
F.	Mrs.J.S.	59	N	9.1	-	15.08
M.	M.P.	53	N	12.6	-	5
M.	W.C.	59	N	11.5	-	6.9
M.	W.M.	64	N	11.13	-	10.2
M.	J.G.	61	N	11.2	-	10.3
F.	Mrs.C.	48	N	10.75	-	3.9
M.	J.O'.D.	72	N	10.75	-	4.4

Note. O = generalised osteoporosis. N = Normal.

Sex	Initials	Age yrs	X-Ray	Serum Calcium mgm%	Serum Phospnorus mgm%	Serum Phosphatase units
M.	J.A.	74	N	11.05	-	8.1
M.	W.B.	63	N	10.5	-	5.3
M.	G.S.	68	N	11.5	-	4.1
M.	J.McL.	69	O	10.75	-	7.85
M.	J.E.	74	N	10	-	5.5
F.	M.R.F.	73	N	8	-	8.5
F.	Mrs.G.	61	N	9.75	-	7.95
F.	Mrs Sro R	73	O	9.93	-	8.55
M.	E.G.	64	N	9.88	-	6.6
M.	J.M.	49	N	10.75,		10.5
Average		68.88		10.15	3.48	6
Range		48-89		8-12.6	2.06-5.85	1.8-19.1

Note:-

O = Generalised osteoporosis

N = Normal

All estimations are serum estimations.

The normal figures for these estimations in adults are said to be:-

Serum calcium	9-11 mgm%	(41)
Serum Inorganic phosphorus	2-5 mgm%	(41)
Serum phosphatase	3-10 units	(?39)

The results in the present series show a wider range than those noted above for healthy adults.

Serum Calcium, Phosphorus and Phosphatase

Table 8. Range of values

Cases	Serum Calcium mgm%	Serum Inorg. Phosphorus mgm%	Serum Phosphatase Units
All	8 - 12.6	2.06 - 5.85	1.8 - 19.1
O	8.8- 12.5	2.06 - 5.85	3.6 - 19.1
N	8 - 12.6	2.29 - 4.15	1.8 - 15.08

O =generalised osteoporosis cases.
N = Normal cases.

The average results, however, fall within the normal ranges quoted above as is shown in this table:-

Serum Calcium, Phosphorus and Phosphatase

Table 9. Mean values

Cases	Serum Calcium mgm%	Serum Inorg. Phosphorus mgm%	Serum Phosphatase Units
All	10.15 (60)	3.48 (38)	6 (60)
O	10.01 (27)	3.56 (23)	8.97 (27)
N	10.26 (33)	3.36 (15)	7.21 (35)

These tables also provide a comparison for the figures obtained for the cases of generalised osteoporosis with those obtained in normal cases and little difference between these groups

is detected. One's attention, however, is drawn to the phosphatase results which show a difference which may be significant and which warrants further examination of the results.

When the results are considered according to age-groups the following is found:-

Serum Calcium, Phosphorus and Phosphatase

Table 10. Mean Values in Different Age-Groups

Age (yrs)	Calcium (mgm%)		Inorg.Phosph. (mgm%)		Phosphatase Units.	
	O	N	O	N	O	N
40-49	-	10.1	-	3.3	-	6.2
50-59	9.3	10.6	2.7	2.3	6.6	6.9
60-69	10.1	10.4	2.9	3.4	8.5	7.5
70-79	10.2	10.1	3.9	3.6	8.7	6.7
80-89	9.8	9.5	3.4	3.2	11.2	9.8

As can been seen there is little variation in the results in osteoporotic and normal cases as regards the serum calcium and serum inorganic phosphorus but the phosphatase tends to rise with increase in age and the values in the osteoporotic cases are higher than the normals in the "senile" groups.

Statistically, however, there is no significant correlation between the incidence of generalised osteoporosis and the height of the phosphatase value except in the 70-79 age group.

Douglas Robertson (24) estimated the blood chemistry in a series of 15 apparently normal people over 60 years of age, the average age being 66.4 years and obtained results as shown below. For comparison I have prepared a table

of all cases in my own series over 60 years of age (i.e. in 48 cases the serum calcium and phosphatase was estimated and in 34 cases the serum phospherus was done). The average age of the 48 cases was 72.58 years.

Douglas Robertson's Series

Table 11.

	Serum Calcium mgm%	Serum inorg. Phosphorus. mgm%	Serum Phosphatase units
Average	10.30	3.68	8.53
Range	9.8-11	3-4.4	5.8-13.6

Table 12.

Present Series

	Serum Calcium mgm%	Serum inorg. Phosphorus mgm%	Serum Phosphatase units
Average	10.13	3.55	8.34
Range	8-12.5	2.05-5.85	3.6-19.1

As the methods employed were similar the results are strictly comparable and as can be seen to differ only slightly.

Douglas Robertson also investigated the blood chemistry in 60 normal adults between the ages of 20 and 40 years and found the following:-

Table 13.

	Serum Calcium mgm%	Serum P inorg. Phosphorus mgm%	Serum Phosphatase units
Average	10.393	3.831	7.195
Range	9.9-11.1	3.1-4.8	3.5-13.5

His results treated statistically showed that the difference

between the serum calcium and phosphprus of adults aged 20-40 and those over 60 years is of no significance but that the higher mean serum phosphatase in old adults may possibly be of significance.

A comparison of the results of the age-group 40-64 years and the "senile" group of 65 years and over, in the present series gives the following results:-

Table 14.

Age yrs.	Av. Serum Calcium mgm%	Av. Serum inorg. Phosphorus mgm%	Av. Serum Phosphatase units
40-64	10.25 (20)	2.92 (7)	7.31 (20)
65 & over	10.10 (40)	3.61 (31)	8.35 (40)

This also shows that the higher phosphatase results are found in the senile group.

Black et al. (17) have published figures for estimations performed in cases of senile osteoporosis of the spinal column but as the method employed for the phosphatase estimation is different from the method used in the above series, only the calcium and phosphorus figures are directly comparable.

Serum Calcium, Phosphorus and Phosphatase in Spinal Osteoporosis of the Aged. (Figures from Black et al.).

Table 15.

		Serum Calcium mgm%	Serum inorg. Phosphorus mgm%	Serum Phosphatase Bodansky units
Black et al. cases of senile osteoporosis of spinal column.	Average	9.8 (68)	3.4 (58)	3.8 (47)
	Range	7.8-12.7	2.1-6.5	2-13.4

Serum Calcium Phosphorus and Phosphatase Mean Values and Range in Patients older than 67 years.

Table 16.

	Serum Calcium mgm%	Serum inorg. Phosphorus mgm%	Serum Phosphatase units
Average	10.12 (24)	3.67 (21)	9.16 (24)
Range	8.8-12.5	2.45-5.85	3.6-19.1

It is readily seen that the figures for serum calcium and serum inorganic phosphorus in the series of osteoporotic patients over the age of 64 years are similar to those obtained by Black et al.

Table A (14) shows that there is little difference between the sexes except that there may be a tendency towards higher serum calcium in the male and higher phosphatase in the female.

Table 14.

Sex	Cases	Av. Serum Calcium mgm%	Av. Serum inorg. Phosphorus mgm%	Av. Serum Phosphatase units
	All	10.62(24)	3.52(10)	7.31(24)
Male	O	10.33(6)	3.78(4)	8.25(6)
	N	10.71(18)	3.36(6)	6.99(18)
	All	9.83(36)	3.47(28)	8.47(36)
Female	O	9.92(21)	3.52(19)	9.18(21)
	N	9.72(15)	3.36(9)	7.47(15)

During the present investigation the incidence of osteoporosis was determined in a group of post-encephalitic patients who had resided for many years in hospital and had been receiving a diet adequate at least in its mineral content. It is of interest to consider the results obtained from a study of the blood chemistry. These are given in the following table:-

Post-encephalitic Cases

Table 18. MALES.

Initials	Age yrs.	X-ray	Serum Calcium mgm%	Serum inorg. Phosphorus mgm%	Serum Phosphatase units
J.McF.	29	N	11.23	2.88	4.5
H.D.	30	N	9.88	3.43	6.7
R.Y.	29	N	10.18	2.78	6.6
A.McP.	31	N	9.38	3.03	7
A.E.	27	N	10.13	3.6	5.1
M.L.	31	O	10.75	3.85	5.4
J.M.	28	O	10.38	2.78	6.5
W.M.	32	O	10.5	3.4	5.6
A.D.	45	N	10.75	3.05	7.4
N.H.	20	N	10.5	2.98	9.6
A.McC.	32	N	10.5	2.98	8
J.S.	36	O	10.63	3.2	6.2
J.L.	50	N	9.13	2.43	5.5
J.W.	26	N	10.75	2.45	5.6
J.McD.	36	N	11	3.08	8.8
J.M.	38	N	9.75	3.1	4.4
G.C.	35	N	10.13	3.25	8.4
P.C.	25	N	10	2.55	9.6
W.B.	29	N	11	3.98	7.5
P.C.	31	N	10	3.1	7.4
Average	32	-	10.34	3.1	6.79
Range	20-50	-	9.13-11.23	2.43-3.98	4.4-9.6

Note: X-ray O = Generalised osteoporosis
N = Normal
All estimations were made using serum.

Post-encephalitic Cases

Table 19. **FEMALES.**

Initials	Age yrs.	X-ray	Serum Calcium mgm%	Serum inorg. Phosphorus mgm%	Serum Phosphatase units
J.T.	57	O	10.13	2.65	5.4
A.P.	37	O	10.38	3.35	5.5
Mrs.R.	47	O	10.25	2.95	7.9
M.B.	69	O	10.5	3.08	8.8
Mrs.H.	63	O	10.75	2.95	9.8
Mrs.S.	57	O	10	2.8	9.1
A.M.	32	N	9.63	3.25	7.5
M.H.	33	O	9.75	2.58	6.2
M.F.	37	N	9.75	3.13	5.2
Mrs.J.McP.	34	N	10.13	3.78	6.6
Mrs.C.	53		9.88	3.4	8.6
Mrs.McK.	39	N	10.5	3.03	5.6
A.N.	23	N	11	4.03	6.3
J.B.	35	N	11.25	2.9	5.3
Mrs.A.	59	N	9.63	4.05	10.5
M.McK.	47	N	9.5	2.95	6.6
Average	45.13	-	10.19	3.18	7.18
Range	23-69	-	9.5-11.25	2.58-4.05	5.2-10.5

Note: X-ray O = Generalised osteoporosis

N = Normal

All estimations were made using serum.

These results, which are essentially normal are summarised in Table:-(20)

Table 20.

	Average Serum Calcium mgm%	Inorganic Phosphorus. mgm%	Phosphatase units
Osteoporosis	10.4(9.7-10.7)	3.1(2.6-3.8)	6.9(5.4-9.8)
No Osteoporosis	10.2(9.1-11.2)	3.2(2.4-4.0)	6.9(4.4-10.5)

There is no appreciable difference between the two groups.

When the results are considered according to sex the following table(21) is obtained:-

Table 21.

Sex	Cases	Serum Calcium mgm%	Average Serum inorg. Phosphorus mgm%	Serum Phosphatase units
	All (20)	10.34	3.1	6.79
Male	O (4)	10.57	3.31	5.93
	N (16)	10.28	3.04	7.01
	All (16)	10.19	3.18	7.18
Female	O (7)	10.25	2.91	7.53
	N (8)	10.17	3.39	6.7

There is No obviously significant variation in the figures constrasting males and females. When the results for the senile and encephalitis groups are compared it is obvious that the senile osteoporotics show a rise in serum phosphatase which is not observed in the osteoporotic section of the encephalitic patients. The latter indeed present a blood

chemistry which is almost identical as far as serum phosphatase is concerned, with the osteoporotics of the general series who are younger than sixty-four years. This strengthens the impression which has already been obtained that the serum phosphatase shows a greater increase in the older age-group.

Morris and Peden have suggested that in elderly patients the bone cells tend to lose their vitality and their capacity to increase the production of phosphatase. It is true that even the greatest rise of serum phosphatase which has been observed in the present group of osteoporotic patients is small compared with the values obtained in the osteoporosis of rickets and osteomalacia. Nevertheless as has just been mentioned, it was the oldest groups of senile osteoporotics in whom the highest values were obtained. The question may be put whether disuse played a part in diminishing the vitality of the bone cells. The encephalitic patients had for years been living restricted lives. As for the general group of patients, observation in a hospital such as Stobhill leads one to the impression that patients who attain the age of seventy before admission to hospital are often much more active and presumably have previously led more active lives than have those who gain admission between the ages of 50 and 70. This can hardly be more than a suggestion but in view of social implications it might be worth consideration.

CONCLUSIONS

In generalised osteoporosis and generalised senile osteoporosis the serum phosphatase tends to be a high normal reading but statistical investigation shows no correlation between the incidence of generalised osteoporosis and the height of the phosphatase value except in the 70 79 age-group. There is no significant difference in the blood chemistry according to sex. The figures obtained agree well with published estimations of other workers. The place, therefore, of the serum calcium, phosphorus and phosphatase in the diagnosis of generalised osteoporosis is a small one and consists in providing negative evidence, as they are within normal limits, thereby helping to exclude conditions such as osteitis deformans or hyperparathyroidism.

A Note on Post-Mortem Findings

This section is included in the chapter on diagnosis as post-mortem findings, when available, can provide indisputable evidence. Naked-eye, the bones are seen to be more brittle and softer than normal. The following description of naked-eye and microscopical examination of the bones in senile osteoporosis has been recorded by Schmorl (18)(42). The cortical bone is thinner than normal and the marrow spaces and medullary cavity are enlarged. The surfaces of the trabeculae are clean and smooth and although the individual trabeculae are much thinner and fewer than is normal their architectural structure is maintained. Severe osteoporosis of the spine results in collapse of the vertebral bodies and expansion of the nucleus pulposus producing disk and "fish-tail" vertebrae. The vertebral bodies may collapse anteriorly giving true compression fractures with mild trauma. Beadle (28) investigated senile kyphosis and attributed it to a necrosis of the anterior portion of the annulus fibrosus. When the bare bony fronts of the vertebral bodies come in contact with each other bony ankylosis is prone to occur. The rest of the disk remains normal (27).

Specimens of rib, in ten cases, were obtained at post-mortem examination. The soft tissue attached to the ribs was removed and the ribs were dried and weighed. They were then ashed in an electric muffle and the calcium content was estimated by the method of Shohl and Pedley (39) and the

phosphorus content by the method of Youngburgh (39). The results are shown in the following table:-(22)

Table 22

Initials	Age yrs.	X-ray	% Calcium	%Phosphorus	Calcium:Phosphorus ratio
J.O'H.	59	O	14.6	8.7	1.7
A.P.	82	O	13	7.7	1.7
R.F.	75	N	17.7	10.5	1.7
J.P.	75	O	13.5	8	1.7
M.F.	73	N	14.7	8.6	1.8
Mrs.P.	66	O	7.2	4	1.8
Mrs.S.	73	O	9.7	5.5	1.8
M.J.	77	O	9.5	5.9	1.6
Mrs.E.P.	68	N	11.1	5.4	2.0
M.B.	68	O	6.6	3.2	2.1

A comparison of these findings gives this result:-

Table 23

	% Calcium	%Phosphorus	Calcium: Phosphorus.
Osteoporosis	10.6	6.1	1.8
NonOsteoporosis	14.5	8.2	1.8

The average percentage contents of calcium and phosphorus were found to be less in the subjects in whom osteoporosis had been demonstrated radiographically during life. The differences, however, when submitted to statistical analysis did not prove to be significant. This is not surprising when one remembers that those subjects without radiographic osteoporosis had conditions which might have had exerted some pathological effect on calcium and phosphorus metabolism. Because of this it is unlikely that chemical analysis of bones obtained at

autopsy ~~is unlikely~~ should to yield accurate information as to the composition of the bones in healthy old age unless one limits the examination to healthy well-nourished subjects who have met with sudden death as the result of an accident.

CHAPTER III

INCIDENCE.

1. AGE INCIDENCE

Generalised osteoporosis may be found at all ages but in this investigation the incidence in subjects over 40 years of age was considered. A series of 80 patients was examined, there being no special selection apart from the age limit as mentioned. Table (24) shows the results obtained:-

Table 24

Initial	Age	Sex	X-ray	Initial	Age	Sex	X-ray
Mrs.W.S.	55	F	N	Mrs.G.	61	F	N
W.B.	65	M	N	R.S.	68	M	O
Mrs.SorR	73	F	O	F.B.	74	M	O
W.B.	59	M	N	E.G.	64	M	N
J.McC.	65	M	N	E.McI.	59	F.	N
J.M.	49	M	N	O.McC	68	M	O
Mrs.C.	57	F	O	Mrs.R.	66	F	O
H.L.	64	M	N	Mrs.B.	62	F	O
Mrs.J.P.	66	F	O	J.McG.	66	M	N
M.S.	80	F	N	J.G.	70	M	N
D.McK.	44	M	N	Mrs.H.	54	F	O
M.B.	48	F	N	A.McM.	58	M	N
Mrs.N.	85	F	O	J.H.	70	M.	N
J.P.	77	M	O	Mrs.W.	72	F	O
R.F.	75	M	N	D.F.	58	M	N
Mrs.J.S.	59	F	N	J.T.	76	M	N
Mrs.N.	85	F	O	M.P.	53	M	N

Note O = osteoporosis N = Normal.

Initial	Age	Sex	X-ray	Initial	Age	Sex	X-ray
Miss B.	49	F	N	Mrs.C.	81	F	O
W.C.	59	M	N	A.A.	89	F	O
Mrs.T.P.	68	F	N	W.M.	64	M	N
Mrs.KorW.	78	F	N	M.B.	68	F	O
J.G.	61	M	N	Mrs.L.	72	F	N
Mrs.A.J.	73	F	O	J.P.	75	F	O
Mrs.M.	82	F	N	J.McK.	74	M	N
Mrs.F.	75	F	O	Mrs.F.	81	F	N
G.C.	81	M	N	Mrs.D.	79	F	O
Mrs.K.	88	F	O	H.R.	73	M	N
Mrs.C.	48	F	N	Mrs.McI.	77	F	O
H.S.	76	M	N	J.O'D.	72	M	N
Mrs.C.	64	F	N	J.S.	72	M	N
J.A.	74	M	N	Mrs.C.	77	F	O
J.M.	76	M	N	W.B.	63	M	N
Mrs.J.	77	F	O	J.McP.	72	M	N
G.S.	68	M	N	M.F.	77	F	O
J.McE.	77	M	N	J.McL.	69	M	O
Mrs.R.	75	F	N	Mrs.McK.	82	F	O
J.E.	74	M	N	Mrs.McC.	74	F	O
Mrs.M.	74	F	O	A.P.	82	M	O
Mrs.N.	73	F	O	J.F.	53	M	N
M.R.F.	73	F	N	W.McM.	71	M	O

Note: X-ray - O = Generalised osteoporosis

N = Normal.

The average ages of the above patients were found to be as follows:- Table 25.

X-ray	Generalised Osteoporosis		Normal	
Sex	Male	Female	Male	Female
Average Age Years.	72.71	74.36	66.41	65.75
	74.0		66.19	

It is seen that the osteoporotic cases tend to show higher average ages than the normal cases.

When the cases are examined according to age-groups the following is observed:-

Table 26.

	MALE			FEMALE		
Age Group	Total No.	Osteop. No.	%Incidence of osteop.	Total No.	Oesteop. No.	Incidence of Osteop.
40-49	2	-	-	3	-	-
50-59	6	-	-	5	2	40
60-69	12	3	25	7	4	57.1
70-79	17	3	17.6	17	13	76.5
80.89	2	1	50	9	6	66.7
Total	39	7	17.9	41	25	61

As the number of cases in each age-group is small calculation of the percentage incidence of generalised osteoporosis is valueless and has been included merely to provide easier comparison of the figures. When no differentiation is made for sex the increasing incidence with increase in age shown above, is demonstrated more

clearly and may be shown diagrammatically (Figure 1.). The over-all incidence is 40% which may seem to be rather high. All 80 patients were in-patients in Stobhill Hospital and the majority of these were drawn from the poorer sections of Glasgow. This figure, therefore, cannot be taken as an indication of the general prevalence of osteoporosis in the population since diet, habits of life and other factors are different.

The numbers of osteoporotic and normal cases may also be represented diagrammatically:- Figure 2.
This demonstrates the increasing number of cases of generalised osteoporosis in each age-group until finally in the 80-89 years age-group they outnumber the normal cases.

Figure 1.

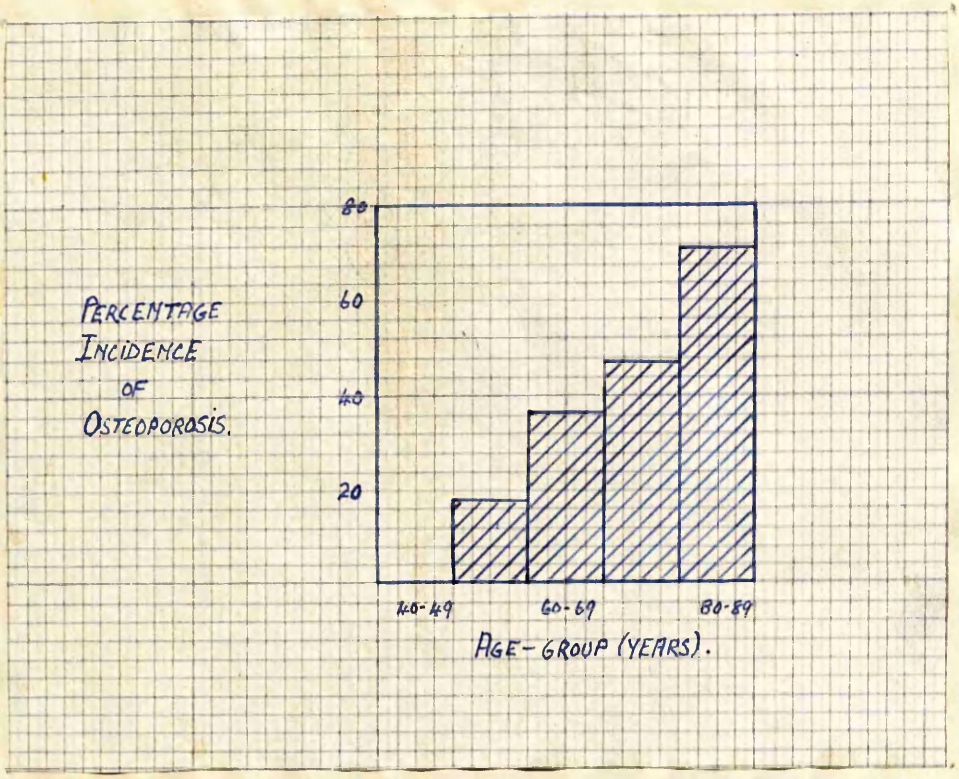
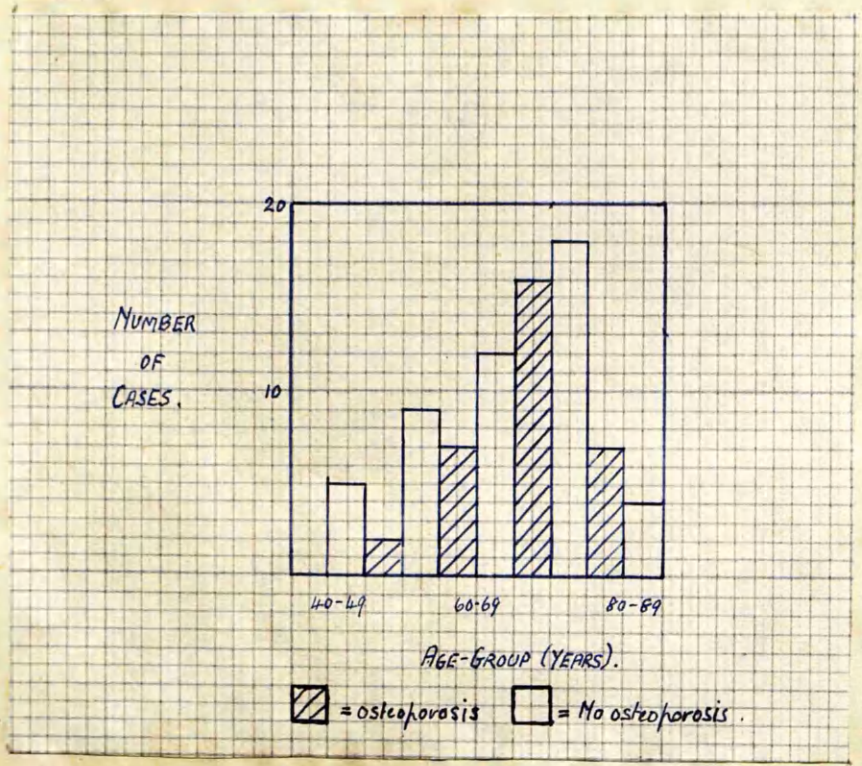


Figure 2.



At this point it is of interest to consider the findings obtained from a survey of the x-rays of the spine which were taken in Stobhill Hospital during the years 1939, 1940 and 1941, again limiting the selection of subjects to those over 40 years of age. It should be stated that cases of carcinomatosis, myelomatosis and other conditions known to produce rarefaction of bone were excluded. Table ~~XY~~ 2Y gives details of this survey.

TABLE XY 2Y.

1939 cases

Name	Age	Sex	X-ray	Name	Age	Sex	X-ray
M.B.	62	F	N	M.K.	78	F	O
J.B.	40	M	N	M.L.	54	F	N
G.B.	42	M	N	M.L.	43	F	N
M.B.	44	F	N	D.H.	44	M	N
M.B.	65	F	N	H.J.	41	M	O
J.C.	55	M	N	J.M.	67	M	N
B.C.	62	M	N	P.M.	58	M	N
N.C.	45	M	N	H.N.	55	M	O
T.C.	68	M	N	M.M.	40	M	N
P.D.	49	M	N	R.M.	49	M	N
M.G.	45	F	N	N.M.	59	M	N
A.G.	59	M	N	M.M.	44	F	N
W.G.	53	M	N	M.P.	41	F	N
M.G.	45	F	N	M.R.	53	F	N
A.G.	67	M	N	D.R.	46	M	N
A.H.	42	M	N	M.R.	64	F	N
M.H.	47	F	N	D.S.	92	M	O
M.H.	53	F	N	S.S.	46	M	N
J.H.	57	M	N	W.S.	58	M	N
M.H.	63	F	O	T.S.	66	M	O
R.L.	49	M	N	J.V.	66	F	O
				A.W.	69	M	O

1939 cases (cont'd.)

Name	Age	Sex	X-ray	Name	Age	Sex	X-ray
R.W.	61	M	N	P.M.	50	M	N
J.B.	43	M	N	W.N.	62	M	N
M.B.	52	F	N	T.R.	80	M	N
J.B.	53	M	N	M.S.	81	F	O
J.C.	69	M	N	M.W.	54	F	O-
B.C.	72	M	O	D.W.	83	M	N
J.C.	55	M	N	R.W.	50	M	N
J.D.	49	M	N	W.B.	40	M	N
T.F.	71	M	N	J.B.	64	F	O-
A.G.	67	M	O	M.B.	62	F	N
B.H.	75	M	O	T.B.	49	F	N
M.H.	42	F	N	M.C.	64	F	N
A.H.	64	F	O	J.C.	55	M	N
M.L.	72	F	O	M.E.	73	F	O
P.M.	66	M	O	M.E.	51	F	N
J.M.	47	M	N	C.J.	-	M	N
M.McC.	63	F	N	J.M.	42	M	N
M.McI.	50	F	N	M.McL.	41	F	N
Y.McP.	65	M	N	P.McC.	70	M	O
J.M.	53	M	N	M.R.	45	F	N
R.M.	59	M	N	M.S.	58	F	N

1940 cases

Name	Age	Sex	X-ray
G.A.	57	M	N
W.C.	42	M	O
J.C.	83	M	O
W.C.	41	M	N
M.D.	71	F	O
M.D.	59	F	N
M.D.	60	F	N
W.E.	47	M	O-
D.F.	46	M	N
W.F.	42	M	N
M.G.	49	F	N
M.H.	68	F	O-
M.H.	60	F	O
R.J.	69	M	N
J.K.	70	M	N
M.McF.	56	F	O
M.McG.	57	F	N

Name	Age	Sex	X-ray
A.McE.	50	M	N
M.McG.	62	F	N
M.McK.	54	F	N
R.McL.	44	M	N
M.McR.	40	F	N
M.M.	47	F	N
M.M.	74	F	O
M.McL.	40	F	N
D.McG.	46	M	N
M.McQ.	76	F	N
J.McM.	49	M	N
W.McV.	48	M	N
M.M.	48	F	N
M.N.	42	F	N
M.P.	60	F	O-
J.S.	70	M	N
M.S.	64	F	O
E.V.	52	M	N

1940 cases (cont'd.)

Name	Age	Sex	X-ray	Name	Age	Sex	X-ray
J.W.	50	M	O	I.McL.	42	F	O
J.W.	67	M	N	B.McH.	41	M	N
L.A.	50	M	N	W.McK.	41	M	N
M.A.	67	F	N	M.N.	45	F	N
R.B.	41	M	O	M.P.	63	F	N
A.B.	50	M	N	M.P.	46	F	N
M.B.	40	F	O	M.S.	68	F	O
M.C.	67	F	O	S.O.	37	F	O
M.C.	40	F	N	M.S.	53	F	O
R.C.	42	M	N	L.S.	53	F	O
J.C.	50	M	O	M.B.	69	F	O
M.E.	49	F	N	J.F.	56	M	O
J.F.	52	F	N	T.L.	72	M	N
M.O.	79	F	O	B.M.	82	M	N
J.G.	63	M	O	D.M.	59	M	O
W.K.	51	M	N	B.S.	42	M	N
C.K.	45	M	N	M.W.	63	F	N
				J.M.	40	M	N

1941 cases

Name	Age	Sex	X-ray	Name	Age	Sex	X-ray
C.A.	52	M	N	M.McD.	58	F	O
M.B.	45	F	N	J.McC.	62	M	N
E.B.	49	M	N	M.McC.	63	F	O
D.B.	56	M	N	J.McD.	66	M	O
J.C.	53	M	N	R.M.	43	M	O
A.C.	44	F	N	T.O.	56	M	N
M.C.	46	F	N	M.P.	78	F	O
M.C.	60	F	O	A.P.	49	M	N
M.D.	42	F	N	B.R.	52	M	N
D.D.	42	M	N	P.R.	47	M	N
M.E.	62	F	O	M.S.	76	F	O
M.F.	62	F	O	D.S.	46	M	N
M.F.	67	F	O	E.S.	45	M	N
T.F.	67	M	N	I.S.	52	M	N
W.G.	48	M	O	M.B.	53	F	O
J.G.	52	M	N	R.B.	52	M	N
W.H.	75	M	O	D.B.	75	M	N
J.H.	70	M	O	R.C.	48	M	N
D.M.	63	M	O	C.D.	50	M	O

1941 cases (cont'd.)

Name	Age	Sex	X-ray	Name	Age	Sex	X-ray
P.F.	77	M	N	A.P.	-	M	N
T.F.	40	M	N	J.S.	40	M	N
M.G.	55	F	N	H.T.	41	M	N
W.G.	66	M	N	M.T.	69	F	N
H.G.	50	M	N	M.T.	44	F	N
T.G.	52	M	N	A.W.	51	M	0
T.H.	60	M	N	W.A.	65	M	0
M.J.	53	F	N	M.C.	60	F	0
J.K.	57	M	N	A.H.	59	F	0
M.K.	59	F	N	M.H.	50	F	N
M.R.K.	69	F	0	J.McG.	65	M	0
W.L.	60	M	N	W.McD.	71	M	0
M.L.	60	F	N	M.McI.	58	M	0
M.M.	49	F	N	L.M.	40	M	N
W.M.	76	M	N	M.M.	62	F	0
A.McK.	41	F	N	M.S.	-	F	N
M.McG.	57	F	N	M.S.	55	F	0
N.McG.	58	M	0	J.N.	42	M	0
M.O.	59	F	N	M.A.	69	F	0

An analysis of this table yields the following results as regards age incidence.

Table 28.

1939 A.

Age group	MALE			FEMALE		
	Total No.	No.of Osteo-porosis	%Incid. of Osteo-porosis	Total No.	No.of Osteo-porosis	%Incid. of Osteo-porosis.
40-49	17	1	5.9	11	-	-
50-59	15	1	6.7	8	1	12.5
60-69	13	5	3.8	9	3	33.3
70-79	4	3	75	3	3	100
80-89	2	-	-	1	1	100
90-99	1	1	100	-	-	-
TOTAL	52	11	21.2	32	8	25

Table 29. 1940 B.

Age group	MALE			FEMALE		
	Total No.	No.of Osteo-porosis	% Incid. of Osteo-porosis	Total No.	No.of Osteo-porosis	% Incid. of Osteoporosis
40-49	16	3	18.8	12	2	16.7
50-59	10	4	40	6	2	33.3
60-69	3	1	33.3	12	7	58.3
70-79	3	-	-	4	3	75
80-89	2	1	50	1	1	100
TOTAL	34	9	26.5	35	15	42.9

Table 30 1941 C.

Age group	MALE			FEMALE		
	Total No.	No.of Osteo-porosis	% Incid. of Osteo-porosis	Total No.	No.of Osteo-porosis	% Incid. of Osteoporosis
40-49	14	3	21.4	7	-	-
50-59	5	4	26.7	9	4	44.4
60-69	9	4	44.4	12	8	66.7
70-79	6	3	50	2	2	100
TOTAL	44	14	31.8	30	14	46.7

Table 31 1939-1941 D.

Age group	MALE			FEMALE		
	Total No.	No.of Osteo-porosis	%Incid. of Osteo-porosis	Total No.	No.of Osteo-porosis	% Incid. of Osteoporosis
40-49	47	7	14.9	30	2	6.7
50.59	40	9	22.5	23	7	30.4
60-69	25	10	40	33	18	54.5
70-79	13	6	46.2	9	8	88.9
80-89	4	1	25	2	2	100
90-99	1	1	100	-	-	-
TOTAL	130	34	26.2	97	37	38.1

The osteoporotic cases show a higher average age than do the others. Indeed the figures are similar to those obtained for the series of patients with generalised osteoporosis although in the "spinal" series the average age is younger. Detailed analysis of the spinal series into age groups strengthens the impression of similarity with the general osteoporosis series, viz. the increasing incidence of bony rarefaction as age advances. The total percentage incidence of spinal osteoporosis is 31.3% compared with 40.0% of generalised osteoporosis. One point of interest may be noted namely, the increasing incidence of spinal and osteoporosis during the years 1939, 1940 and 1941.

Table 32

Year	Total % Incidence of Spinal Osteoporosis
1939	22.6
1940	34.8
1941	37.8

All the conditions of life have changed considerably during this period but it is tempting to postulate dietary deficiency in the shape of less milk and milk-containing products as an important factor in causing this increasing incidence. It would be dangerous to go further than this because with changes in modes of occupation especially of the younger members of the community there might have been an increasing demand for hospital treatment by the elderly because of disabilities which in peace-time would have been treated at home.

Statistical analysis of the above data, however, only allows one to say that the increase in generalised osteoporosis with age may be significant. The results are not conclusive.

While generalised osteoporosis is more common after the age of 65 years it occurs to a certain extent in middle-aged people and the question as to whether the senile type differs in any way from the other naturally arises. Radiologically there is no difference and the blood chemistry results, as shown above, are similar although there is a tendency towards slightly higher readings in the serum 'alkaline' phosphatase in the senile group. Apart from this the conditions appear to be identical.

The series of post-encephalitic patients which was investigated consisted mainly of younger patients and the results are shown as follows:-

Table 33.

MALES			FEMALES		
Initials	Age	x-ray	Initials	Age	x-ray
J.McF.	29	N	J.T.	57	O
H.D.	30	N	A.P.	37	O
R.Y.	29	N	Mrs.N.McP.	54	N
A.McP.	31	N	A.McQ.	26	N
A.E.	27	N	Mrs.R.	47	O
M.L.	31	O	Mrs.L.	52	N
J.M.	28	O	Mrs.M.	41	N
W.M.	32	O	M.B.	69	O
A.R.	45	N	Mrs.H.	63	O

Note O = osteoporosis N = Normal.

MALES			FEMALES		
Initials	Age	x-ray	Initials	Age	x-ray
N.H.	20	N	Mrs.M.	59	O
A.McC.	32	N	Mrs.S.	57	O
J.S.	36	O	A.M.	32	N
J.L.	50	N	M.H.	33	O
J.W.	26	N	M.F.	37	N
J.McD.	36	N	Mrs.J.McP.	34	N
J.M.	38	N	Mrs.H.B.	55	N
G.C.	35	N	Mrs.McK.	39	N
P.C.	25	N	A.N.	23	N
W.B.	29	N	I.B.	35	N
P.C.	31	N	Mrs.A.	59	N
J.B.	53	N	Mrs.S.	46	N
J.B.	34	N	J.H.	33	N
R.B.	33	N	Mrs.F.	45	N
J.C.	40	N	M.G.	31	N
W.C.	41	N	M,McD.	31	N
P.D.	32	N	J.W.	57	N
J.F.	37	N	H,McG.	22	N
G.G.	50	N	Mrs.McG.	35	O
C.H.	32	N	M.McK.	47	N
J.McN.	30	N	Mrs.L.	47	N
A.P.	62	N	Mrs.D.	48	N
W.R.	34	N	Mrs.M.	50	N
W.S.	36	N	C.U.	38	N
Average	35.06	-	Average	43.78	-
Range	20-62	-	Range	22-69	

Note O = osteoporosis N = Normal.

As may be seen above, generalised osteoporosis does occur in patients under 40 years of age. The cause of the osteoporosis in these cases was investigated and is discussed later. The average ages of the above patients are as follows:-

Table 34.

Cases	Average Age (yrs)	
	Male	Female
All	35.06 (34)	43.78 (32)
O	31.75 (4)	50.78 (9)
N	35.5 (30-	41.04 (23)

The figures in brackets are the number of cases.

This table (34) shows that on an average the male series was younger than the female. A detailed analysis gives this result:-

Table 35

	MALE			FEMALE		
Age group (yrs)	Total No.	Osteo-porosis No.	%Incid. of osteoporosis	Total No.	Oesteo-porosis No.	% Incid. of osteoporosis
20-29	8	1	13	3	-	-
30-39	19	3	16	11	3	27
40-49	3	-	-	7	1	14
50-59	3	-	-	9	3	33
60-69	1	-	-	2	2	100
TOTAL	34	4	12	32	9	28

It is seen therefore that seven patients under the age of 40 years exhibited generalised osteoporosis. This

demonstrates that age per se need not be the sole factor in the aetiology of generalised osteoporosis.

SEX INCIDENCE

This may now be conveniently discussed here as the above tables provide the necessary data. As regards the series of 80 ordinary patients over 40 years of age 7 males out of a total of 39 i.e. 18% had generalised osteoporosis and 35 females out of a total of 41 i.e. 61% exhibited generalised osteoporosis. The ratio of males:females is therefore 1:3.6 as regards the osteoporotic patients. The detailed analysis according to age groups shows a preponderance of females in each group but the numbers are too small to provide anything but a very rough comparison. Similarly in the spinal series one finds a higher incidence of porosis in the females although it is not so striking, viz. 26% in males and 38% in females giving a ratio of 1:1.5. When the results are examined statistically they reveal a significant predominance of generalised osteoporosis in the female.

This predominance of osteoporosis in the female is possibly the reason why intracapsular fracture of the neck of the femur in old patients is much more common in women than in man (46). This fracture is usually attributed to the osteoporotic condition of the bone (47). It has been pointed out in a previous section that pathological fracture is one of the complications of senile osteoporosis. When the results in the series of post-encephalitic patients are considered a similar sex preponderance is noted.

4 of 34 males (12%) and 9 of 32 females (28%) are osteoporotic. The ratio of males: females is 1:2.3 as regards the osteoporotic patients in this series. This is not so striking as the results in the previous series and its significance may even be partly offset by the predominance of older patients amongst the females but it is quite definite none the less. Owen et al. (22) examined 7 males who had been living on diets containing a very poor intake of calcium, the ages being all about 70 years with the exception of one who was 44 years old. They found generalised osteoporosis in 3 and "slight porosis" in 3, the remaining one being normal. This suggests that a fairly high incidence of generalised osteoporosis may be found amongst males of the poorer classes. If poor calcium intake is a factor, or the only factor, in the causation of generalised osteoporosis, then this condition is a form of osteomalacia. It is interesting to note the observation of Hume and Nirenstein (48) who detected an increasing incidence of "hunger osteomalacia" with age. Of 131 patients examined 115 were over 40 years of age and 1/3 were between 60 and 70 years. Meulengracht (31) described 18 cases of osteomalacia of the spinal column and all of these were over 40 years, 6 being male and 12 female, a ratio of 1:2. These similar findings in osteomalacia again indicate that the possibility of poor diet being of importance in the aetiology of generalised osteoporosis should be investigated.

Albright et al. (16), investigating "menopausal" osteoporosis found only 2 cases in males and 40 in females. They found none in females before the menopause. This finding gives a ratio of 1 male:20 females and, of course, emphasises the age factor also. Black et al. (17) in a series of 208 cases of senile osteoporosis of the spine found a ratio of 1 male: 4 females and the results in the above smaller series of cases of generalised senile osteoporosis give a ratio of 1:3.1. Black et al. suggest that because the life expectancy of the female is longer than the male, more women live to the ages in which osteoporosis is common and also that perhaps females live more sedentary lives than males and that disuse atrophy may play a part in producing this incidence.

CONCLUSIONS

Generalised osteoporosis can occur at all ages of adult life. There is an increasing incidence with increasing age which according to statistical examination, may be significant. The incidence of generalised osteoporosis was found to be 40% in the series of 80 patients over 40 years of age drawn from the poorer sections of the population of Glasgow. In the spinal series the incidence was found to be 31%.

There is no evidence to suggest that the generalised osteoporosis found in patients under 65 years, which figures was selected arbitrarily as the lower limit of the senile group, differs in any way from generalised senile osteoporosis.

The sex incidence was found to be 18% in males and 61% in females in 80 patients over 40 years of age. This gives a ratio of 1 male to 3.6 females. This increased indicence in females has been noted by other observers quoted above.

CHAPTER IV.

A Study of Some Possible Causes of Osteoporosis in the Old.

The present chapter is concerned with a study of some factors which may be of importance in the aetiology of generalised osteoporosis in the later decades of life. The discussion here is limited to the undernoted causes.

A. Diet (1) Defective intake of lime.

(2) Defective absorption and/or retention of lime.

(3) Inability to utilise lime for bone formation.

B. Disuse

C. Vascular Disease

D. Hormonal Disturbance.

A. Diet

1. Defective intake of calcium

Meulengracht and meyer in 1936 (19) after studying five cases of senile osteoporosis suggested that the cause of senile osteoporosis might be long-standing calcium deficiency. Two years later Meulengracht (49) re-affirmed this view when considering a case of senile osteoporosis in which there was a history of repeated purgation with sodium sulphate. That quite a proportion of people in Great Britain live on diets which fail to supply the extimated physiological requirements of calcium has been shown by Orr (50), a finding which is particularly appropriate for the class of elderly patient admitted to the wards of a municipal hospital. It has been

demonstrated experimentally that osteoporosis can be produced in pigs (51) dogs of all ages (52) adult rabbits (53) and adult cows (54) by dietary means and these findings immediately suggest the possibility of a similar condition being produced by prolonged calcium deficiency in adult human beings. Meulengracht's theory has received considerable support in this country from Leitch (20), Owen (21) and Owen et al. (22).

If defective intake of calcium is the cause of generalised senile osteoporosis one would expect to be able to cure the condition by treatment with adequate amounts of calcium in the diet. Conclusive proof of this has yet to be demonstrated. Black et al. (17) investigated a series of 208 patients suffering from senile osteoporosis of the spinal column, of whom 167 were female and 41 male. Treatment with an adequate diet, which included foods such as milk, cheese and eggs, supplemented with salts of calcium and phosphorus and with vitamin D, was given. Of these patients 72 were followed up for periods up to 9 years and averaging 2.3 years from the initial examination. Symptomatic improvement was found in 54% of patients treated with calcium and phosphorus, with vitamin D, or with all three. In patients having none of these 33% were benefited. In the group on treatment with calcium, phosphorus and vitamin D only 43% treated for less than 6 months showed improvement but of those treated for 6 months or longer 70% were improved symptomatically.

Follow up x-rays were available in 18 cases, the average period of treatment being 29 months. In no case was there sufficient change to enable the radiologist to say that it was due to recalcification and not to variation in the technique used in taking the films. It is interesting to compare the above findings with those recorded by Maxwell (30) in cases of osteomalacia associated with pregnancy, in which symptomatic relief was obtained after 1½ or 2 months' administration of calcium and vitamin D. Meulengracht (31) in a series of 18 cases of osteomalacia of the spinal column, 6 male and 12 female all over 40 years of age, also obtained relief of symptoms with treatment by good diet supplemented by calcium and vitamin D. Subjective improvement, however, may not always be reliable evidence as a test of the efficiency of the drug therapy as is illustrated by the following three cases of generalised senile osteoporosis. (a) Mrs.A.J. 73 years had suffered from lumbar pain, which radiated into the abdomen and also down into the thighs, for 4 months before admission to hospital. Rest in bed without any drug therapy relieved the acute pain in a few days and complete relief was experienced in four weeks. (b) O.McC. male 68 years, had had occasional pains in the back for 9 years and two weeks before admission to hospital developed severe lumbar pain which disappeared gradually with rest in bed and the oral administration of gentian "placebo" containing infusion of gentian. He believed that the medicine "did him good". (c) Mrs.W.N.

73 years, complained of pain in the back and abdomen for 3 weeks before admission, and rest in bed for 5 days did not give relief but a "gentian placebo" produced striking releif within two days.

The assessment of symptomatic relief with drug therapy therefore, requires careful and cautious consideration. Black et al. noted that 33% of their patients who were not receiving calcium, phosphorus or vitamin D, apart from the amounts contained in their food, improved symptomatically. That the precentage of cases relieved symptomatically jumpted from 43% to 70% when those before and after 6 months treatment were contrasted, should also, however, be especially noted. If the objective test of x-ray examination showed improvement it would be very much more important and convincing evidence of the specific effect of calcium enrichment of the diet.

The following series of cases were treated under direct supervision in hospital with 10 grams of calcium gluconate and 1000 units of vitamin D per day, orally, in addition to the ordinary hospital diet. A daily intake of 10 grams calcium gluconate represents an intake of about 1 gram of calcium and, as has been pointed out, this is supplementary to the ordinary intake in the food. It has been calculated by Sherman (55) that an intake of 0.45 gram of calcium daily should provide an equilibrium between intake and output in a 70 Kg subject, and this figure is more or less generally accepted. The treatment used in the following cases, therefore,

provided a more than adequate intake of calcium:-

Table 36.

No.	Initials	Sex	Age yrs.	Duration of treatment. (months)	X-ray
1.	R.S.	M	68	1	
2.	Mrs.H.	F	54	3	
3.	Mrs.W.	F	72	3	
4.	A.P.	M	82	3	
5.	Mrs.B.	F	62	4	
6.	Mrs.N.	F	85	4	Generalised osteoporosis
7.	Mrs.P.	F	66	7	
8.	J.P.	F	75	8	
9.	Mrs.R.	F	66	8	
10.	A.A.	F	89	12	
11.	Mrs.D.	F	79	10	
12.	Mrs.F.	F	75	15	
13.	E.McI.	F	59	$3\frac{1}{2}$	No osteoporosis
14.	J.T.	M	76	13	

Only one of the 12 osteoporotic cases was under 65 years of age, the remaining 11 being considered as generalised senile osteoporosis. One of the two controls who received the above treatment was under 65 years of age. X-ray examinations were repeated at monthly intervals in each case and no change in the condition of the bones was demonstrable in any case whether osteoporotic or normal. A few cases were treated for some months with 9 tablets of

Calfos, a proprietary preparation each tablet of which contains 0.112 gram of calcium.

~~Calfos~~ ℘ daily, orally, in addition to their ordinary hospital diet. This treatment provided an intake of about 1 gramme calcium and about 0.5 gramme phosphorus quite apart from the amounts of these substances contained in the food. The results are shown below:-

Table 37

Initials	Sex	Age	Duration of treatment (months)	X-ray
Mrs.J.F.	F	81	6	
Mrs.N.	F	85	6	Generalised Osteoporosis
F.B.	M	74	8	
Mrs.McK.	F	82	8½	
Mrs.G.L.	F	72	6	Normal

Once more, repeat x-ray examinations failed to reveal any change in the condition of the bones. These findings correspond with those of Black et al. who were unable to detect any appreciable change in senile osteoporosis of the spine treated for as long as 29 months. In the above series only 10 osteoporotic and 2 controls were treated for 6 months or longer and the longest period of treatment was 15 months. The criticism that the period of treatment was not long enough, in view of the generalised nature of the condition, to allow of sufficient calcium to be deposited to produce x-ray changes, might be made. It is well known that localised osteoporosis such as seen in fractures of in cases of rickets show x-ray evidence of healing within a matter of weeks, but, of course only relatively small areas of bone need recalcification. How long should elapse

before generalised disease of bone should show x-ray change? Maxwell (30) has described a case of osteomalacia in a woman aged 37 years who had a kyphosis which was cured after two months treatment, as shown by x-ray. Hunter et al. (45) have recorded a case of a woman aged 33 years suffering from osteomalacia. X-ray showed osteoporosis of the bones of the skull, right femur, tibia, humerus, radius, ulna and hand, as well as other bones, when contrasted with the corresponding bones of a control subject. After 3 months treatment the pains disappeared and x-ray examination repeated after 7 months showed union of many of the fractures which had been present and complete healing of the defects in the calvaria. As this was a case of generalised bone disease and x-ray changes were not only demonstrable but were marked, one is tempted to suggest that a period of about 6 months is a suitable time within which to expect x-ray changes in generalised senile osteoporosis if changes are going to occur. If this assumption be accepted one must conclude that neither the findings of Black et al. nor those recorded in the present investigation support the view that deficient calcium intake is the cause of senile osteoporosis although they do not necessarily exclude this hypothesis.

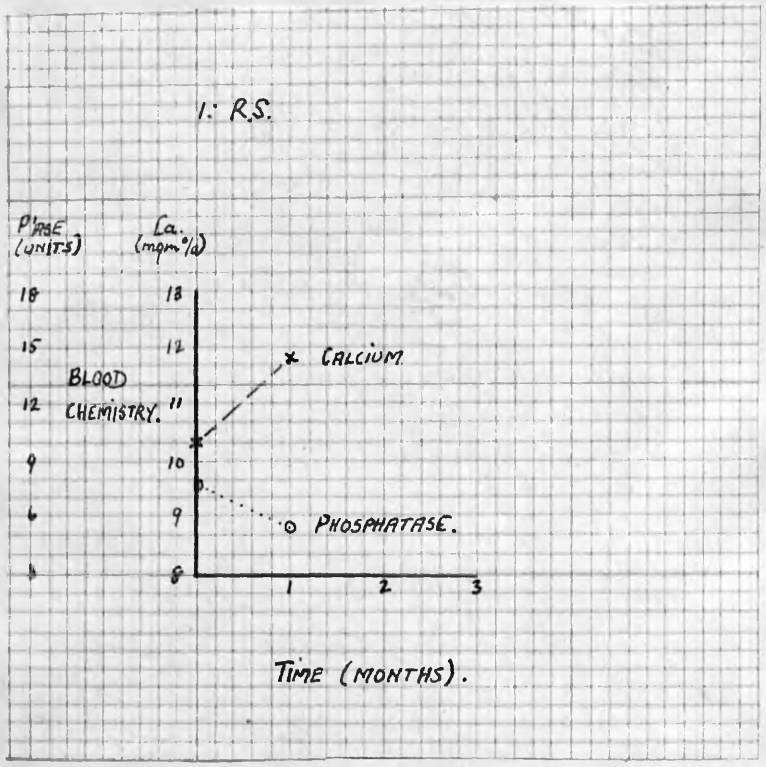
The above series of cases treated with calcium gluconate and vitamin D was also observed with regard to the blood chemistry to determine if any change in the serum calcium, inorganic phosphorus or phosphatase was produced during such treatment. The biochemical methods employed

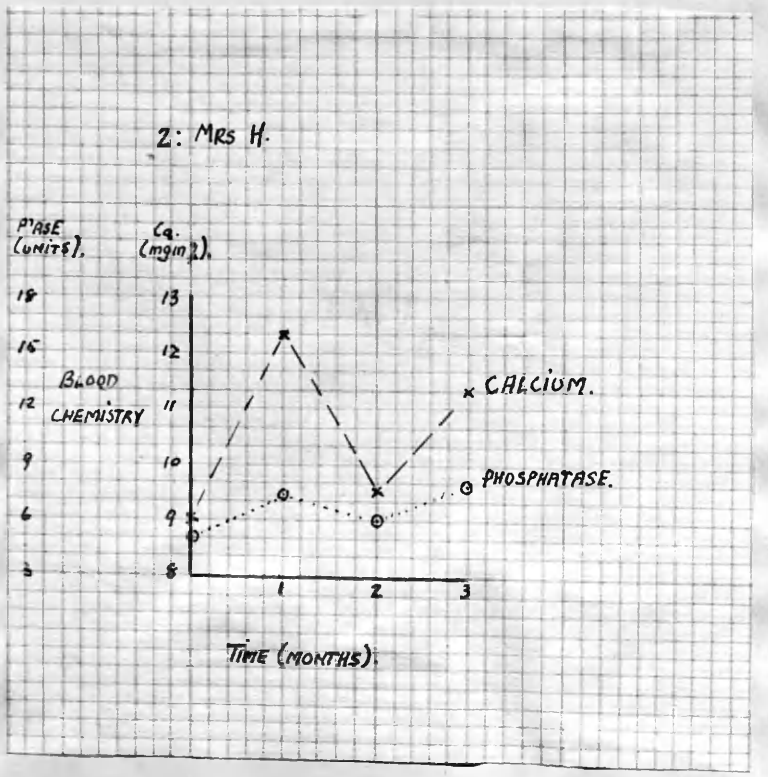
were the same as those used previously and the results obtained are shown below. Owing to faulty reagents it has only been possible to graph the serum inorganic phosphorus in four cases. Cases number 1 to 12 are, osteoporotic and 13 and 14 are controls.

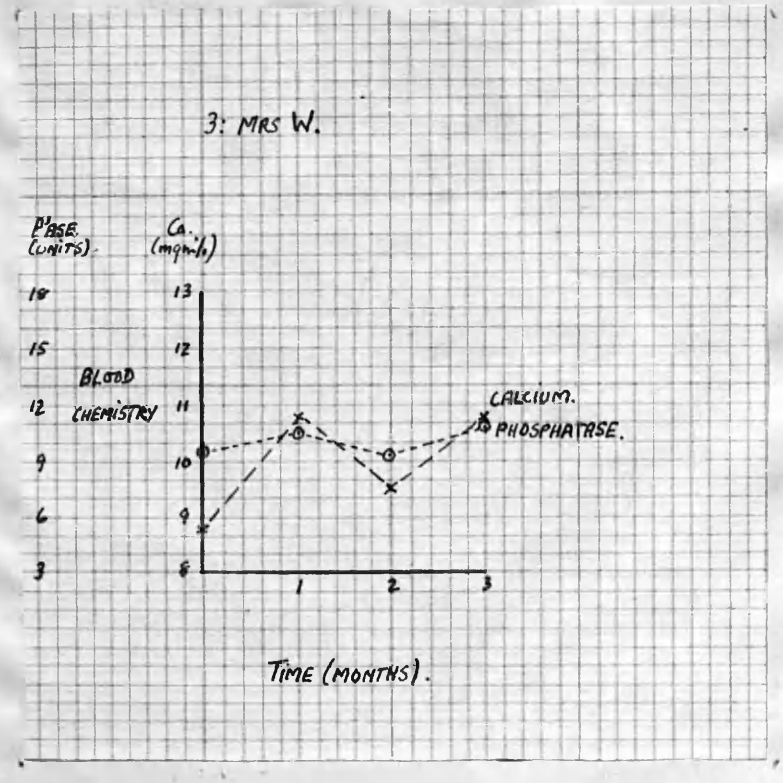
No striking consistent alteration is seen in the readings graphed above. As regards the osteoporotic cases, the serum calcium ends in a higher reading that the initial one in 7 cases, is the same in 1 case and is lower in 4 cases. The serum inorganic phosphorus ends in a higher reading than the initial reading in 3 cases and is lower in 1 case. The serum alkaline phosphatase ends in a higher reading in 3 cases and a lower reading in 9 cases. These findings suggest that with treatment the serum calcium and phosphorus in the osteoporotic cases may tend to rise and the phosphatase to fall, although the changes are very slight. In figure 4 the values for calcium, phosphorus and phosphatase are plotted.

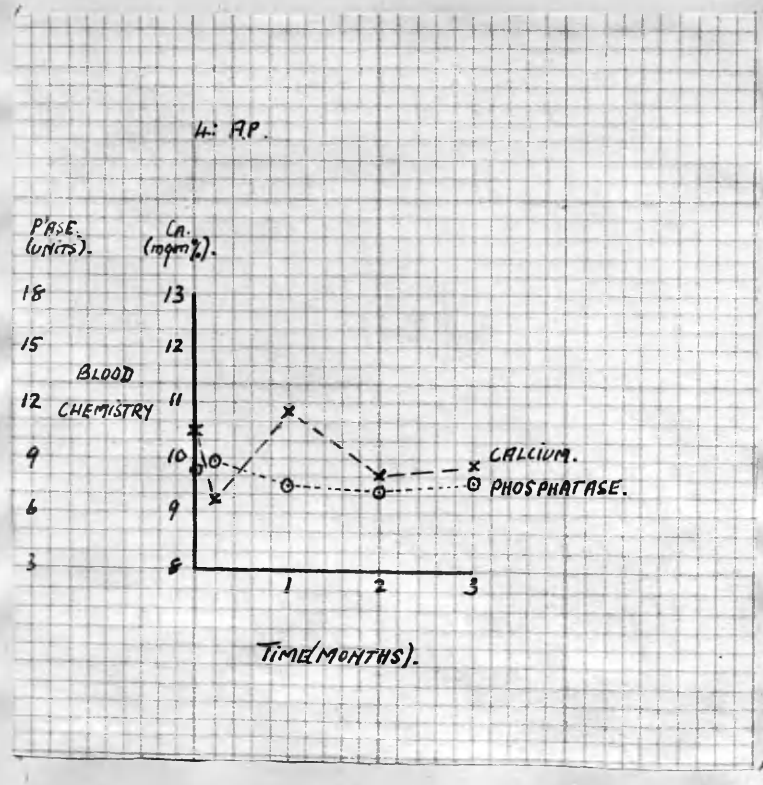
The majority of the calcium readings fall between 9.5 and 11.5 mgm%, most of the phosphorus results between 3 and 5 mgm% and most of the phosphatase between 5 and 11 units. In an attempt to determine whether treatment might be responsible for slight alterations in the results, as is suggested above, the following device was used. The ratio of the number of calcium readings above the midpoint of (10.5 mgm%) to the number of readings below the midpoint, before and after three months treatment, was noted. Similar ratios for the phosphorus and phosphatase

Figure 3. Blood Chemistry during treatment with Calcium Gluconate and Vitamin D.

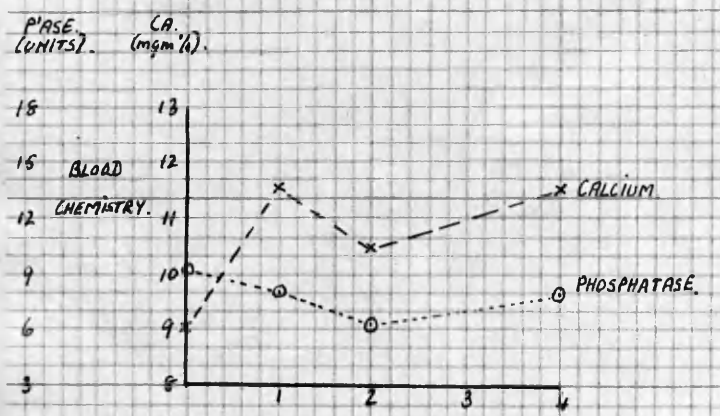




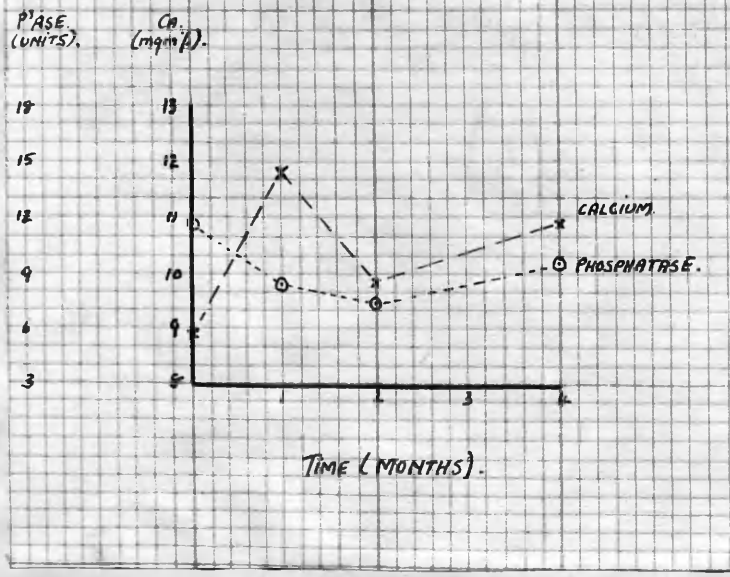

3: MRS W.
P'ASE. (UNITS).
Ca. (mgm%).
18
15
12
9
6
3
13
12
11
10
9
8
BLOOD CHEMISTRY
CALCIUM.
PHOSPHATASE.
1
2
3
TIME (MONTHS).


4: A.P.
P'ASE. (UNITS).
Ca. (mgm%).
18
15
12
9
6
3
13
12
11
10
9
8
BLOOD CHEMISTRY
CALCIUM.
PHOSPHATASE.
1
2
3
TIME(MONTHS).

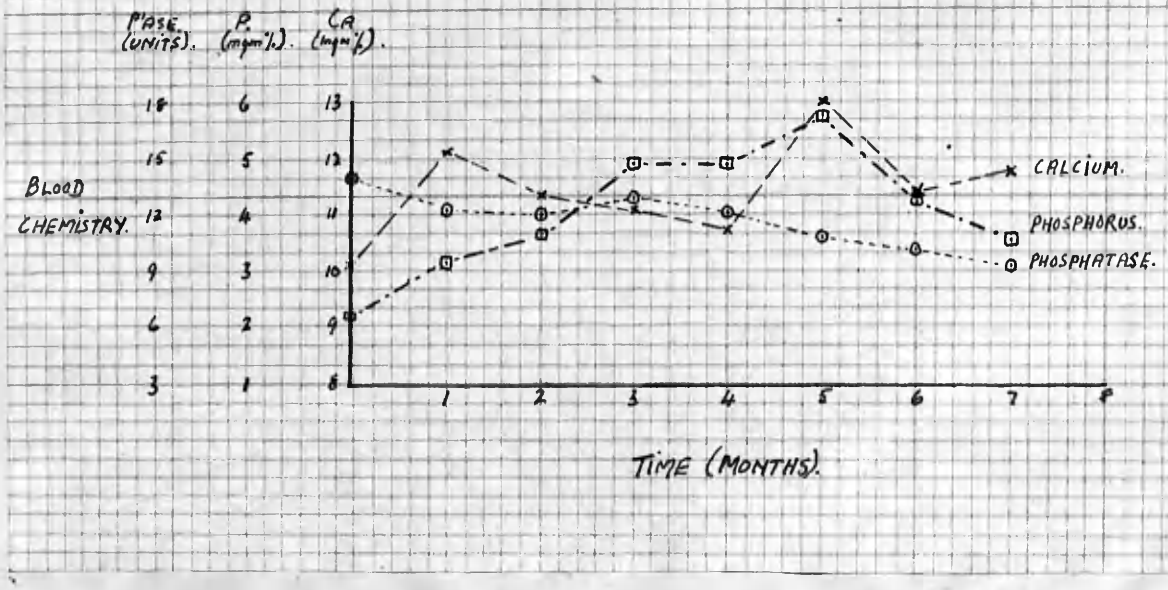
5: MRS. B.


P'ASE. (UNITS).
CA. (mgm %).
18
15
12
9
6
3
13
12
11
10
9
8
BLOOD CHEMISTRY.
CALCIUM.
PHOSPHATASE.
1
2
3
4
TIME (MONTHS).

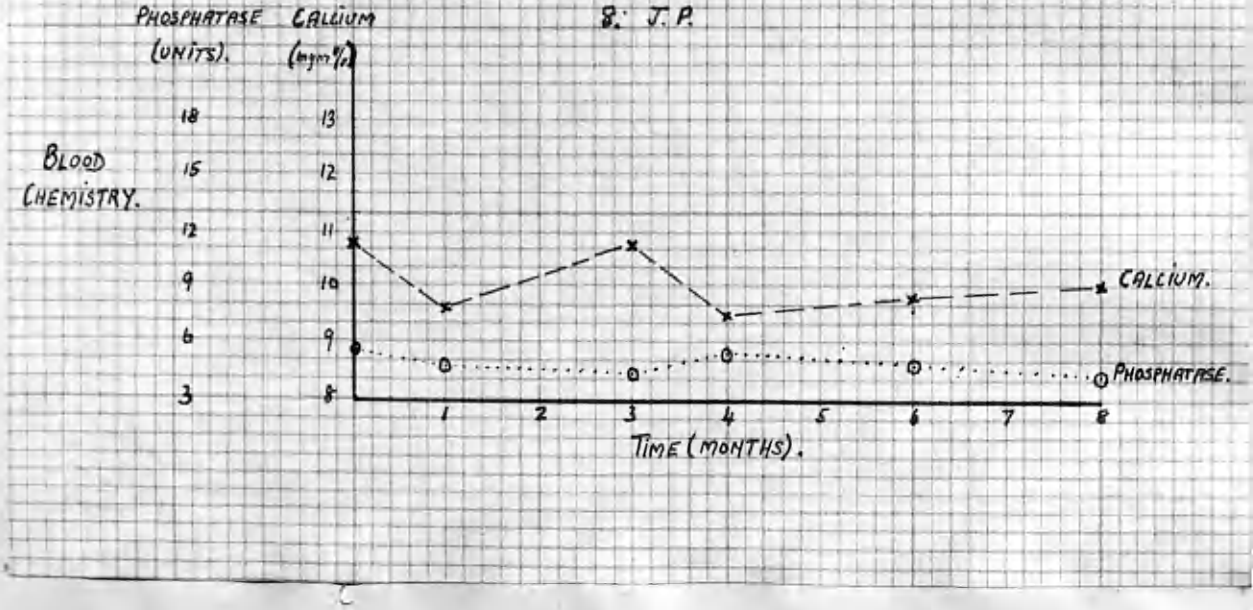
6: MRS. M.


P'ASE. (UNITS).
CA. (mgm %).
18
15
12
9
6
3
13
12
11
10
9
8
CALCIUM.
PHOSPHATASE.
1
2
3
4
TIME (MONTHS).

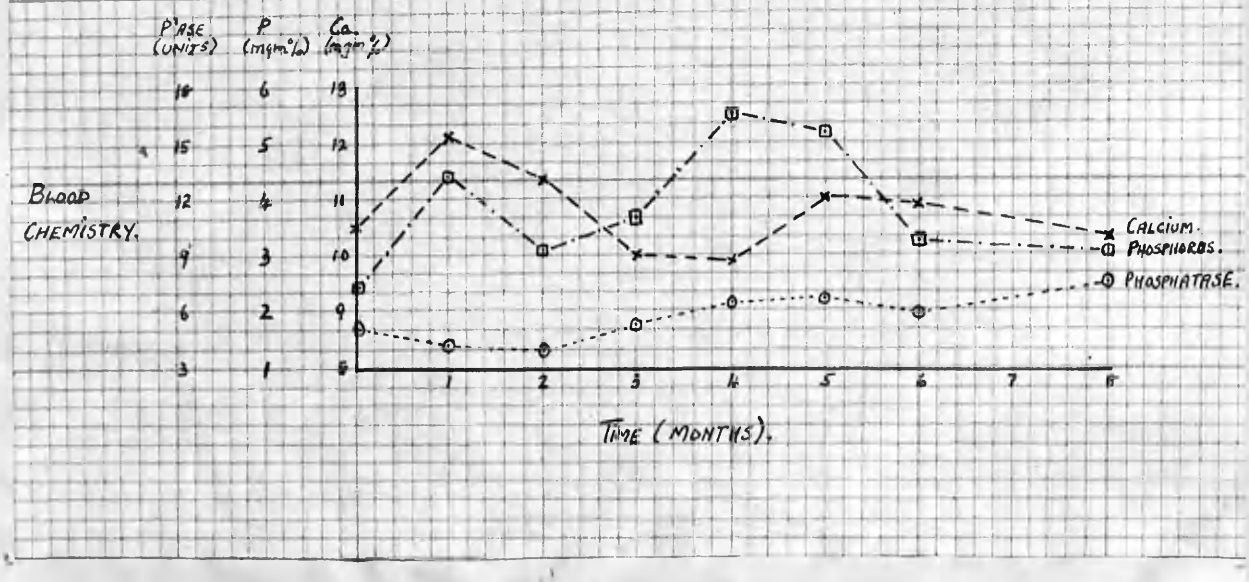
7. MRS. P.


P'ASE (UNITS).
P. (mgm%).
CA (mgm%).
BLOOD CHEMISTRY.
CALCIUM.
PHOSPHORUS.
PHOSPHATASE.
TIME (MONTHS).

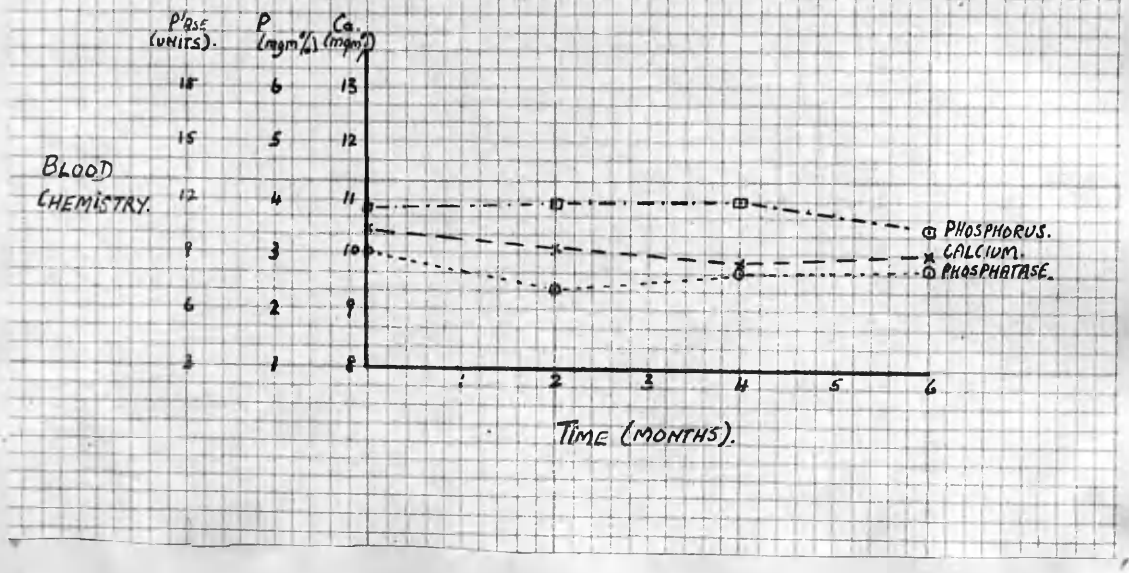
8. J. P.

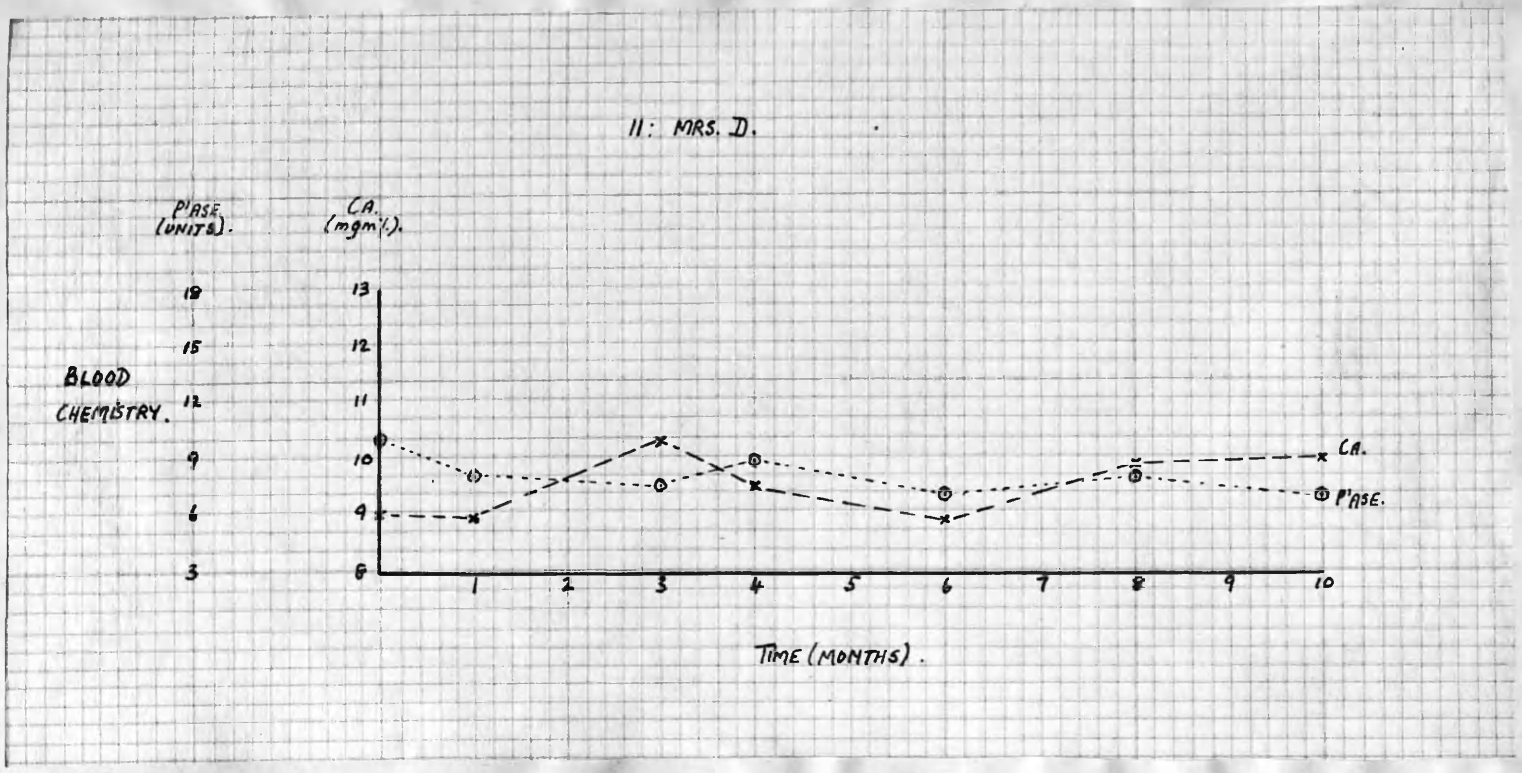

PHOSPHATASE (UNITS).
CALCIUM (mgm%).
BLOOD CHEMISTRY.
CALCIUM.
PHOSPHATASE.
TIME (MONTHS).

9. MRS. R.

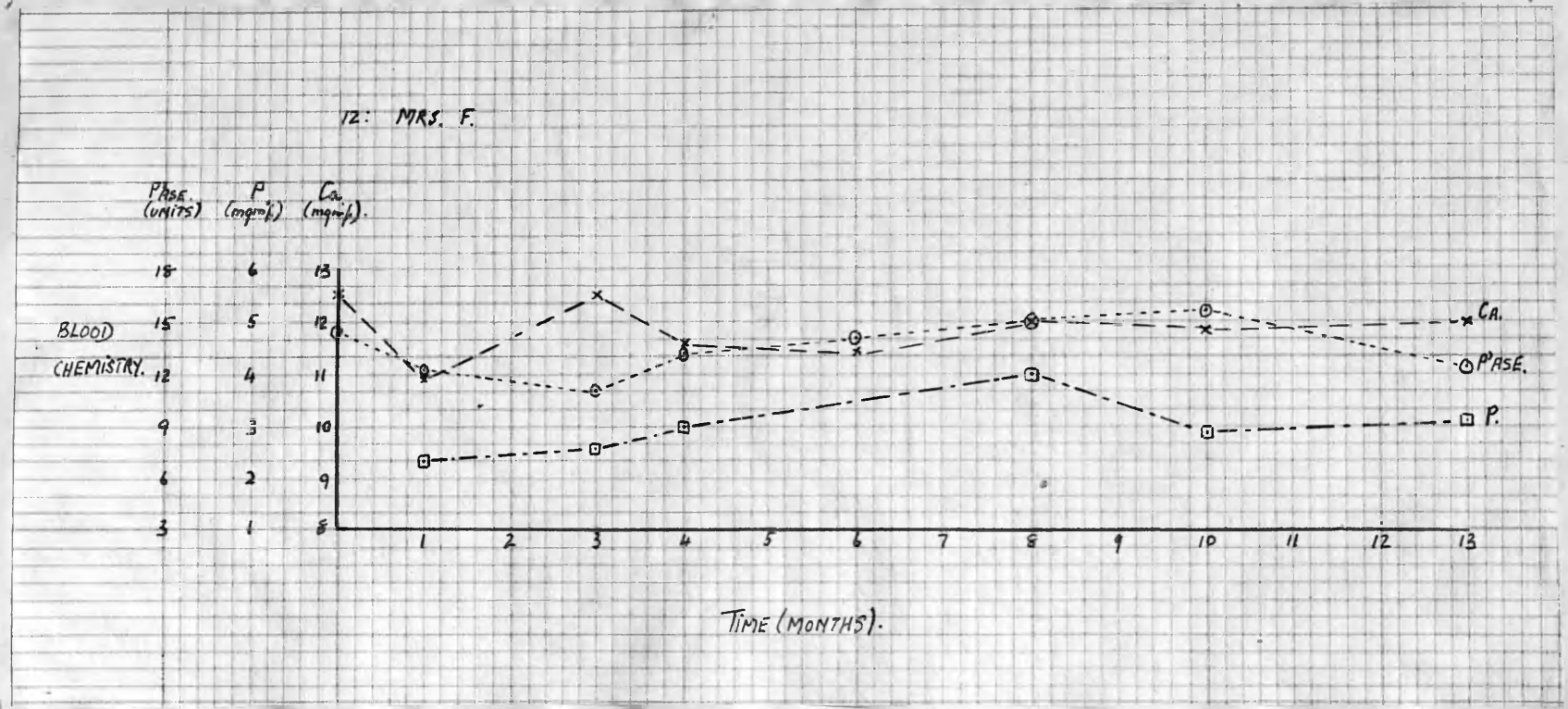

P'ASE (UNITS)
P (mgm%)
Ca. (mgm%)
BLOOD CHEMISTRY.
CALCIUM.
PHOSPHORUS.
PHOSPHATASE.
TIME (MONTHS).

10. A. A.

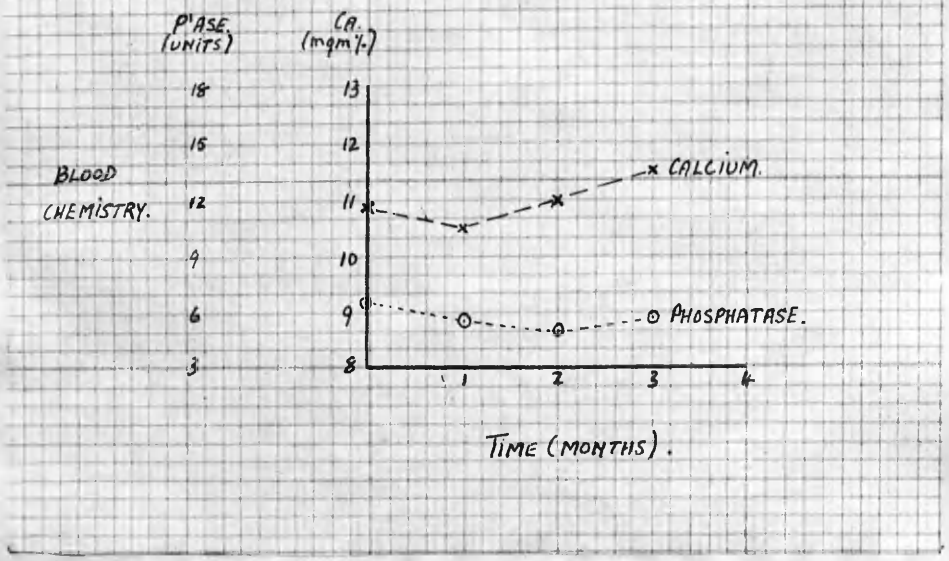

P'ASE (UNITS).
P (mgm%)
Ca. (mgm%)
BLOOD CHEMISTRY.
PHOSPHORUS.
CALCIUM.
PHOSPHATASE.
TIME (MONTHS).


11: MRS. D.
P'ASE (UNITS).
CA. (mgm%).
BLOOD CHEMISTRY.
18
15
12
9
6
3
13
12
11
10
9
8
1
2
3
4
5
6
7
8
9
10
CA.
P'ASE.
TIME (MONTHS).

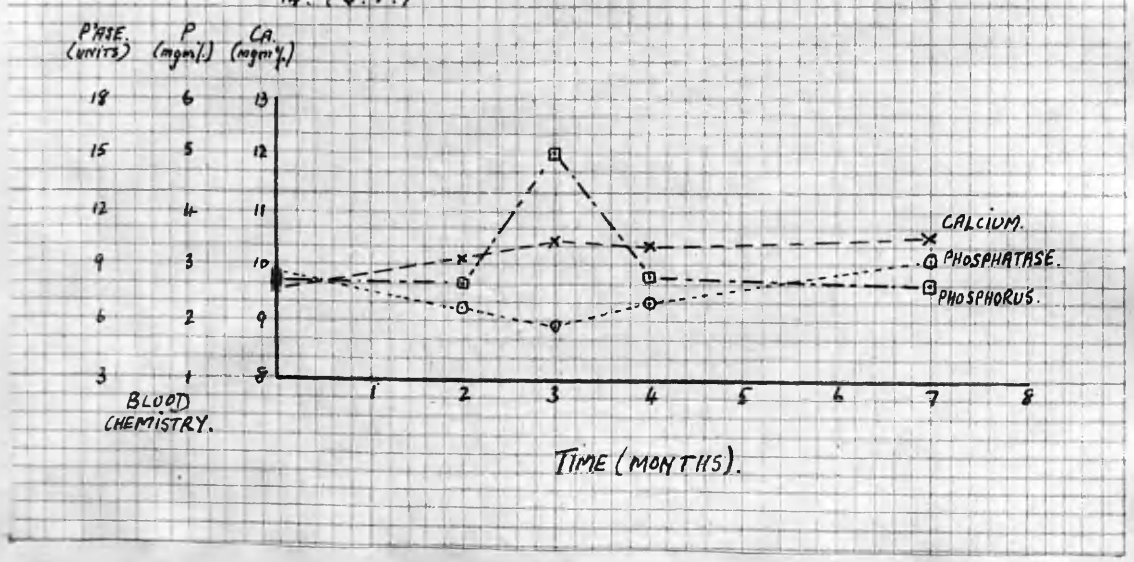
12: MRS. F.


PASE. (UNITS)
P (mgms%)
Ca (mgms%).
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
BLOOD CHEMISTRY.
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME (MONTHS).
CA.
P'ASE.
P.

13: E. M. I.


P'ASE. (UNITS)
CA. (mgm%)
18
15
12
9
6
3
13
12
11
10
9
8
1
2
3
4
CALCIUM.
PHOSPHATASE.
BLOOD CHEMISTRY.
TIME (MONTHS).

14: (J. T.)


P'ASE. (UNITS)
P (mgm%)
CA. (mgm%)
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
5
6
7
8
CALCIUM.
PHOSPHATASE.
PHOSPHORUS.
BLOOD CHEMISTRY.
TIME (MONTHS).

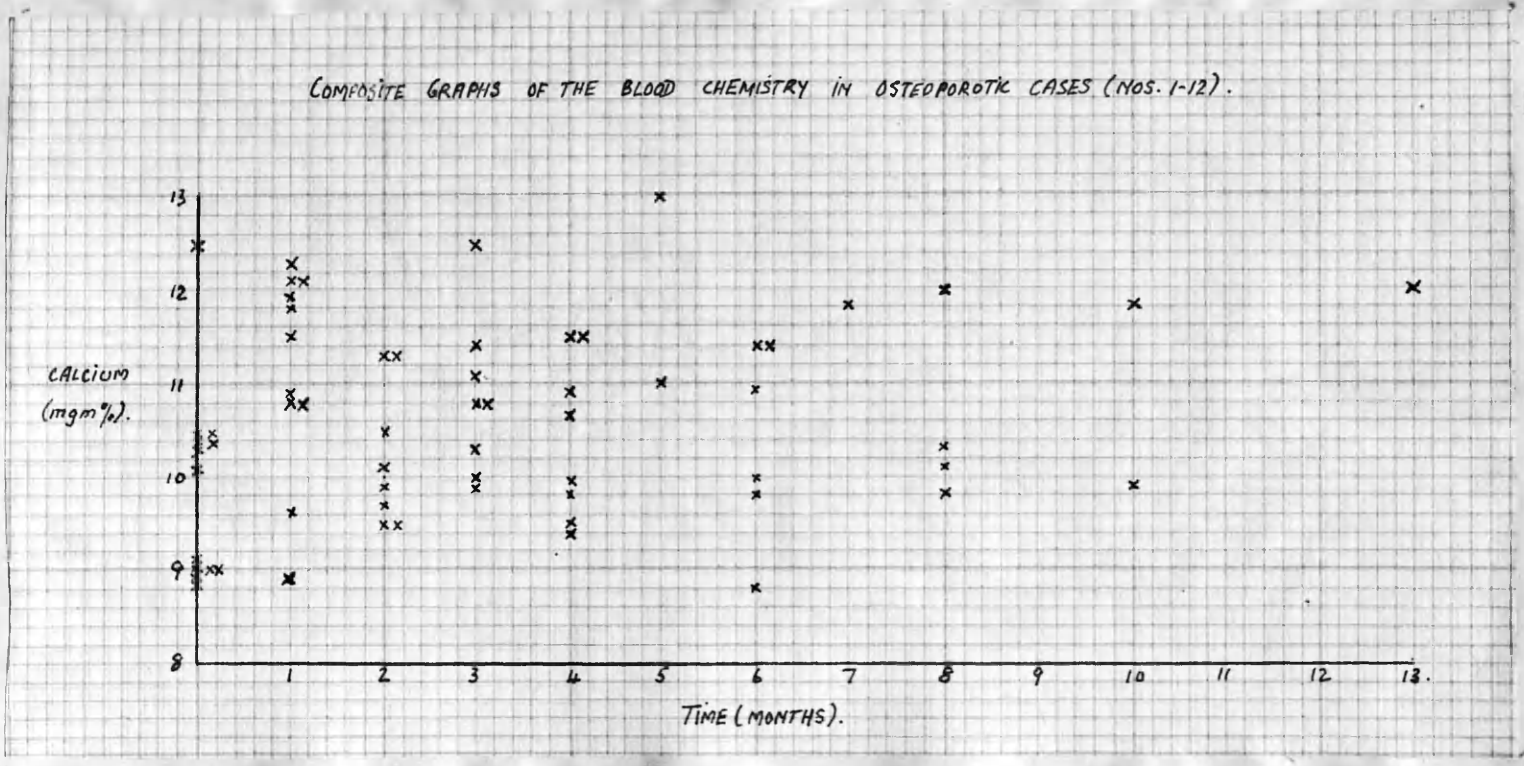
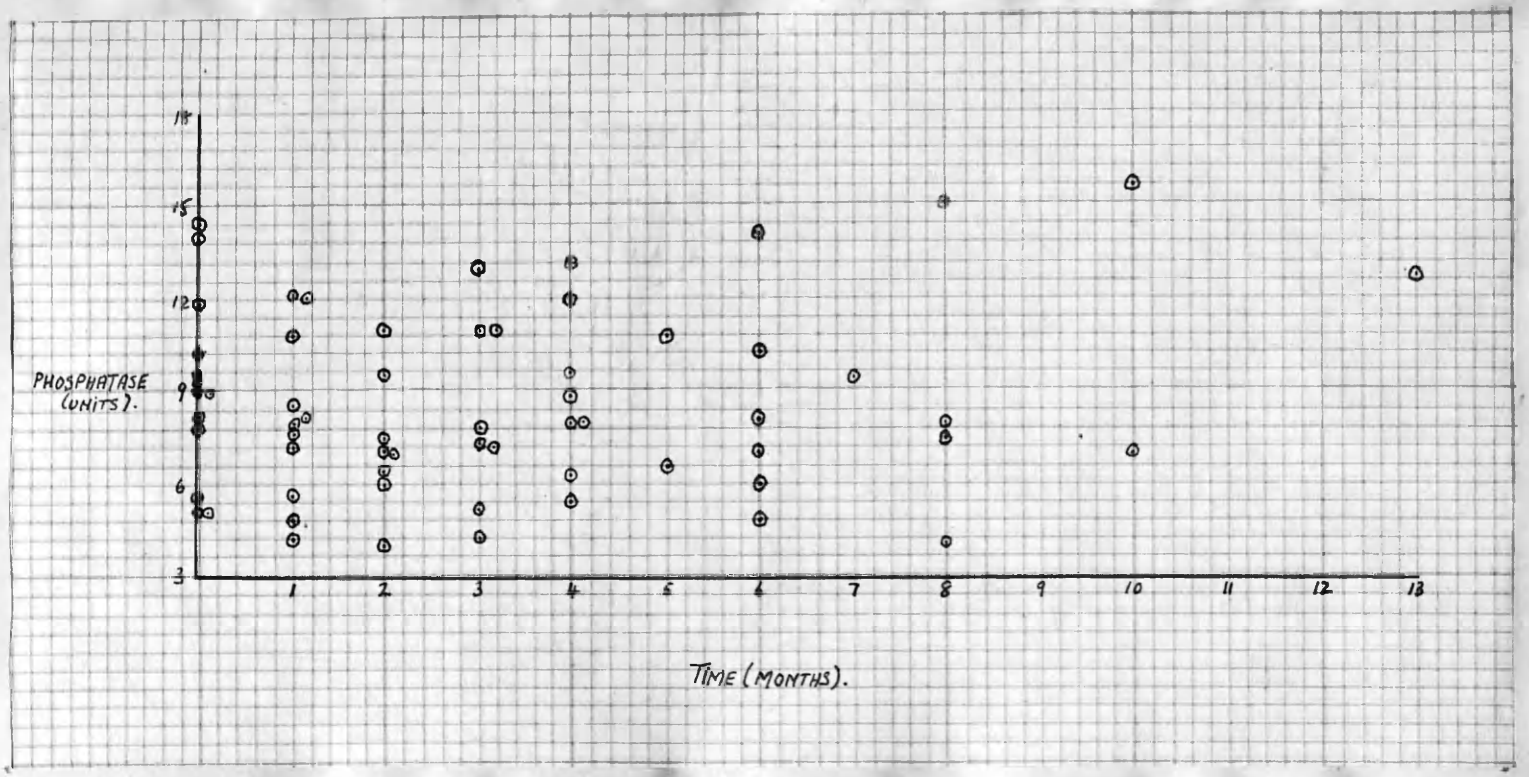
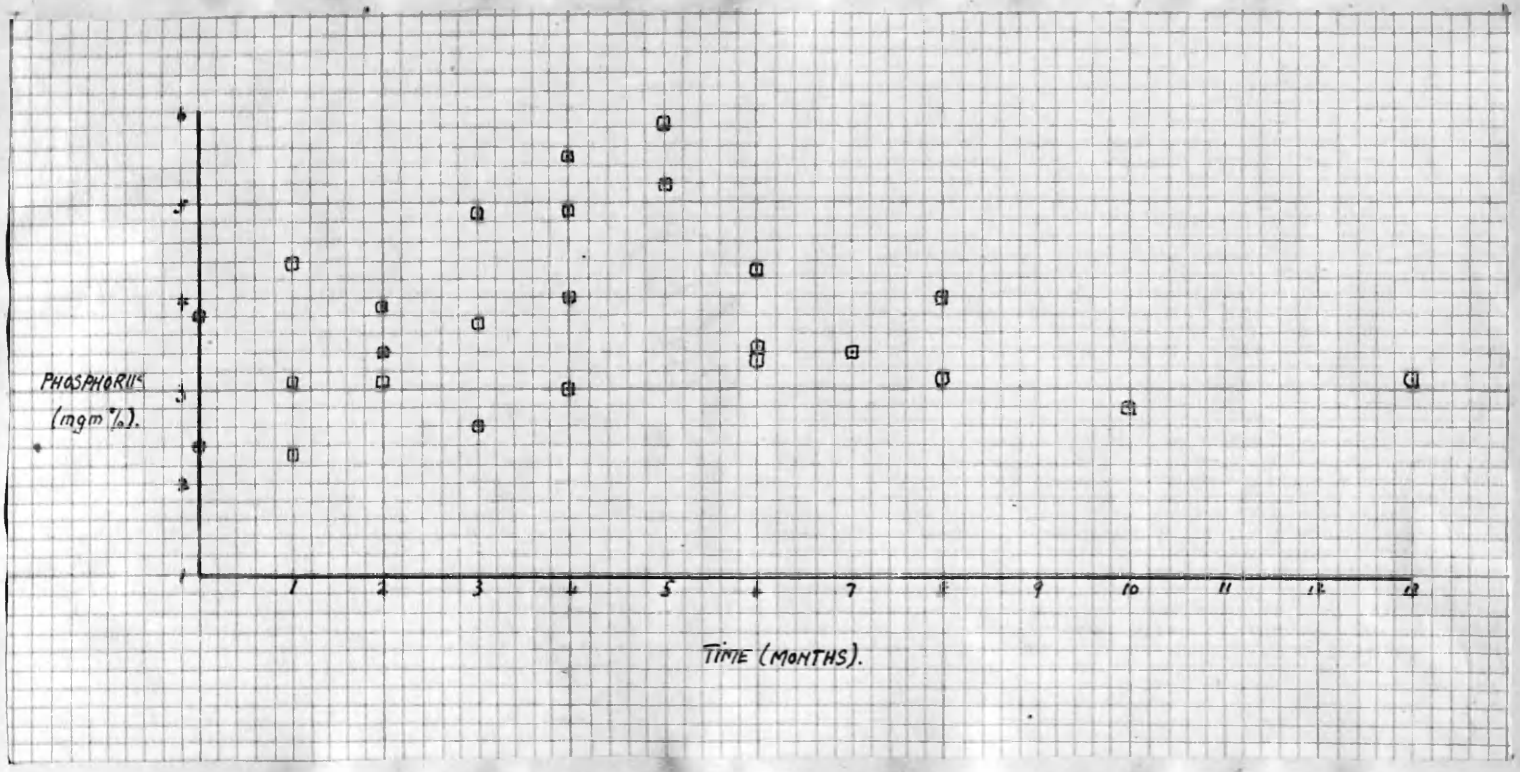

COMPOSITE GRAPHS OF THE BLOOD CHEMISTRY IN OSTEOPOROTIC CASES (NOS. 1-12).
CALCIUM (mgm%).
13
12
11
10
9
8
1
2
3
4
5
6
7
8
9
10
11
12
13.
TIME (MONTHS).

FIGURE 4.


PHOSPHATASE (UNITS).
18
15
12
9
6
3
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME (MONTHS).


PHOSPHORUS
(mgm %).
TIME (MONTHS).

results were calculated using the midpoints of 4mgm% and 8 units, respectively.

Table 38

Estimation	Ratio		Result
	No.of readings above 10.5 mgm% / No.of readings below 10.5 mgm%		
Serum Calcium	Before 3 months treatment: 12/17	After 3 months treatment: 18/14	Increased ratio

Table 39

	No.of readings above 4 mgm% / No.of readings below 4 mgm%		
Serum Inorganic Phosphorus	Before 3 months treatment: 1/8	After 3 months treatment: 6/9	Increased ratio

Table 40

	No.of readings above 8 units. / No.of readings below 8 units.		
Serum 'Alkaline' Phosphatase.	Before 3 months treatment: 16/15	After 3 months treatment: 16/15	No change

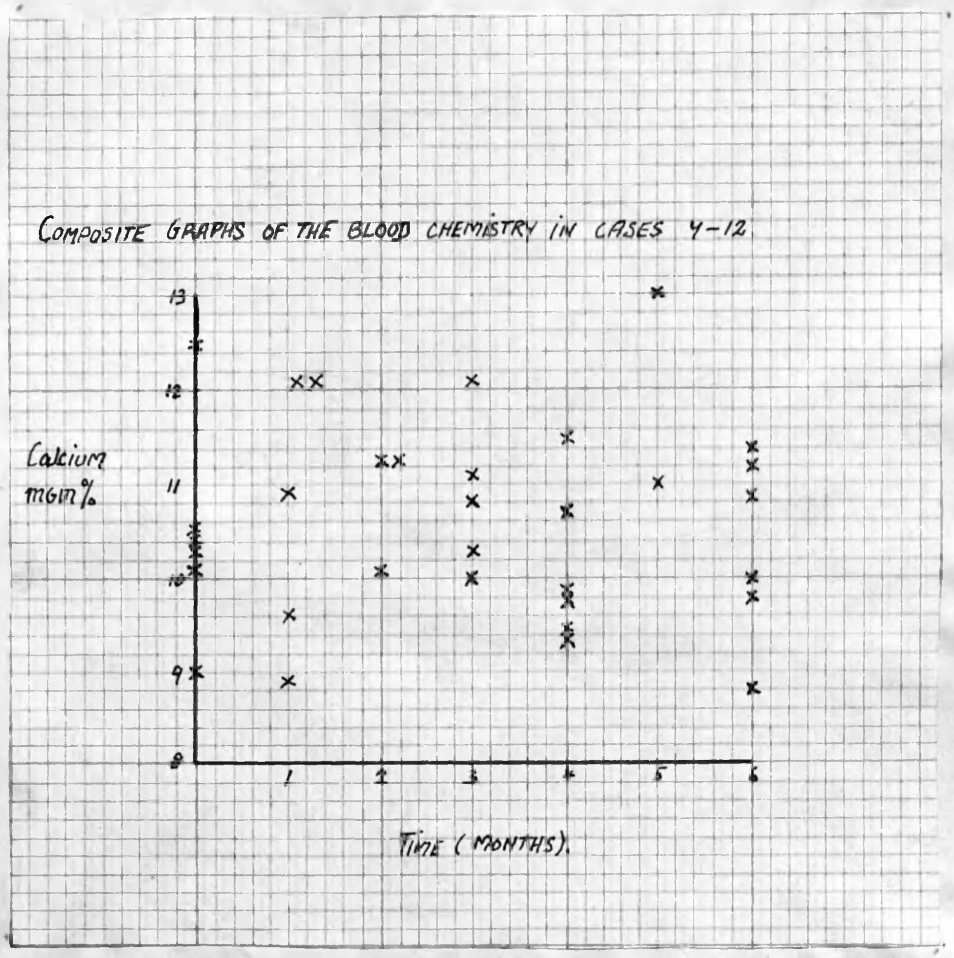
This demonstrates a tendency for increase in the serum calcium and phosphorus while the serum phosphatase is unaltered, during treatment of cases of generalised osteoporosis with calcium glucogonate and vitamin D. These alterations, however, are very slight and are in most cases within the recognised "normal" ranges for these estimations.

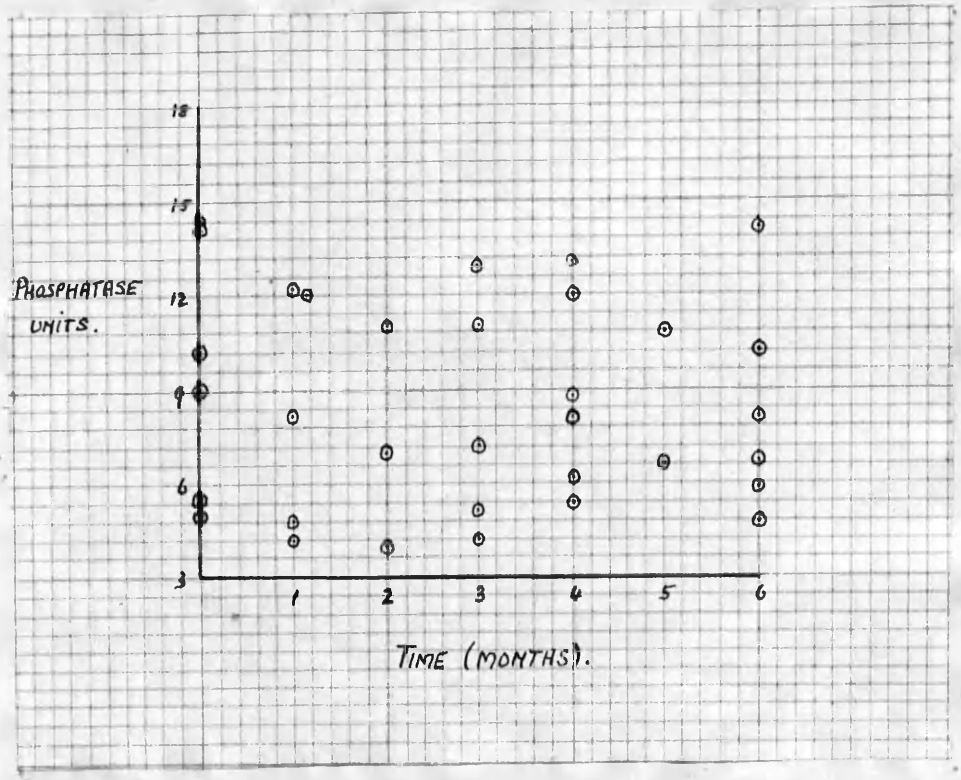
To counter-check these findings, 6 of the osteoporotic cases who were treated for 6 months were selected and composite graphs of the blood chemistry readings were constructed as before:- (Figure 5).

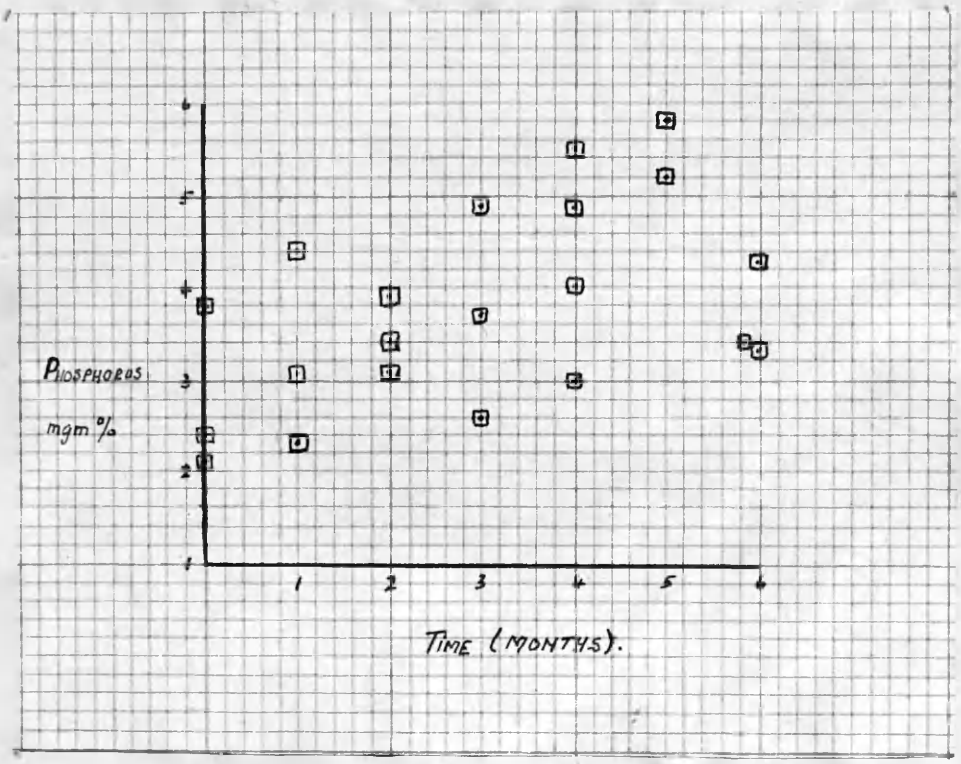
Ratios were again calculated as above with the following results:-

Estimations	Ratio		Result
Table 41	No. of readings above 10.5 mgm% / No. of readings below 10.5 mgm%		
Serum Calcium	0-3 months treatment	3-6 months treatment	Increase
	$\frac{6}{7}$	$\frac{10}{9}$	
Table 42	No. of readings above 4 mgm% / No. of readings below 4 mgm%		
Serum Inorganic Phosphorus	0 - 3 months treatment	3 - 6 months treatment	Increase
	$\frac{1}{8}$	$\frac{6}{5}$	
Table 43	No. of readings above 8 units / No. of readings below 8 units		
Serum 'Alkaline' Phosphatase	0-3 months treatment	3-6 months treatment	
	$\frac{8}{6}$	$\frac{10}{9}$	Slight Decrease

Figure 5.


COMPOSITE GRAPHS OF THE BLOOD CHEMISTRY IN CASES 4-12.
Calcium
mgm%
13
12
11
10
9
8
1
2
3
4
5
6
TIME (MONTHS).


PHOSPHATASE
UNITS.
18
15
12
9
6
3
1
2
3
4
5
6
TIME (MONTHS).

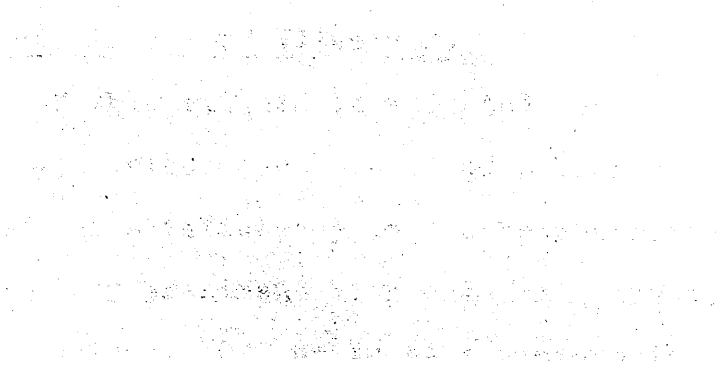

PHOSPHORUS
mgm %
4
3
2
1
1
2
3
4
5
6
TIME (MONTHS).

This is perhaps better controlled than the previous calculation in that the same 6 cases are used over equal periods of time although it may be pointed out that as more cases and more readings over longer periods of time were used in the first group. At all events the end results are similar, which is satisfactory.

CONCLUSIONS.

An attempt has been made to judge the effect of treating cases of generalised senile osteoporosis with a good diet supplemented by calcium gluconate and vitamin D or by calcium and phosphorus. This may be done by noting the effect on the symptoms of the condition if they are present, but this method is uncertain as rest in bed alone or rest plus a placebo may in some cases produce relief. The second method of assessing treatment, namely by the objective test of x-ray examination produced negative results in spite of treatment for as long as 15 months in one case, 10 of the cases being treated for longer than 6 months. All 16 cases were treated under supervision in hospital. The third method of repeated examinations of the blood chemistry produced no significant findings although there appears to be a tendency for a slight rise in the serum calcium and the serum inorganic phosphorus and perhaps a fall in the serum alkaline phosphatase. These alterations are so slight that they usually fall within the normal ranges for these estimations. On the whole, the above evidence does not support the theory of defective

intake being the cause of senile osteoporosis but it does not exclude this possibility.



2. Defective absorption and/or retention of calcium.

The calcium intake may be perfectly adequate but it would matter little what the dietary intake was, if there were failure of absorption or failure to retain calcium after it had been absorbed. The effect of these factors therefore, must be studied next. Proper absorption of calcium depends on a number of things of which the following are more important:-

(a) An adequate intake of vitamin D. (8)

(b) Absence of bowel disease. (7b)

(c) Presence of free gastric hydrochloric acid in the stomach.

(d) A sufficiently acid pH in the intestines. (8)

(e) Sufficient amounts of phosphatase in the intestinal secretions. (7b)

(f) Adequate amounts of bile. (56)

(g) Reasonable balance between calcium and phosphorus in the diet. (23)

(a) Adequate intake of Vitamin D.

Lack of this vitamin is accepted as the cause of rickets in childhood and osteomalacia in older patients. To exclude any possibility of a deficiency in the osteoporotic patients investigated by treatment with calcium gluconate over prolonged periods, 1000 units of vitamin D (in the form of Radiostol) was given orally per day, as has been described above. As no change in the x-ray appearance was observed in any of the cases so treated, it is unlikely that a deficiency of vitamin D is of importance in the aetiology of senile

osteoporosis, because radiologically evidence of cure is usually demonstrable in osteomalacia. (30)(45).

A comparison between osteomalacia and senile osteoporosis is of interest. Clinically an identical picture may be found. Stiffness, weakness and pain in the back are symptoms common to both. Tenderness and spasm of the erector spinae muscles, and shortening of the spine are also found in both conditions. Deformities of the spine such as kyphosis and scoliosis are often present, but kyphosis is very commonly associated with senile osteoporosis whereas scoliosis, according to Maxwell (30), is more common in osteomalacia. The x-ray appearances of the lesions in the spine may be identical, as has been noted previously. Pelvic deformities and deformities of the long bones are found in osteomalacia and are absent in senile osteoporosis. Furthermore osteomalacia may affect the skull (45) whereas in senile osteoporosis this is uncommon. (16) The sex indidence is similar; for example Meulengracht (31) describes a series of 18 cases of osteomalacia of the spinal column all over 40 years of age, of which 6 were males and 12 were females. The predominance of senile osteoporosis in females has already been discussed. According to Meulengracht the blood chemistry in osteomalacia is normal with the exception of a slightly raised blood phosphatase sometimes. This again is similar to the findings in generalised senile osteoporosis.

The response to treatment with calcium and vitamin D, however, reveals a difference. Symptomatic improvement may

be found in both conditions but while radiological proof of cure can be obtained in osteomalacia, sometimes within relatively short periods, it has yet to be deomonstrated in senile osteoporosis. This suggests that senile osteoporosis is a different condition from osteomalacia. In view of these data it may be concluded that vitamin D deficiency is of little importance as an aetiological factor in senile osteoporosis.

(b) Absence of bowel disease.

Intractable diarrhoea from any cause is likely to produce failure of absorption of calcium or vitamin D. Thus in coeliac disease there may be marked osteoporosis, for example.(9) Idiopathic steatorrhoea may also be cited as another example (7a). This factor did not play a part in the origin of the cases of generalised senile osteoporosis investigated above. It may also be noted that Meulengracht (31) stresses abuse of laxatives as a potent factor in some of the cases of osteomalacia of the spine which he investigated. Careful inquiry into the previous history of each of our patients failed to reveal the possibility of diarrhoea being a factor in mal-absorption of lime. Throughout their stay in hospital none of the subjects of this study suffered from diarrhoea, slight or severe.

(c) Presence of free gastric hydrochloric acid.

The presence of free gastric hydrochloric acid must tend to increase the acidity of the intestinal contents which in turn favours increased calcium absorption (8). Any failure in gastric secretion which might occur with advancing age may, therefore, have some influence in this matter. During the past five years in the University Clinic at Stobhill Hospital test meals were performed on 81 patients over the age of sixty five. Of these 46 (56.8 per cent) showed achlorhydria, an indication that achlorhydria may be a factor in diminishing the absorption of calcium by older individuals. This factor, however, can only be a minor one since normal assimilation of calcium can occur in the absence of free hydrochloric acid from the gastric juice (57). Furthermore the experimental results obtained in the course of the present work do in fact show that whether or not hydrochloric acid is present in or absent from the gastric juice retention of lime takes place if an adequate amount is ingested.

(d) A sufficiently acid pH in the intestines.

This is generally accepted as a factor of importance in the absorption of calcium from the bowel. An increased acidity causes the conversion of insoluble calcium salts into soluble ones and an increased absorption of calcium, whereas reduction in acidity has the opposite effect (7a). This question was not investigated in the above cases.

(e) Sufficient amounts of phosphatase in the intestinal secretions.

This enzyme hydrolyses the phosphoric esters of the food to provide soluble salts of calcium and phosphorus which can be absorbed, and therefore must be considered as likely to be an important factor in ensuring calcium absorption (7a). This factor was also not investigated in the above series.

(f) Adequate amounts of bile.

The presence of bile is necessary for proper fat absorption from the gut, and if it is deficient the excess fat unites with calcium to form insoluble soaps (8). Inspection of the faeces in all cases showed that there was no deficiency of bile products or excess of fat in the stool.

(g) Reasonable balance between the calcium and phosphorus in diet.

A high phosphorus intake in the diet tends to produce insoluble calcium phosphate and therefore to reduce the amount of calcium absorbed (8), but a correct calcium: phosphorus ratio is of less importance than the absolute amounts in the food (23).

As there was a considerable excess of calcium in the diet used in the above cases, there can be no question of large amounts of insoluble calcium salts of having been produced.

In conclusion it may be stated that in old age the conditions necessary for adequate absorption of calcium

are generally fulfilled. This raises the question whether old people are capable of absorbing calcium properly. As regards young adults and middle-aged people, it has been shown by Douglas Robertson (24) that there is no difference in calcium metabolism. He compared the metabolism of 12 adults, ages ranging from 19-39 years, mean age 29.5 years, with that of 12 adults, aged from 40-60 years, mean age 52.1 years, and found no significant difference. Owen (21) and Owen et al. (22) carried out calcium balance experiments in older male subjects, including patients in the senile age group, and found that these patients were capable of storing calcium and phosphorus when given diets containing more of these elements than their customary intake. Furthermore Owen et al. demonstrated the same capabilities in 5 patients, aged from 69-79 year, suffering from senile osteoporosis. These findings suggest that calcium metabolism in the senile age group is similar to that in the younger age groups. The following calcium balance experiments were undertaken to determine whether adequate absorption of calcium and phosphorus was possible in senile patients. Nine patients were selected, eight of these having generalised osteoporosis and one being normal. Each patient was put on a 'standard' diet as follows, slight variation in the amounts, however, being allowed:-

Breakfast	Cereal	2 oz.
	Milk	5 oz.
	Bread	2 oz.
	Margerine & Tea	
Dinner	Spam	3 oz.
	Potato	6 oz.
	Pudding	4 oz.
	Milk	4 oz.
Tea	Bread	4 oz.
	Margerine & Tea	
Supper	Bread	2 oz.
	Milk	10 oz.
	Margerine	

This diet has a calorie value of approximately 1850 cals. as estimated from Bridges' food tables (58). Each patient was given this diet for one week, to allow of slight adjustments in the quantities to suit individual appetities. When the diet had been stabilised for one week, the intake and output of calcium and phosphorus were determined. All urine and faeces passed were collected separately. Weekly collections being made over a period of two weeks. Four of the osteoporotic patients were then given calcium gluconate g 10 and 1000 units of vitamin D (as Radiostol) daily, by mouth, in addition to the diet and, after another stabilising interval of one week collections of the excreta were made for a further two weekly periods. The control

case was treated similarly but in the remaining four osteoporotic cases, calcium and phosphorus were administered orally in the form of nine tablets of 'CALFOS' per day during the third and fourth weekly periods. The procedure adopted to define the end-points in the collection of faeces was, initially to give an enema and discard the result and thereafter to collect all faeces. Exactly 7 days later the period was terminated by giving an enema and saving the result, and again after 14 days the enema was repeated and the result saved, thereby ending the second weekly period. The third and fourth periods were similarly conducted. There was no difficulty as regards urine collection, the bladder being emptied and the result discarded at the beginning of the experiment and at the end of each period the bladder was emptied and the result saved. Each weekly collection of urine was pooled and aliquot portions were analysed for calcium and inorganic phosphorus. The faeces were similarly treated. Analysis of the diets was also performed in this fashion. The estimation of calcium in urine was performed by the method of Shohl and Pedley (39) and food and faeces were ashed in an electric muffle and then dealt with as for urine. The estimation of the acid soluble phosphorus was performed by the method of Youngburg (39) food and faeces being, of course, ashed first of all. Details of the methods employed are given in the appendix. All the patients were confined to bed in hospital through-out the duration of the experiment. The results are shown below:-

Mrs. D. aet. 79 years.

Generalised Osteoporosis

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	842	40	465	505	+337	605	331	255	586	+19
14	Standard +Calc. gluc. +Vit.D.	1732	39	335	374	1358	605	205	131	336	269

Mrs. W. aet 72 years.

Generalised Osteoporosis

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	734	113	762	875	-141	542	312	478	790	-248
14	Standard +Calc. Gluc. +Vit.D.	1624	103	630	733	891	542	340	369	709	-167

A.P. ♂ aet. 82 years.

Generalised Osteoporosis

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	861	145	739	884	-23	676	479	301	780	-104
14	Standard + Calc. Gluc. + Vit. D.	1751	134	535	668	1083	676	521	291	812	-136

A.A. ♀ aet. 89 years.

Generalised Osteoporosis.

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	842	43	297	340	502	605	351	171	521	84
14	Standard + Calc. Gluc. + Vit. . .	1732	47	394	441	1291	605	277	155	432	173

J.T. ♂ aet. 76 years.

No Osteoporosis

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	907	119	461	580	327	696	480	295	774	-78
14	Standard + Calc. Gluc. 1000 units Vit.D/day	1797	91	701	792	1005	696	514	440	953	-257

F.B. ♂ aet. 74 years.

Generalised Osteoporosis

Period of Observation	Diet	Calcium mgm/day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	907	174	239	412	495	701	568	165	733	-32
14	Standard + Calfos	1927	122	712	834	1093	1163	537	301	838	325

88

Mrs. J. aet 73 years.

Generalised Osteoporosis

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	877	162	468	630	247	617	516	372	888	-271
14	Standard + Calfos	1897	146	639	785	1112	1079	680	267	947	132

J.McK. ♂ aet 74 years.

Generalised Osteoporosis.

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	907	80	508	588	339	696	401	468	869	-173
14	Standard + Calfos	1927	59	1313	1371	556	1158	348	479	827	331

89

Mrs. McK. aet. 82 years

Generalised Osteoporosis.

Period of Observation	Diet	Calcium mgm / day					P mgm / day				
		Intake	Output			Balance	Intake	Output			Balance
			Urine	Faeces	Total			Urine	Faeces	Total	
14	Standard	745	75	208	283	462	579	301	123	423	156
14	Standard + Calfos	1765	51	648	699	1066	1041	320	197	517	524

As regards calcium the "standard" diet provided a good intake in all cases, the average being 847 mgm / day which is considerably more than the maintenance figure of 450 mgm / day calculated by Sherman (55) or that of 550 mgm / day by Leitch (20) or of 520 mgm / day estimated in older men by Owen (21). On the intakes provided by the diet all the osteoporotic cases with the exception of two were in positive calcium balance and the single normal case was also in positive balance. When the calcium of the diet was reinforced by oral administration of calcium salts as shown, every case including the control showed a positive balance. It is interesting to note that the higher results were achieved in the osteoporotic cases treated with calcium gluconate and vitamin D in spite of the fact that in the main the intakes were slightly lower than in the osteoporotic cases treated with Calfos, as is shown thus:-

Table 44

Calcium gluconate & vitamin D			Calfos.		
Case	Calcium Intake (mgm / day)	Net Gain (mgm / day)	Case	Calcium Intake (mgm / day)	Net gain mgm/day
Mrs.D.	1732	1021	F.B.	1927	598
Mrs.W.	1624	1032	Mrs.J.	1897	865
A.P.	1751	1106	J.McK.	1927	217
A.A.	1732	789	Mrs.McK.	1765	604

The control case on an intake of 1797 mgm / day while under treatment with calcium gluconate and vitamin D, had a net gain of 678 mgm / day. This net gain is lower than that

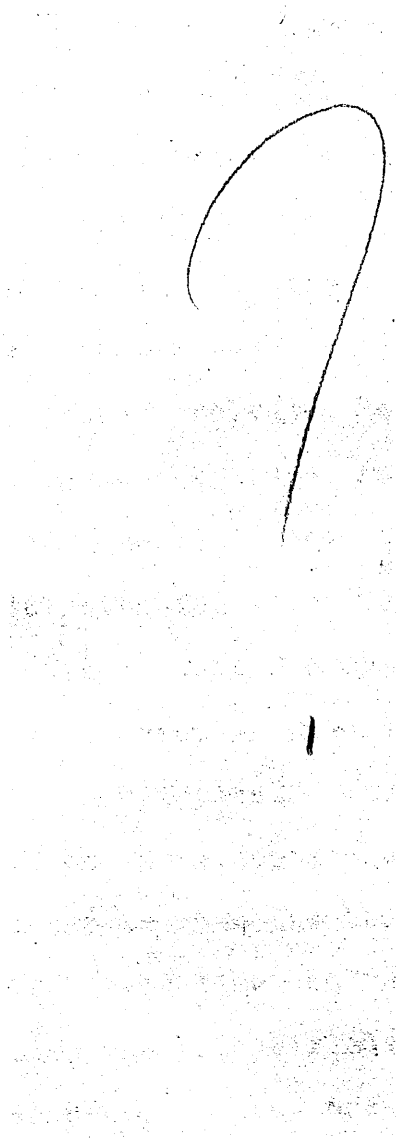
of each of the four osteoporotic cases treated in the same fashion and yet the intake is higher than any of these four cases, which suggests that the osteoporotic cases were more in need of calcium.

The average phosphorus intake provided by the "standard" diet was 635 mgm / day which is lower than the maintenance estimate of Sherman, of 900 mgm / day and roughly half of that found by Owen. (1200 mgm / day). It is not surprising therefore that five of the eight osteoporotic cases and the control cases were in negative phosphorus balance and the remaining three osteoporotic cases were only in slightly positive balance. Of the four osteoporotic cases treated with calcium gluconate and vitamin D the two in slightly positive phosphorus balance became more positive, one of the two negative ones improved and one became more negative. Three of the four osteoporotic cases treated with Calfos were in negative balance on the low phosphorus intake and were thrown into positive balance with the treatment and the positive balance of the remaining case treated thus, became more marked. The average phosphorus intake on this treatment was 1110 mgm / day which is higher than the maintenance level suggested by Sherman and approximates to that given by Owen, so it is not surprising that this intake produced positive balances of a moderate degree. All cases excreted calcium chiefly in the faeces whereas phosphorus was excreted chiefly in the urine in every case with the exception of two. The above results demonstrate that patients

suffering from senile osteoporosis are quite capable of absorbing calcium and phosphorus. Inability to absorb calcium and phosphorus cannot therefore be the cause of senile osteoporosis. This finding corroborates the results obtained by Owen et al.

Will osteoporotic patients maintain this absorption over a prolonged period or is the storage which takes place when the intake of calcium and phosphorus is increased merely a temporary one? Adams et al. (25) investigated a case of senile osteoporosis in a woman aged 65 years who had been on a low intake of calcium and phosphorus for years. During a control period of three 7 day balances, the results for both calcium and phosphorus were negative, but treatment with 8 g tribasic calcium phosphate daily for three weeks produced a storage of calcium and phosphorus, the amount stored decreasing in each succeeding period. The addition of m 30 of Viosterol per day caused a more marked retention for the next two weeks. The case was then investigated under treatment with calcium lactate and calcium lactate plus vitamin D and positive balances were obtained which were not increased by the addition of the vitamin. Over a period of 19 weeks 29.3g of calcium and 13.3g of phosphorus were retained. This finding suggests that cases of senile osteoporosis may be quite capable of remaining in positive balance of calcium and phosphorus over prolonged periods if given adequate intakes. Two of the above cases, one having generalised osteoporosis and one being normal,

were treated for 14 and 18 weeks respectively, with calcium gluconate g 10 and 1000 units vitamin D daily, and repeat estimations were then performed with the following results:-



The positive calcium balance had been maintained in both cases although it was not nearly as marked in the osteoporotic case as in the control. The phosphorus balance was found to have changed from positive to negative in the osteoporotic case and vice versa in the normal one. In view of the low intake of phosphorus it is rather surprising that both cases were not found to be in negative balance. These results show that both osteoporotic and normal cases are capable of continued storage of calcium over a period of about 3-4 months if placed on intakes which are much higher than those to which they are accustomed. They confirm the findings of Adams et el. that a positive balance of calcium may be maintained over a prolonged period in a patient suffering from senile osteoporosis. Further investigation over longer intervals of time would need to be conducted in order to find out if this retention would continue in cases so treated. It is worthy of note that the control case showed a considerable retention of calcium which was in fact much greater than that of the osteoporotic one. This suggests that stress should not be laid on the retention of calcium in the osteoporotic case. It may be that the body would adapt itself to the high intake, given time and reach an equilibrium. It is known that as the intake rises so does the daily requirement for maintenance, (24) and one would expect an initial period of increased retention prior to equilibrium on a higher level, Similarly adjustment to intakes which are lower than the

accepted minimal levels may be found (22). It is likewise to be expected that there would be a lag period during which there would be a negative balance before such equilibrium were established.

CONCLUSIONS

Cases of senile osteoporosis show no deficiency in ability to absorb and retain calcium and phosphorus when put on suitable intakes. The absorption and retention of calcium may continue over a period of 14 weeks. A normal senile patient also exhibited the same abilities. Deficiency of absorption and retention of minerals do not ordinarily play a part in the aetiology of senile osteoporosis.

3. Inability to utilise calcium for bone formation.

It is feasible that although absorption of calcium and phosphorus is normal in senile osteoporosis they may not be utilised to form bone. It is possible for example that the calcium is deposited in the arteries. Reference will be made later to the relationship of arteriosclerosis and calcification of the arteries to senile osteoporosis. Suffice it to say here that in none of the 12 osteoporotic cases treated over several months with calcium gluconate and vitamin D was any alteration observed radiographically in the calcification of the arteries. It may be that the process by which senile osteoporosis is produced is irreversible. Perhaps prolonged reduced intake of minerals leads to

osteoporosis in senile patients and once this has been brought about it cannot be cured by increasing the intake, although the process may be halted by such treatment. This would explain why improvement has so far not been demonstrated radiologically in cases treated over long periods of time although symptomatic improvement is often obtained. Alternatively it is possible that senile osteoporosis develops over a number of years and correspondingly, improvement in the condition may be so slow that radiological proof of cure might not be available until treatment had continued for a number of years. Further investigation is obviously necessary before this problem can be elucidated. It may be significant that in his anatomical description of the condition Schmorl (18) states that the surfaces of the trabeculae are clean and smooth and indicate a long slow vascular resorption, and that the individual trabeculae are much thinner and fewer than is normal although their architectural structure is maintained. This finding would indicate a slow development of the condition and as the trabeculae are fewer than normal it is feasible that the formation of the new trabeculae may not be possible, as it is well known that repair of bone in old people is often uncertain and incomplete e.g. healing of fractures. Advanced senile osteoporosis therefore might quite well be irreversible.

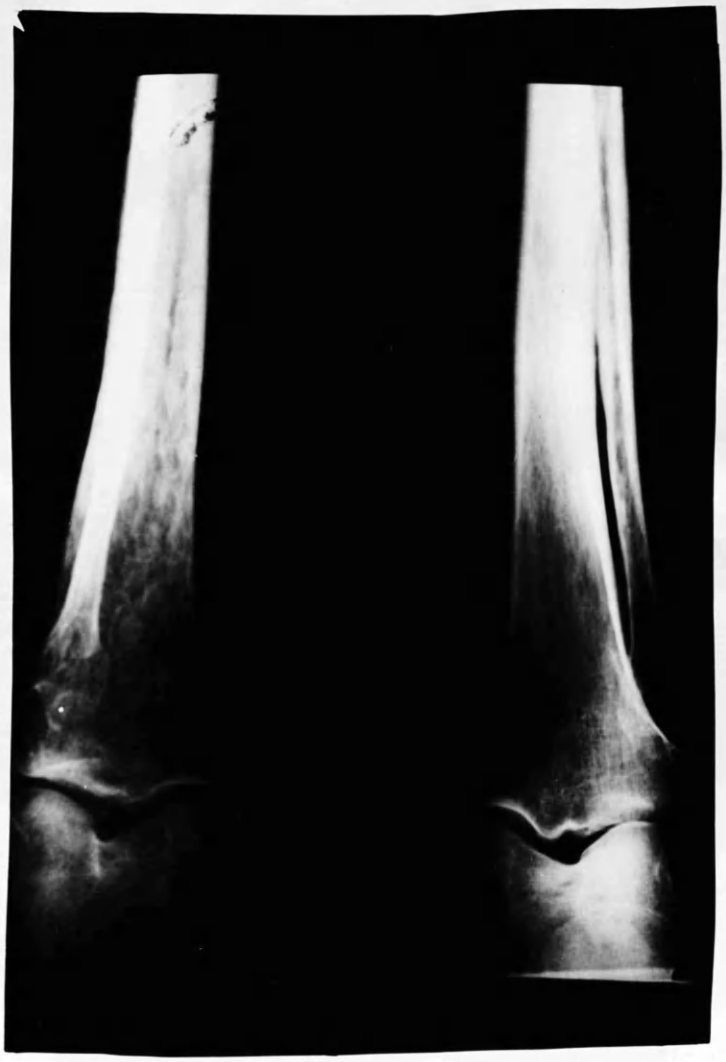
B. Lack of Exercise.

Localised osteoporosis as a result of disuse is not uncommon (1a) and is recognised as a cause of pathological fractures (26). The following case provides a good illustration of local disuse osteoporosis:-

J.F. (male) 53 years.

This man was kicked on the left knee in May 1942, and was admitted to hospital the same night. The left patella was fractured and this was treated conservatively but eventually at the beginning of September the fragments of the patella were removed at operation. He was discharged from hospital at the end of September. He was able to move around with the aid of a stick but did not really use his left leg much. On 27th October he was again admitted to hospital and x-ray on 29th October showed osteoporosis of the lower end of the left femur and upper end of the left tibia. A film of the left ankle on 22nd December showed osteoporosis, the right one being normal. Controlled x-ray films were taken on 18th January, 1943 both legs being x-rayed on the one film and both feet were taken on another film. This provided an accurate control as regards x-ray technique. Osteoporosis of the left tibia and of the bones of the left foot was demonstrated as is shown below. No calcification of the lower limb vessels was seen.

J. F. 53 yrs. X-Ray of leg.



If local disuse can produce osteoporosis it is logical therefore to consider what effect lack of exercise, for example confinement to bed, might have on the bones of older people.

The age and sex incidence of generalised osteoporosis has already been discussed. As a general rule as people grow older their lives become less and less active so it is possible that the increasing incidence of generalised osteoporosis with age and the increasingly sedentary existence might be correlated. Again as a general rule females live more sedentary lives than males which may possibly have some relation to the definite predominance of generalised osteoporosis in the female. The commonest sites of osteoporosis have been discussed previously. The fact that the feet and spine tend to be more severely affected suggests that disuse might be concerned in the aetiology but it must be remembered that the hands also often exhibit it to a considerable degree, and the use of the hands is usually retained in the majority of patients confined to bed. Black et al.(17) state, moreover, that senile osteoporosis may affect people who have always been very active. In the above series of patients over 40 years of age who were examined with regard to the incidence of generalised osteoporosis the duration of the stay in bed immediately prior to being investigated, was noted. This produced the following results:-

Table 45

	No. of cases	Average stay in bed (months)
Osteoporosis	31	5.8
Normal	46	4.7

This finding suggests that further investigation of the possible effect of disuse is warranted. It was accordingly decided to investigate generalised osteoporosis in a group of patients in whom the main disability was loss of mobility. This stipulation appeared to be fulfilled in a series of patients suffering from post-encephalitis who exhibited all degrees of helplessness. These patients had been in hospital for a long time, in most cases for years, two of them actually for 17 years. The dietaries as regards calcium and phosphorus were adequate, the daily intakes being calculated to amount to at least 1.2g calcium and 1.5g phosphorus (58). Vascular disease was conspicious by its absence, only 1 out of 34 males and 5 out of 34 females showing any signs of arteriosclerosis, and no correlation between the incidence of generalised osteoporosis and vascular disease was demonstrable. The age and sex incidence of these patients have already been discussed. Perhaps the fact that the female series were older on an average, may be related to the higher number of cases of vascular disease in that group. There was no evidence of hormonal disturbance. The blood chemistry was essentially normal as has already been shown. This eliminates the majority of the possible causes of generalised osteoporosis in these patients with the exceptions of trophic disturbance of bone in post-encephalitis as far as one could find (59)(60)(61). No correlation was detected between the duration of the disease and the incidence of osteoporosis, several cases which

were normal having suffered from the disease for as long or longer than those exhibiting osteoporosis. This suggests that trophic disturbance is not responsible for the osteoporosis as one would expect a correlation if such were the case. For these reasons therefore it was decided that the main factor in the production of osteoporosis in the post-encephalitic patients was disuse. A series of 34 females and 34 males suffering from post-encephalitis were examined for generalised osteoporosis which was found to be present in 9 females and 4 males, shown thus:-

Table 46

	Below 50		50-59 years		6069 years	
	Osteoporotic	Total	Osteoporotic	Total	Osteoporotic	Total
Female	4^{x}	22	3^{xx}	10	2^{xxx}	2
Male	4^{f}	30	0	3	0	1

x 3 Helpless and 1 semihelpless

xx 3 semihelpless

xxx 1 Semifit and 1 helpless

f 4 Helpless.

This classification of the degree of inactivity was devised as follows:- Semi-fit = Slight disability e,g. some stiffness and/or tremor

Semihelpless = Considerable disability e.g. severe stiffness, inability to walk but can feed and perhaps clothe herself or himself.

Helpless = Can do nothing for herself or himself.

The correlation between the degree of inactivity and incidence of osteoporosis is shown thus:-

	No Osteoporosis	Osteoporosis
Semi-fit	24	1x 5xx (16%)
Semi-helpless	26	5x 7xxx (58%)
Helpless	5	7xxx (58%)

x ♀ Age 63 years

xx All ♀ Ages 35:47:57:57:59 years.

xxx ♀ Ages 33:37:69

♂ Ages 28:31:32:36: years.

Statistically there is a positive correlation between the degree of inactivity and the incidence of osteoporosis. It is worth noting that the osteoporotic cases in the semi-fit and semi-helpless categories are older than the cases in the helpless group. An attempt was made to detect a correlation between the duration of the inactivity and the incidence of osteoporosis but none was demonstrable. As the histories were rather indefinite this is not surprising. Two films in post-encephalitic patients, one osteoporotic and one normal, are shown below:-

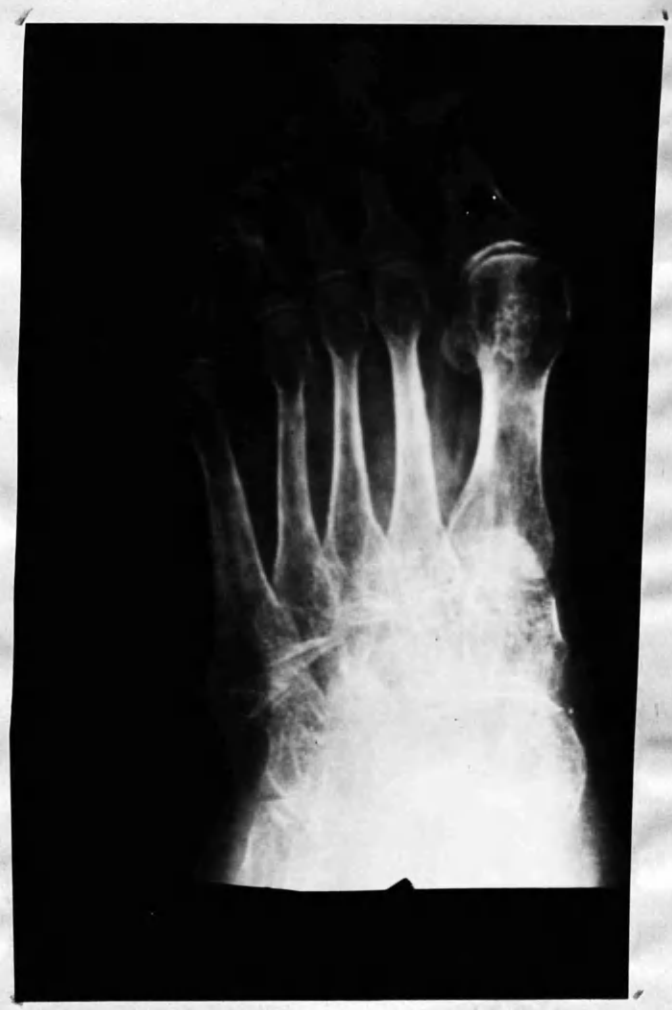
A.M. ♀ 32 years — Osteoporosis of foot.

Mrs.McK. 39 years — "Normal foot.

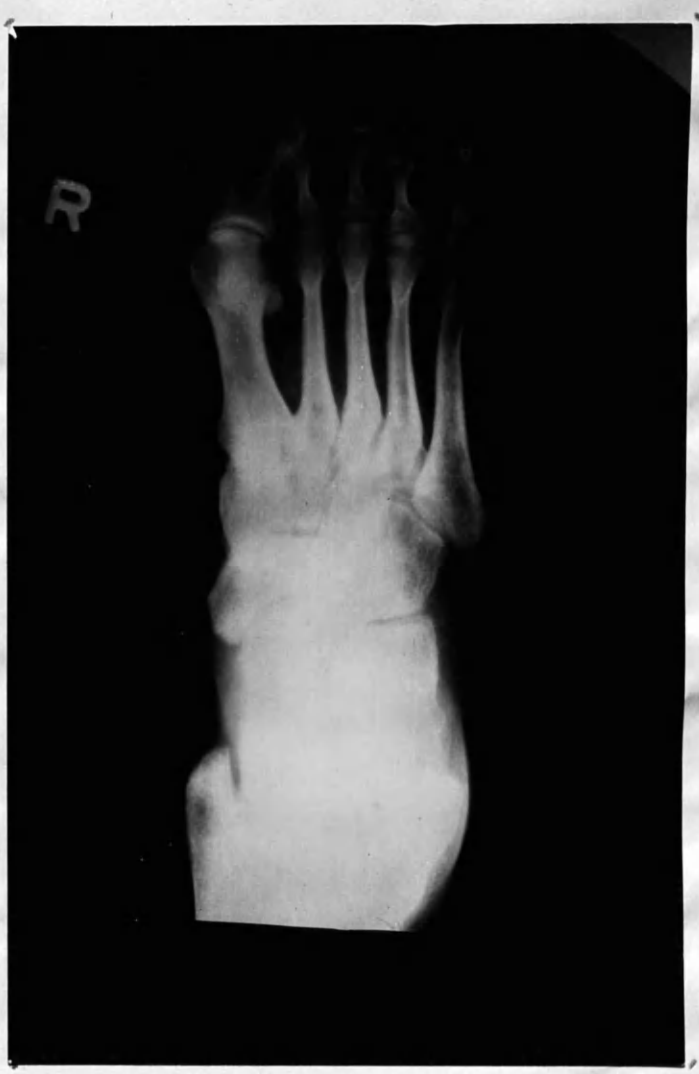
CONCLUSIONS

Generalised osteoporosis may be produced by disuse if the degree of disuse is great enough. Accordingly this possible cause must be considered in generalised senile osteoporosis. Further investigation would be required to find the exact

A.M. 32 yrs. X-Ray of foot.



Mrs. McK. 39 yrs. X-Ray of foot.



relation of disuse to senile osteoporosis but as senile osteoporosis may occur in patients who have always been active it is likely that disuse plays only an auxiliary part in the aetiology.

C. Vascular Disease.

It is recognised that local hyperaemia tends to produce osteoporosis.(62) Jung (5) considers that one of the three main factors in the production of osteoporosis is vasomotor upset; in his opinion the direct cause of post-traumatic and infective osteoporosis is local hyperaemia. Osteoporosis of the bones of the wrist and hand following injuries in the neighbourhood is also well known (2b). What effect does local diminution of blood supply produce? The following cases were examined with this question in view.

1. J.M.E. ♂ 77 years.

This man suffered from auricular fibrillation and arteriosclerosis. He had been troubled with intermittent claudication affecting the left leg since 1930, this being brought on by walking for about 5 minutes. On October 29th 1942 he developed a "cramp" in the left calf while at rest in bed. The next day he complained of pain in the left ankle and foot and numbness and coldness of the foot. Examination revealed evidence of diminished arterial blood supply to the leg. The foot was slightly cyanosed and the leg and foot were colder than the right. Sensation was impaired as also was movement of the toes. On December 4th 1942, x-rays were taken of both legs on one film and both

feet on one film to provide a controlled result. At this time the evidence of diminished arterial blood supply was present as before. Apart from the previous findings no pulsation was present in the left femoral, popliteal arteries although not in the right dorsalis pedis. No difference was detected between the limbs on x-ray. Calcification in the tibial and dorsalis pedis arteries in both limbs was noted. The history suggests that there was some restriction of arterial blood supply in the left leg for 12 years and there was certainly a considerable diminution in it for a period of 5 weeks previous to the x-ray examination.

2. Mrs.J.D. 66 years.

This patient suffered from intermittent claudication of the left leg for 6 months, the pain in the left calf coming on after walking a distance of about 100 years. Examination revealed that the left foot was colder than the right. There was no pulsation in the left popliteal, posterior tibial and dorsalis pedis arteries while it was present in both femorals and in the distal arteries of the right lower limb. X-rays of the legs and feet, controlled as before, showed no abnormality in the density of the bones. Calcification in the tibial arteries in both legs was noted. The history suggests that diminished arterial blood supply in the left leg was present for 6 months previous to the x-ray examination.

3. J.H.♂ 73 years.

This man developed gangrene in the right big toe in April, 1942, and the toe gradually separated off. He was

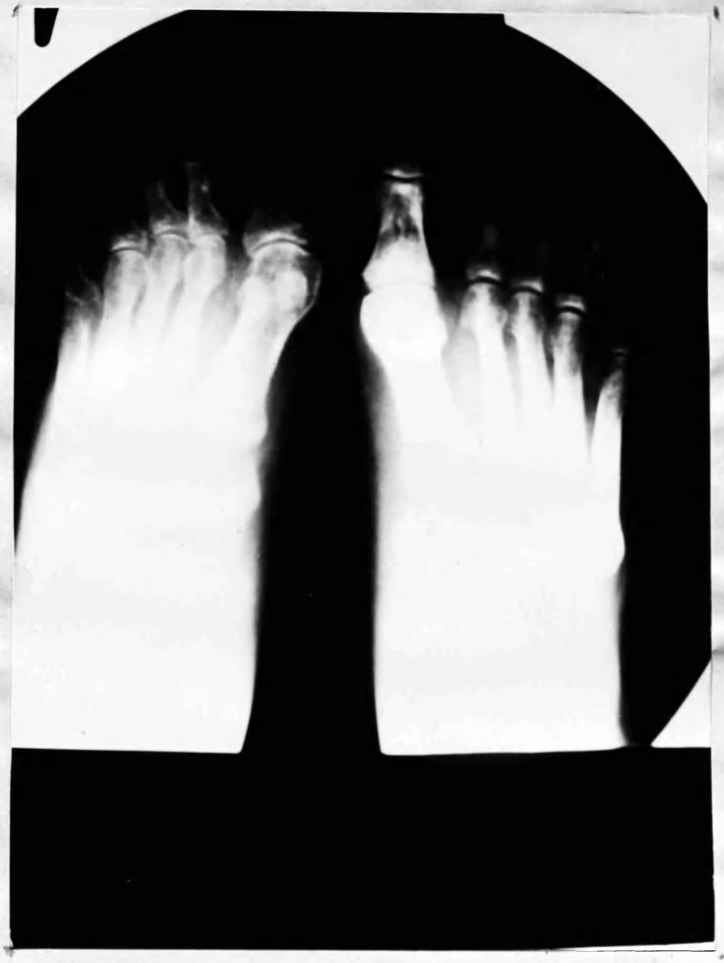
admitted to hospital in November, 1942 complaining of pain in the right foot. There appeared to be a line of commencing demarcation extending from the 1st metatarsal head to the head of the 5th metatarsal and the skin distal to this was blae. Pulsation was detedted in the femoral and popiteal arteries of both limbs and in the left posterior tibial artery but none was found in the right posterior tibial or in the dorsalis pedis artery. Controlled x-rays on 7th December showed osteoporosis of both feet but that in the right foot was more marked, especially in the 1st metatarsal. Diminished arterial blood supply in the right foot had probably been present for at least 8 months previous to x-ray:-

J.H. ♂ 73 years. Localised osteoporosis associated with diminished arterial blood supply.

It was found, therefore, in two of the above cases that considerable diminution in arterial blood supply in a leg over a lengthy period produced no change in the density of the bones in the affected part. The third case showed more marked osteoporosis in the affected foot than was present in the other. That there might be a disuse factor to be considered in this case cannot be overlooked but it is possible that the severe reduction in arterial blood supply might be responsible in part for the difference noted.

It is known that vascular disturbance in a variety of diseases can lead to irregular erosion or amputation of the extremities of the terminal phalanges, for example in thrombo-angiitis obliterans and Raunaud's disease (2f). If local disturbance

J. H. 43 yrs. X-Ray of feet.



of arterial blood supply can produce osteoporosis it is possible that generalised vascular disease such as widespread arteriosclerosis might play a part in generalised osteoporosis. Todd (3) has suggested that arteriosclerosis by causing defective nourishment of bone might be a factor in the demineralisation of the skeleton found in old age. Harris (1d) states that changes in the intervertebral disks tend to be shown by individuals with high blood pressure and arteriosclerosis and that changes in the vertebrae are found secondarily. The distribution of senile osteoporosis to a certain extent suggests that arteriosclerosis may be responsible. The feet are commonly affected to a marked degree, as has been noted previously, and arteriesclerosis is very common in the arteries of the leg (5c) being present there long before it is detectable elsewhere. It may be mentioned in passing that arteriosclerosis as shown by calcification of the vessels is rare in the upper limbs compared with the lower limbs. Of 45 patients over 40 years of age who had calcified vessels only 6 showed calcification in the vessels of the upper limb and in none of these 6 was there any calcification proximal to the radial and ulnar arteries. This predilection for calcification of the vessels of the lower limb is probably the reason for the frequency of gangrene there, gangrene in the upper limb being correspondingly rare.

The incidence of arteriosclerosis in 79 patients over 40 years of age was determined with the following results:-

Table 47

Degree of Arteriosclerosis	No. of Cases: No Osteoporosis	Osteoporosis	% of cases with osteoporosis.
Nil	13	8	38.1
Slight	14	12	46.2
Marked	20	12	37.5

This shows no special association of osteoporosis with arteriosclerosis.

The blood pressure was recorded in 80 cases over 40 years of age and a comparison of the 32 osteoporotic and 48 normal patients is shown thus:-

Table 48

B.P.	O	N
Average Systolic	164	167
Average Diastolic	96	96
Average Pulse Pressure	68	72

The similarity is very close.

Calcification of the vessels, as seen by x-ray, was recorded in 79 cases with this result:-

Table 49.

Calcification of Arteries (x-ray)	No. of cases: No Osteoporosis	Osteoporosis	% of cases with osteoporosis
Nil	23	11	25.0
Slight	7	11	61.1
Marked	18	9	33.3

A greater percentage of normal cases showed no calcification of the arteries andslight calcification was present in more of the osteoporotic cases but moderate and severe calcification was more marked in normals. Statistically there is no correlation between the incidence of osteoporosis and either arteriosclerosis, blood pressure or calcification of the arteries. The following case demonstrates clearly that senile osteoporosis may be present to a marked degree and yet no arteriosclerosis be demonstrable:-

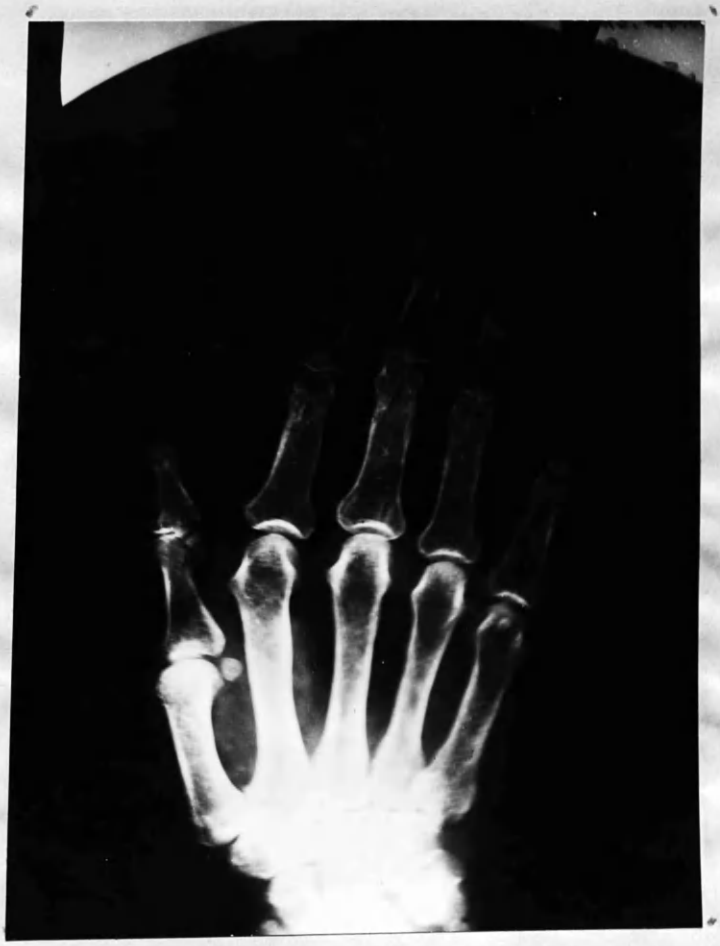
Mrs.M. aged 85 years.

This patient lived an active life, walking and doing chores such as washing clothes, until the age of 83 years, since when she has been semi-invalid. The blood pressure was $\frac{140}{110}$ and the walls of the radial arteries were soft. Unfortunately the fundus oculi could not be observed as the pupils were very small and fixed from old iritis. There was no calcification of the arteries seen on x-ray. Osteoporosis of the spine, pelvis andlong bones and of hands and feet, was present.

(Demonstration Photo. Mrs.Napier - hand and foot)

It may be noted that in all, 8 cases of generalised osteoporosis having no arteriosclerosis were found and that 12 cases of osteoporosis in patients with very slight arteriosclerosis were also observed. The converse may also be seen, marked arteriosclerosis being present in patients with no osteoporosis viz:- J.T.♂ 76 years - Hand showing calcification of the arteries (Demonstration film - John Tweedale). (See chapter 2)

Mrs. N. 83 yrs. X-Ray of hand.



Mrs. M. 83 yrs. X-Ray of foot.

It has been suggested by Harris et al. (63) that excessive calcium intake might be responsible for aiding calcification of the arteries. This idea was based on (a) evidence of high percentage of calcium in the aortae of two rabbits fed on a high calcium diet as compared with one control rabbit and (b) arteriosclerosis being more prevalent in the affluent classes according to the Registrar-General's returns and the affluent classes having a diet rich in calcium and protein. Accordingly, careful note was made in the 16 osteoporotic and normal cases treated either with a very high intake of calcium and vitamin D or of calcium and phosphorus as has been described previously, to see if any calcification developed in those who had none or increased in those who had calcification of the arteries. These cases were treated over several months, the longest being 15 months. In only one of these cases, Mrs.R. an osteoporotic case treated for 8 months, was there a suspicion of increase in the calcification already present in the arteries. No acceleration of this process was detected therfore, in 15 of the 16 cases. It should be especially noted that no change was observed in the 3 normal cases. One concludes that there is little or no danger in causing or increasing calcification of the arteries by using a high calcium diet over prolonged period, as the very high intake used in these cases should have produced evidence of changes in the arteries if such could be caused in this way. Douglas Robertson (24) has pointed out that overdosage of calcium

cannot exist among an adult population because the healthy body rejects in the faeces whatever calcium it does not require.

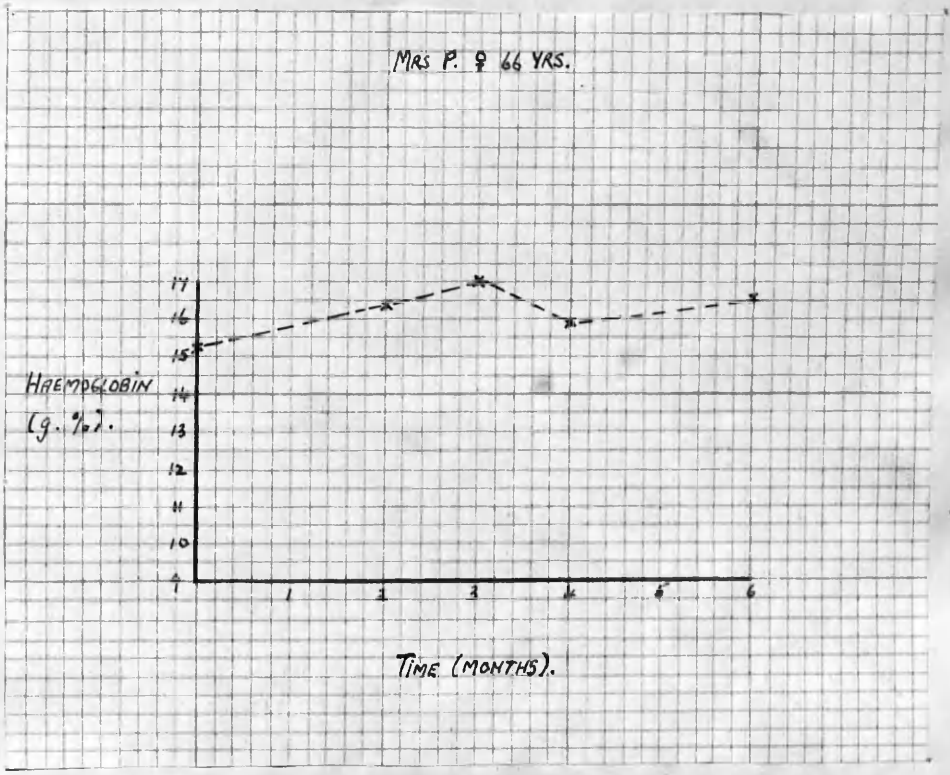
Osteoporosis has been found in association with certain disorders of the blood, for example in sickle-cell anaemia, Cooley's anaemia, acholuric jaundice and multiple myelomatosis (11a). The question of a relation between generalised osteoporosis and anaemia was therefore considered. The haemoglobin level was estimated by Sahli's method in 76 cases over 40 years of age, and a comparison of the findings in 30 osteoporotic and 46 normal cases was made:-

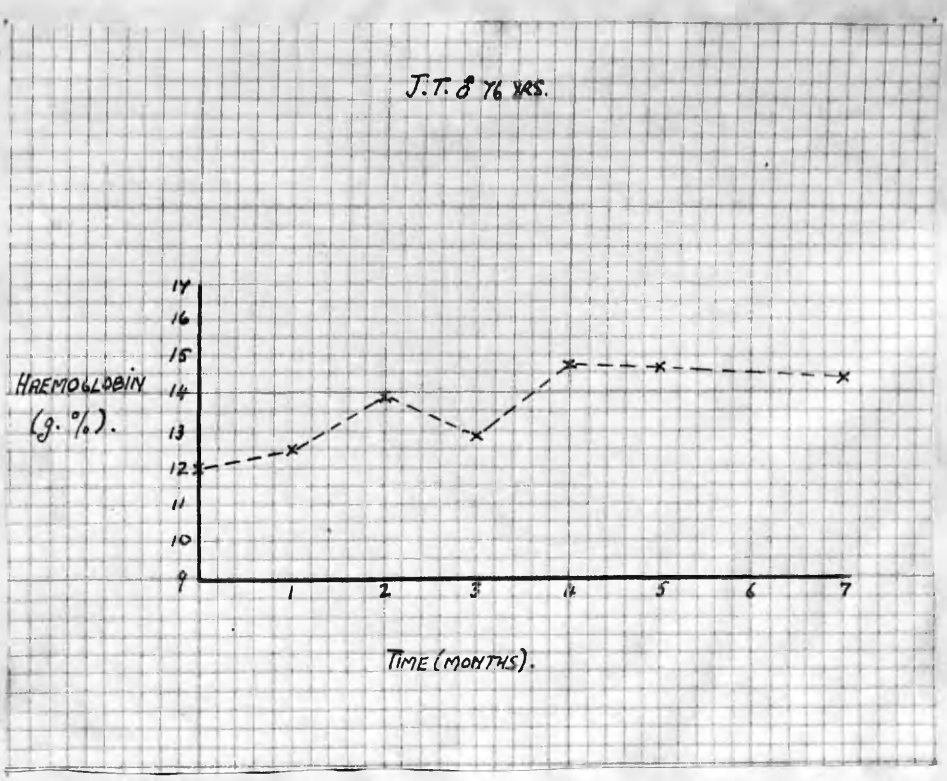
Average Haemoglobin g/100 cc.	Osteoporotic 12.7	Normal 13.4

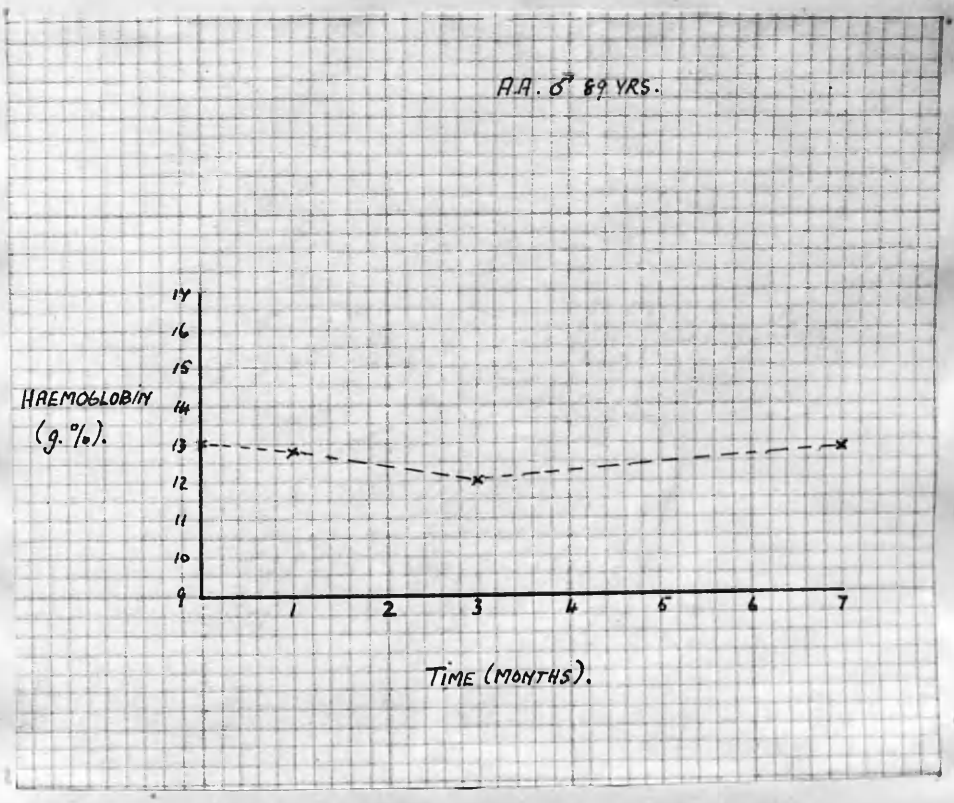
These findings may be compared with those of Black et al. who found the average haemoglobin in 33 cases of senile osteoporosis to be 12.5 g%. There is therefore no significant association of anaemia with senile osteoporosis.

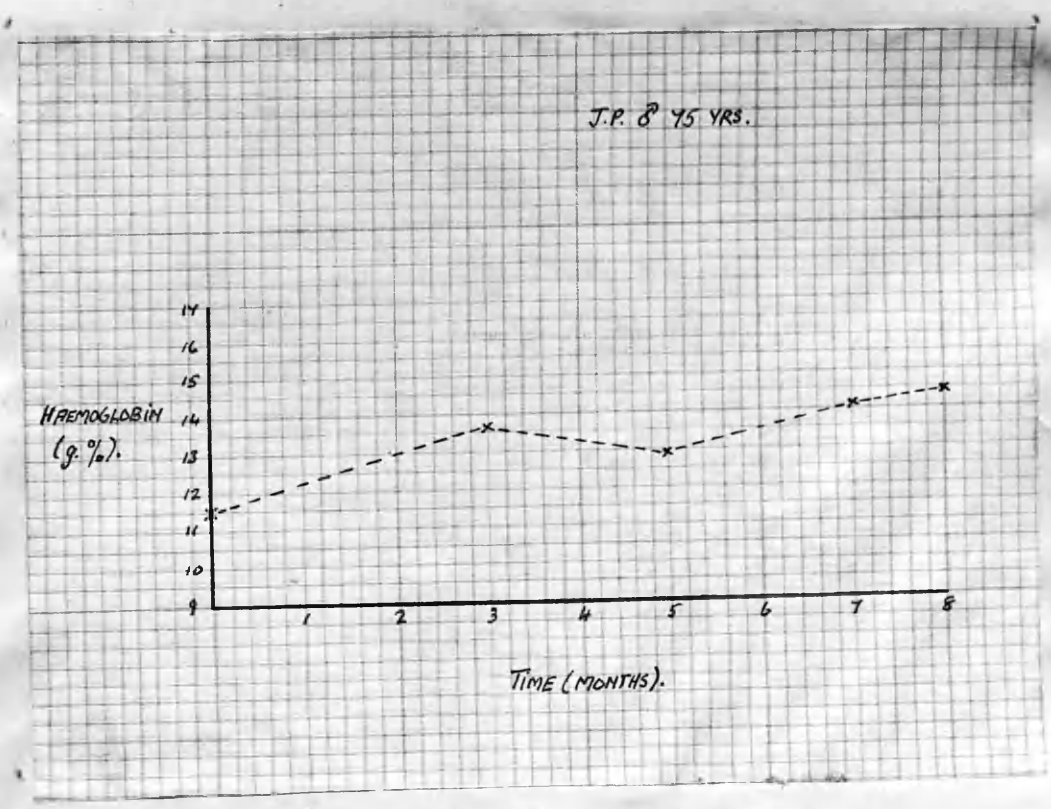
It has been found by Kletzien (64) and Tompsett (65) that the addition of large amounts of calcium containing substances to the food of mice and rats modifies the absorption of iron and reduces the iron stores of the body. To determine whether a high calcium diet would have an adverse effect in human beings or not, the haemoglobin readings in the patients treated over several months with calcium gluconate and vitamin D were followed up, with the following results:- (Figure 6.)

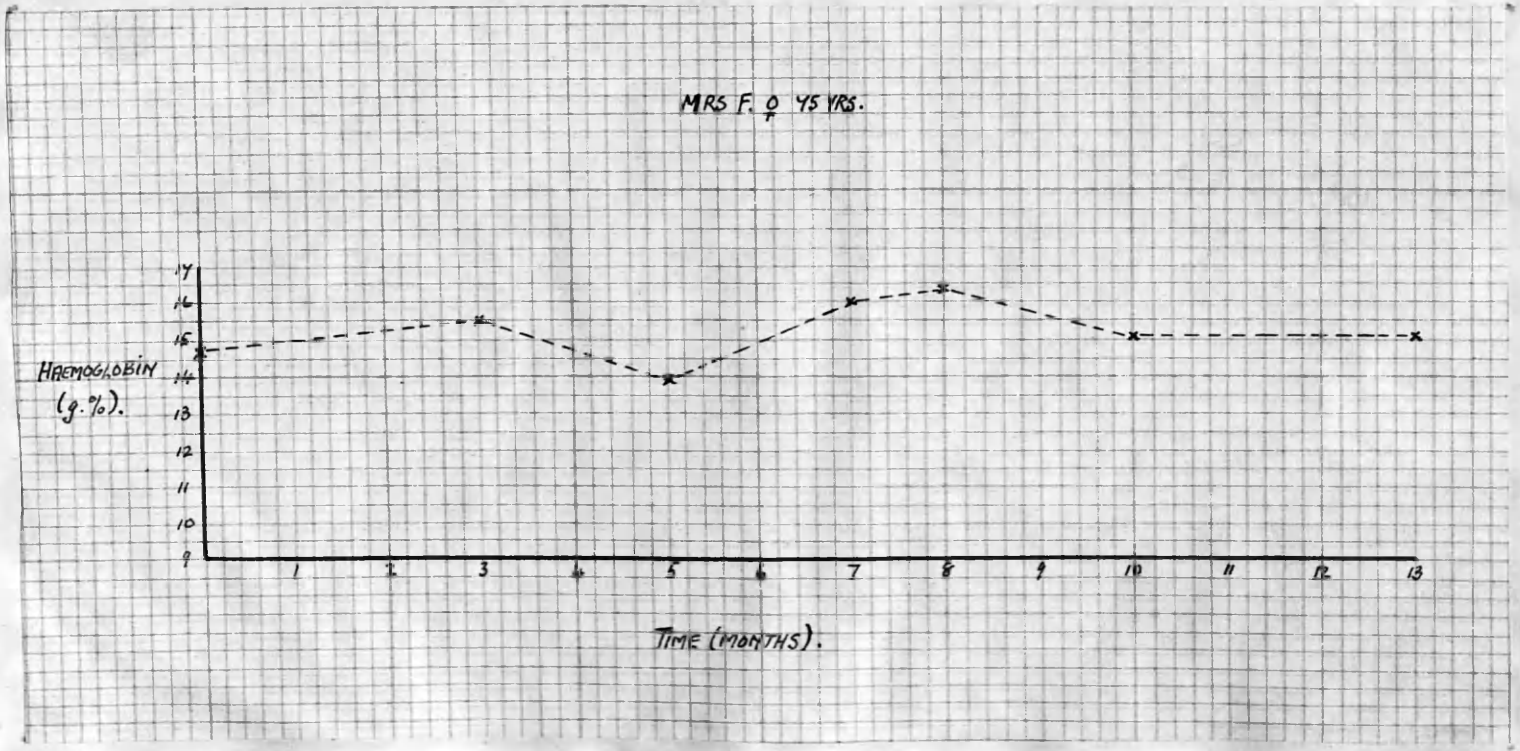
Figure 6.

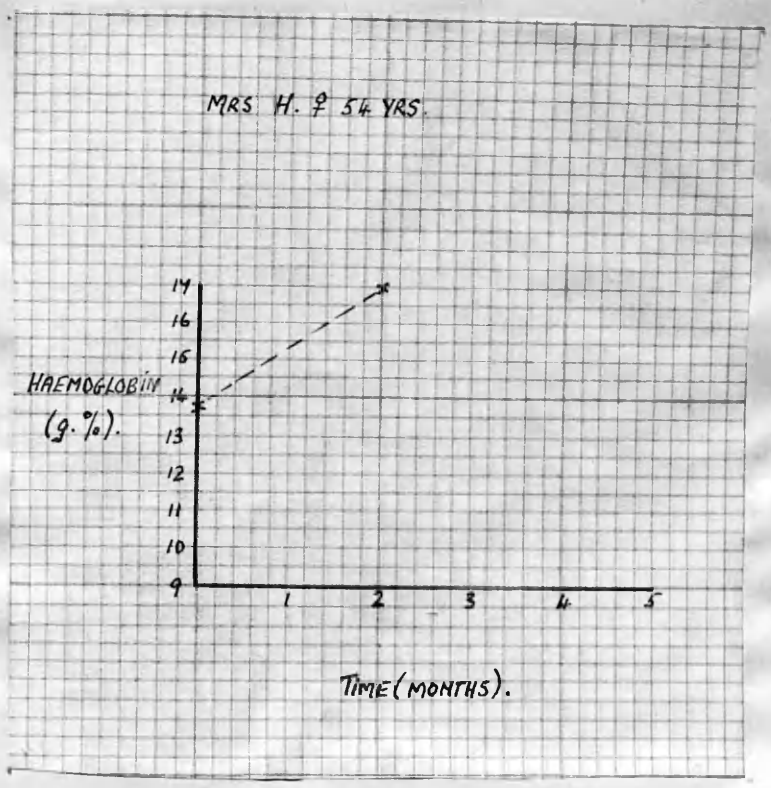

MRS P. ♀ 66 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
1
1
2
3
4
5
6
TIME (MONTHS).

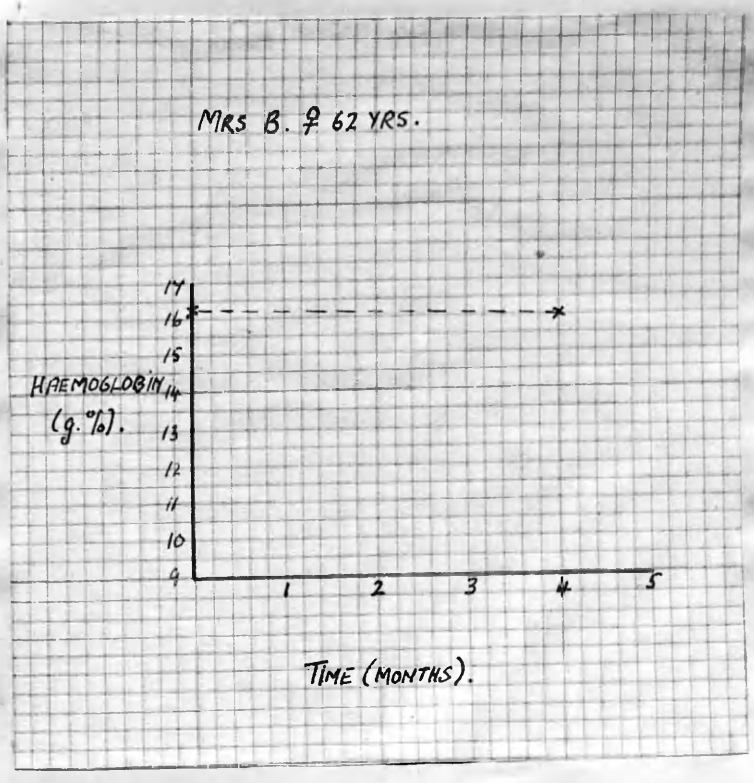

J.T. ♂ 76 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
6
7
TIME (MONTHS).

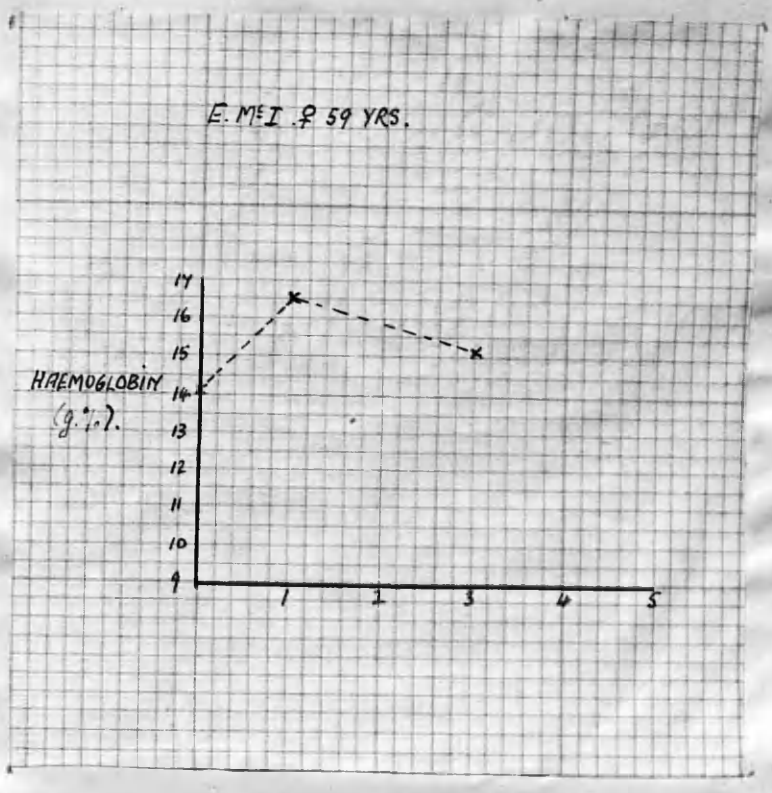

A.A. ♂ 69 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
6
7
TIME (MONTHS).

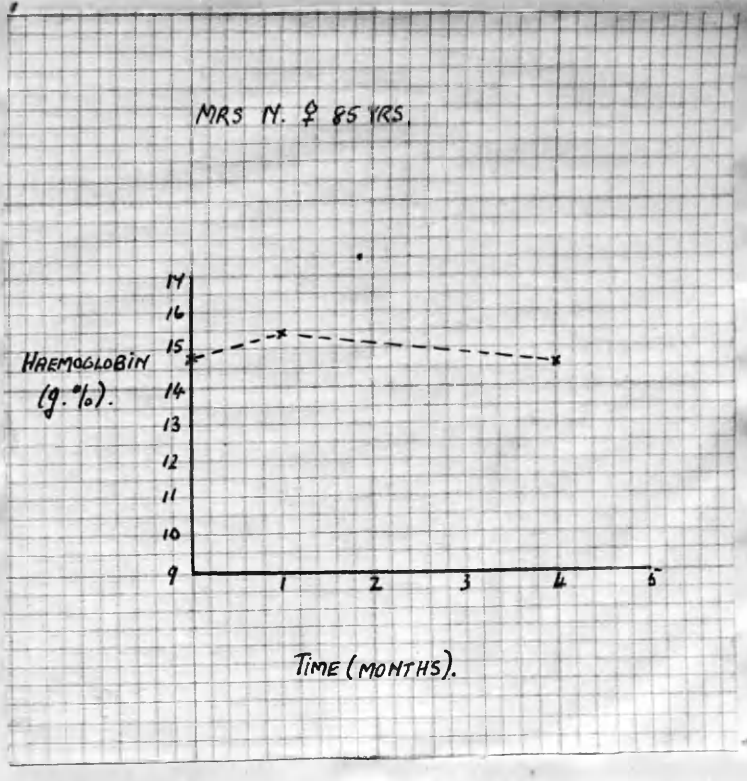

J.P. ♀ 75 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
6
7
8
TIME (MONTHS).

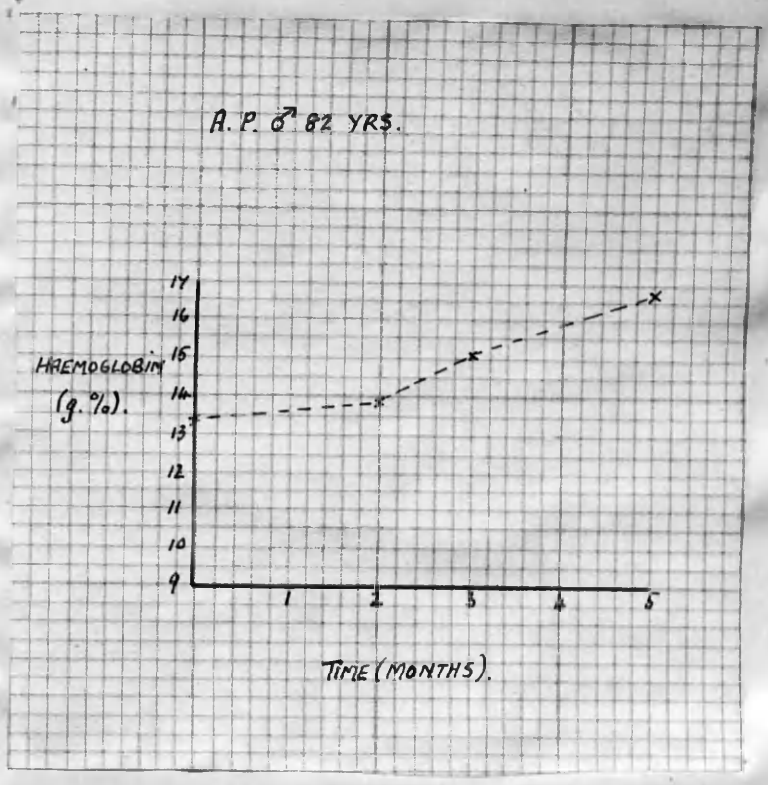

MRS F. O/F 45 YRS.
HAEMOGLOBIN (g.%).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME (MONTHS).

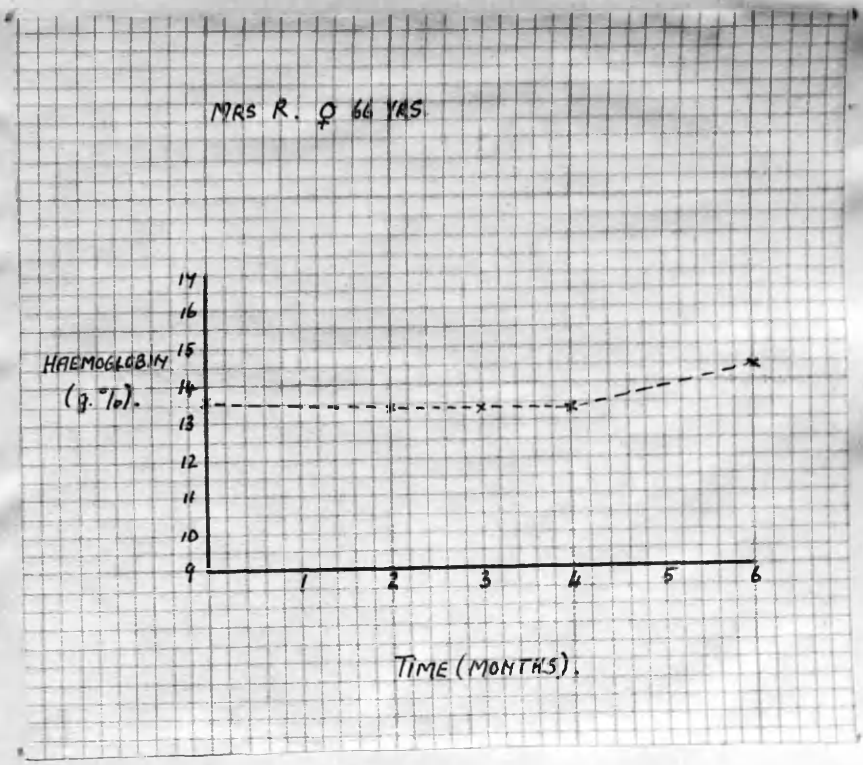

MRS H. ♀ 54 YRS.
HAEMOGLOBIN (g.%).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
TIME (MONTHS).


MRS B. ♀ 62 YRS.
HAEMOGLOBIN (g.%).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
TIME (MONTHS).


E. MEI ♀ 59 YRS.
HAEMOGLOBIN (g.%).
17
16
15
14
13
12
11
10
9
1
2
3
4
5


MRS N. ♀ 85 YRS.
HAEMOGLOBIN (g.%).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
TIME (MONTHS).


A. P. ♂ 82 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
TIME (MONTHS).


MRS R. ♀ 66 YRS.
HAEMOGLOBIN (g. %).
17
16
15
14
13
12
11
10
9
1
2
3
4
5
6
TIME (MONTHS).

One case, Mrs.D. 79 years, was anaemic when first observed and was treated initially with ferriet ammon. cit. as well as calcium gluconate and vitamin D and responded to this treatment. In this instance the calcium therapy certainly did not prevent a response being obtained. No deleterious effect on the haemoglobin level was observed in the other cases, on the contrary, there is a tendency to improvement if anything. This finding does not conflict with the opinion that calcium helps to conserve iron (11b), and demonstrates once more that conclusions drawn from animal experiments may be fallacious with regard to human beings. Barer et al. (66) found that medicinal iron had no effect on calcium, phosphorus and nitrogen balances in 16 patients with hypochromic anaemia and in 3 healthy persons, which is worthy of note.

CONCLUSIONS.

Generalised arteriosclerosis is not a factor in the production of generalised senile osteoporosis. There is no evidence to suggest that prolonged treatment with a high calcium intake may induce calcification of the arteries. There is no relation between senile osteoporosis and anaemia and treatment with high calcium intake does not affect the haemoglobin level adversely but may possibly have a beneficial effect.

D Endocrine Imbalance

1. Post-menopausal State

It has been found experimentally in birds that elevation

of the blood lipids and blood calcium can be produced by the administration of oestrogens, natural or synthetic (67). Levin et al. (68), however, could detect little or no influence on the serum calcium level in normal or ovariectomized rats, rabbits and immature monkeys, treated by the administration of oestrin. The relation of oestrin to calcium metabolism in human beings is, however, worth considering. Albright et al. (16) carried out an investigation into the cause of generalised osteoporosis in patients in the menopausal years, all cases over 65 years being omitted to exclude senile osteoporosis. In a series of 42 osteoporotic patients only 2 were male. They found no cases in females prior to the menopause. That generalised osteoporosis is commoner in females than in males there is no doubt, as has been discussed previously. While this predominance in females may be significant the fact that the condition may be found in males at all suggests that the sole cause cannot be concerned with oestrin metabolism. On the grounds that oestrin therapy had a beneficial effect in their cases and that the sex incidence was so striking, Albright et alii consider that the post-menopausal state is very important in the aetiology of the generalised osteoporosis in the age-groups investigated by them.

In the present series of patients over 40 years of age the incidence of osteoporosis was correlated with parity as follows:-

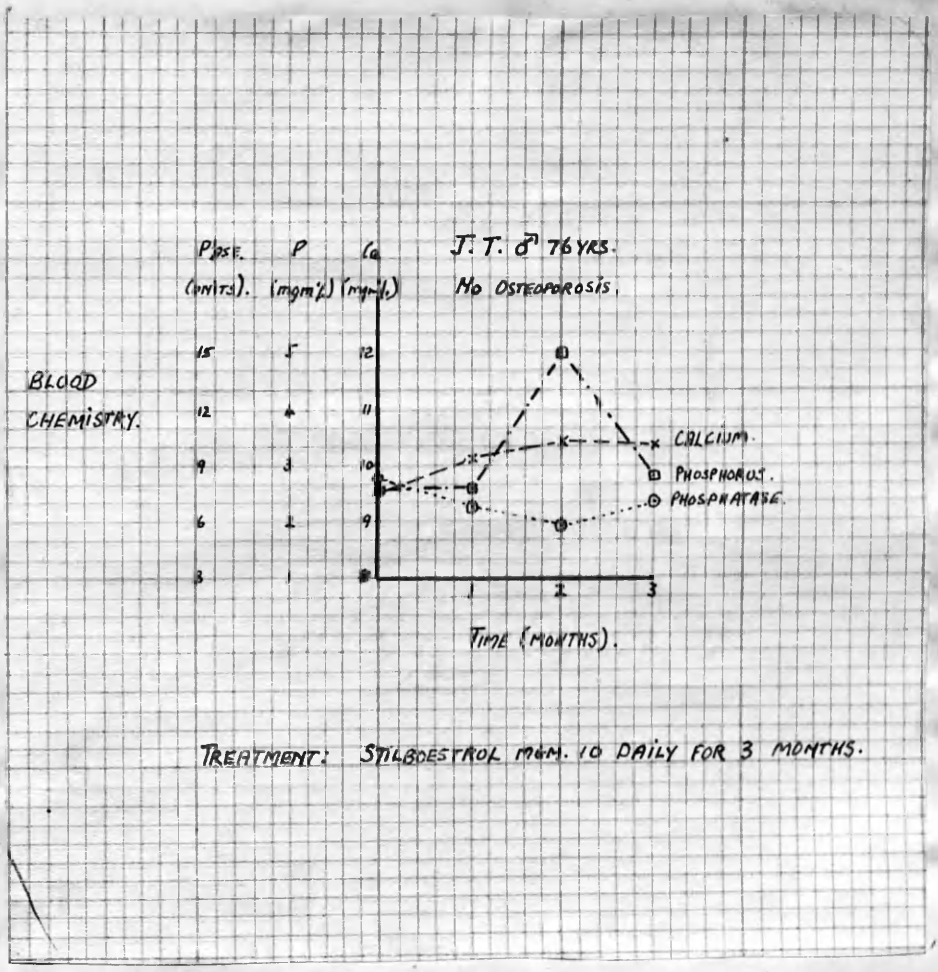
Table 50

	Nulliparae			Multiparae		
	Osteo-porotic	Total	Percentage	Osteo-porotic	Total	Percentage
All ages	6	15	40%	18	25	72%
Below 70	1	6	17%	5	9	56%
Above 70	5	9	56%	13	16	81%

This table shows that osteoporosis appears to be more common in parous females, even when considered in age-groups as above. When this is enquired into more closely, however, it is clear that multiparity can have only a subsidiary influence on the incidence of osteoporosis as some patients who had large numbers of pregnancies showed no osteoporosis e.g. one patient had 20 pregnancies and was normal. Statistically there is no correlation between the incidence of osteoporosis and multiparity.

Does the administration of a synthetic oestrogen, e.g. stilboestrol, have any effect on the blood chemistry in human beings? A preliminary investigation in 10 males between the ages of 53 and 74 years, average age 65 years, was carried out. Stilboestrol mgm 10 was given orally daily for 7 days and estimations of the serum calcium, inorganic phosphorus and phosphatase were made before and after. No appreciable constant difference was detected. A further series of 10 males ages ranging from 49 to 82 years, average age 70 years, were then treated with the same dosage of stilboestrol for 14 days and again no appreciable change in the blood chemistry was found. One normal male J.T. 76 years

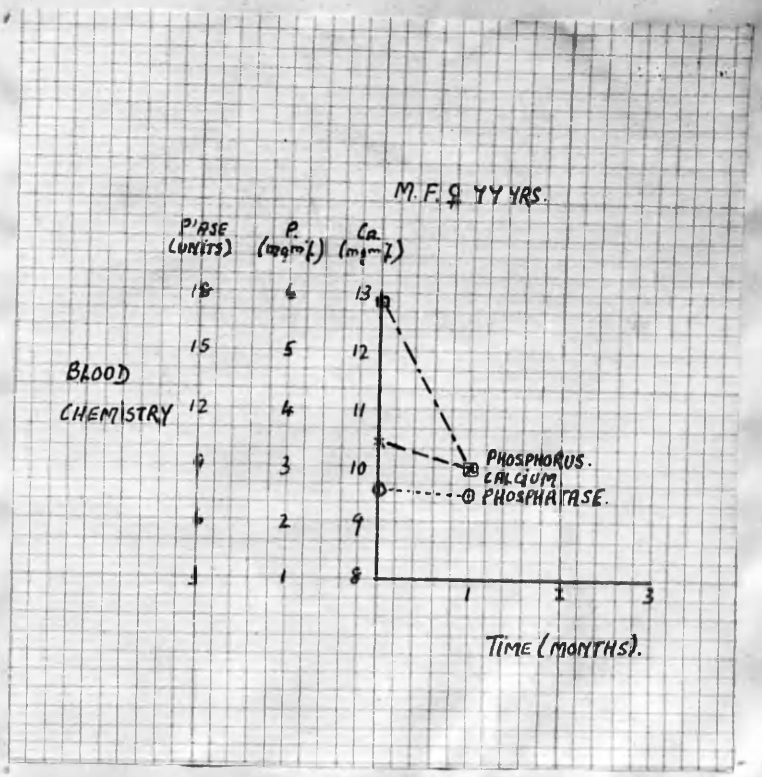
Figure 4.

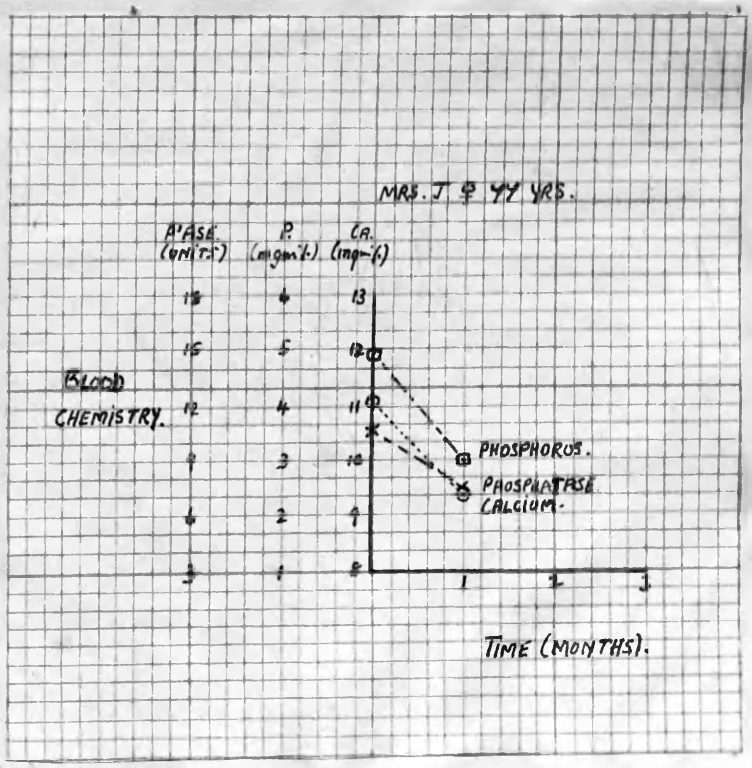

J. T. ♂ 76 YRS.
No OSTEOPOROSIS.
BLOOD CHEMISTRY.
P'ase. (units).
P (mgm%)
Ca (mgm%)
15
12
9
6
3
4
3
2
1
12
11
10
9
1
2
3
CALCIUM.
PHOSPHORUS.
PHOSPHATASE.
TIME (MONTHS).
TREATMENT: STILBOESTROL m&m. 10 DAILY FOR 3 MONTHS.

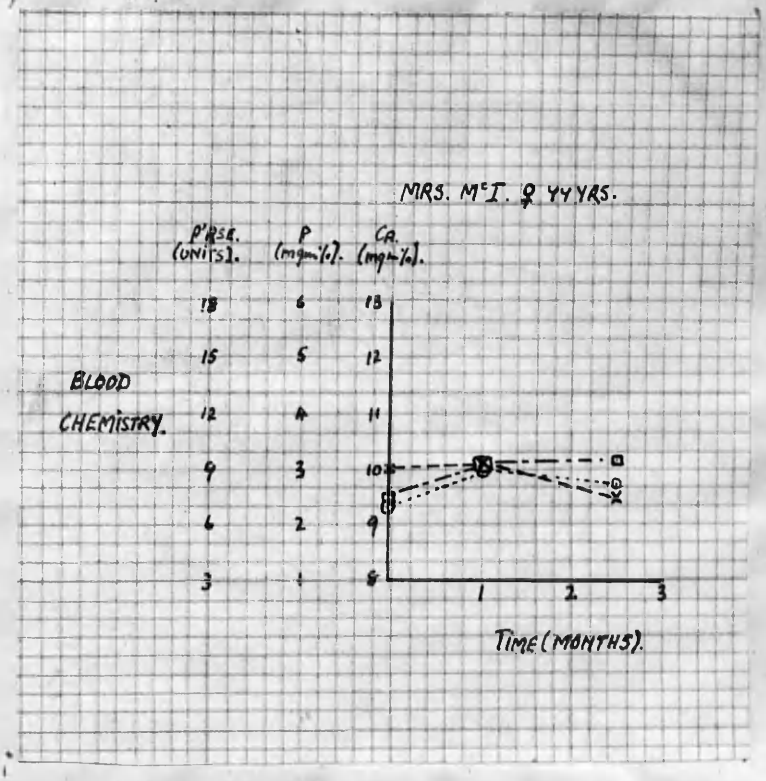
was given stilboestrol mgm 10 daily for 3 months and the blood chemistry was followed up with this result:- (Figure 4.) The Ultimate readings show little change when compared with the initial results.

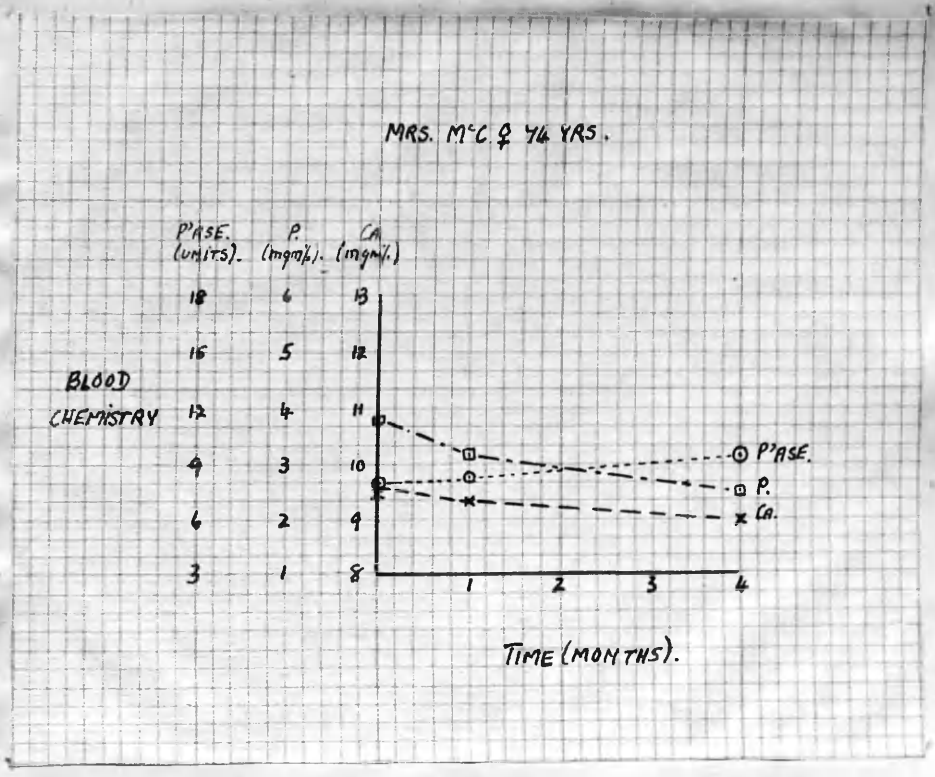
A series of females, 8 having generalised osteoporosis and 3 being normal, ages ranging from 49 to 88 years, average age 74 years, were then treated with stilboestrol mgm 2 orally daily for several months; repeat estimations of the blood chemistry gave readings as follows:- (Figure 5).

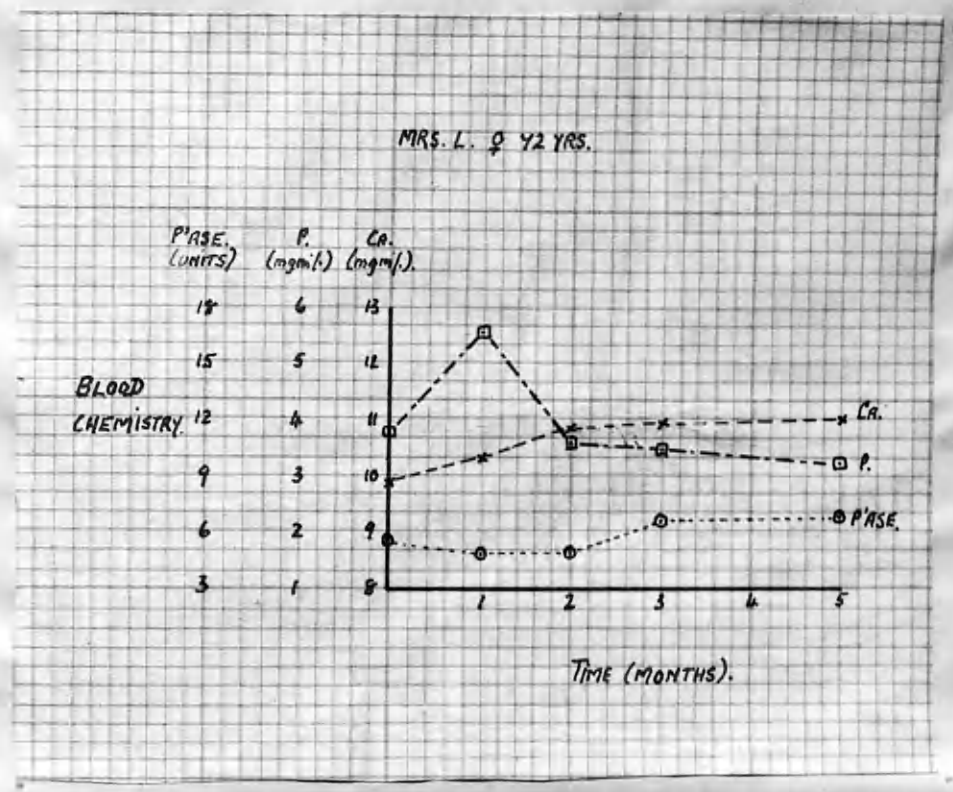
Figure 8. Blood Chemistry during treatment with Stilbestrol.

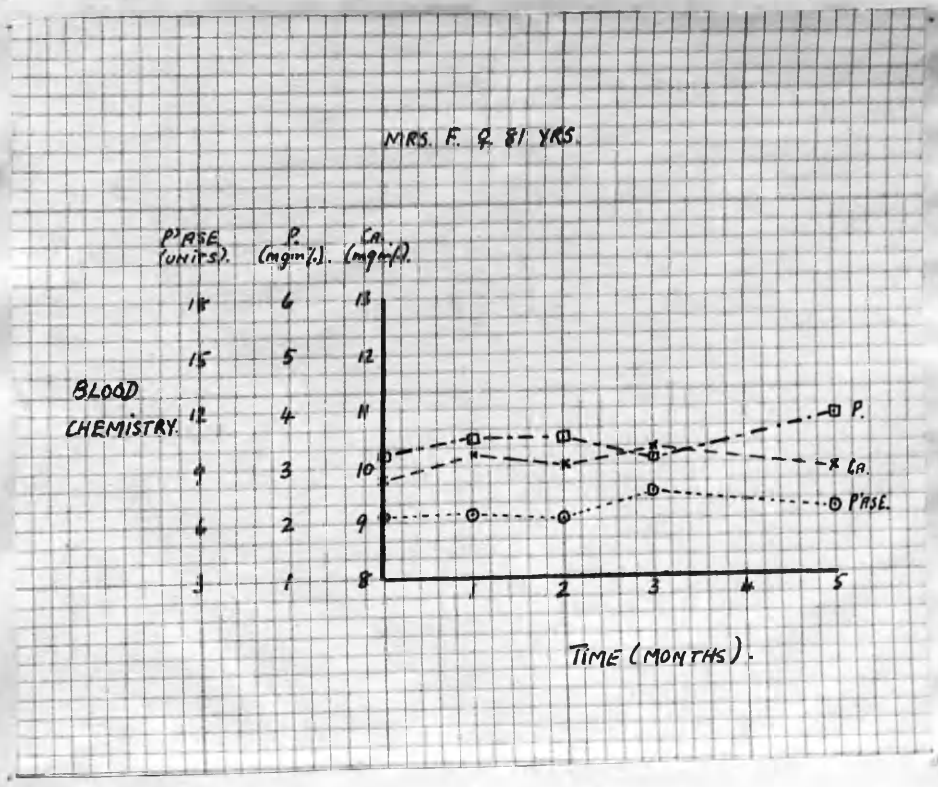




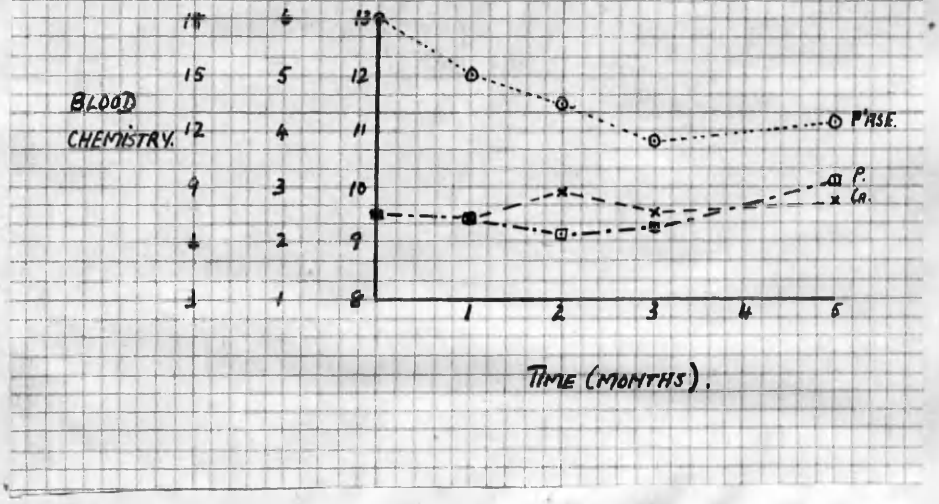

MRS. M°I. ♀ YY YRS.
P'ASE. (UNITS).
P (mgm%).
CA. (mgm%).
BLOOD CHEMISTRY.
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
TIME (MONTHS).


MRS. M°C. ♀ 74 YRS.
P'ASE. (UNITS).
P. (mgm%).
CA. (mgm%).
BLOOD CHEMISTRY
18
16
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
P'ASE.
P.
CA.
TIME (MONTHS).

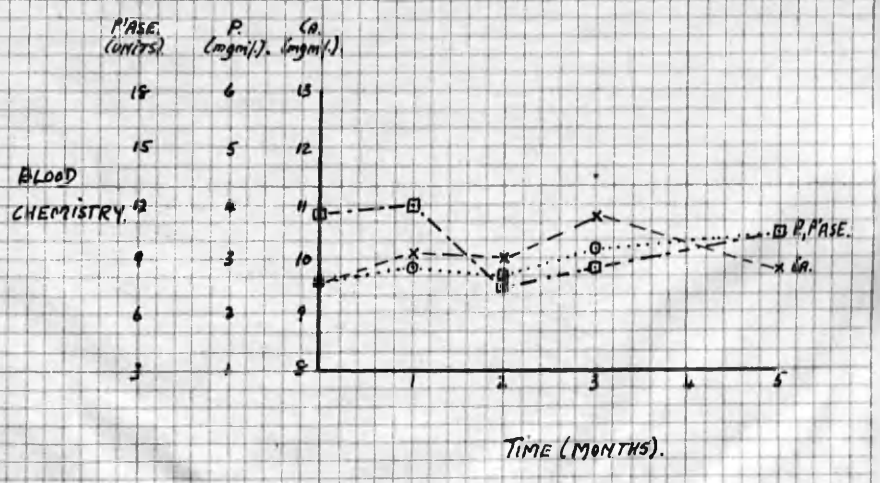

MRS. L. ♀ 42 YRS.
P'ASE. (UNITS)
P. (mgm%)
CA. (mgm%)
BLOOD CHEMISTRY.
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
5
CA.
P.
P'ASE.
TIME (MONTHS).

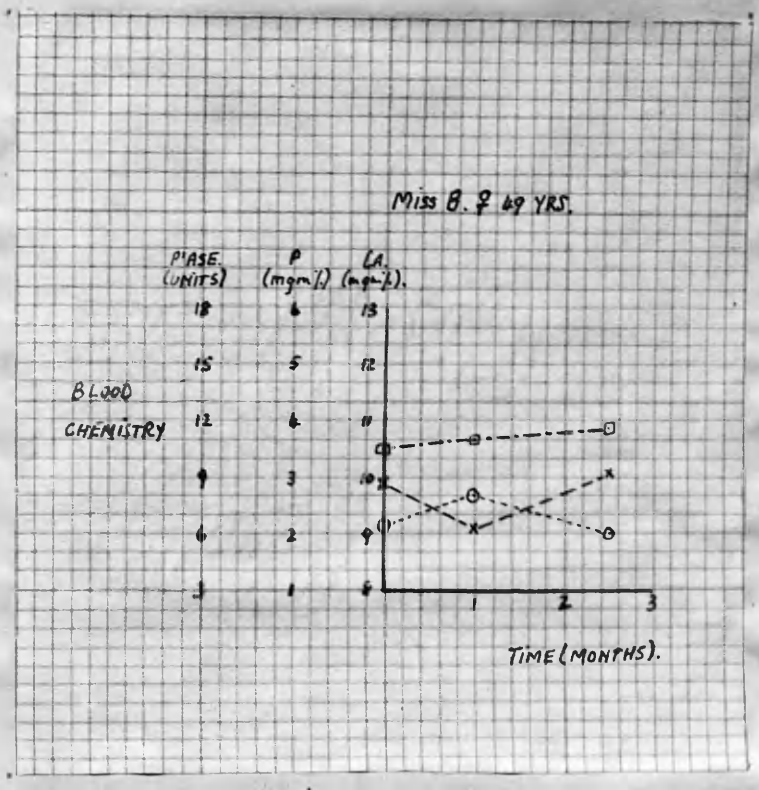

MRS. F. ♀ 81 YRS.
P'ASE. (UNITS).
P. (mgm%).
CA. (mgm%).
BLOOD CHEMISTRY.
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
5
P.
CA.
P'ASE.
TIME (MONTHS).

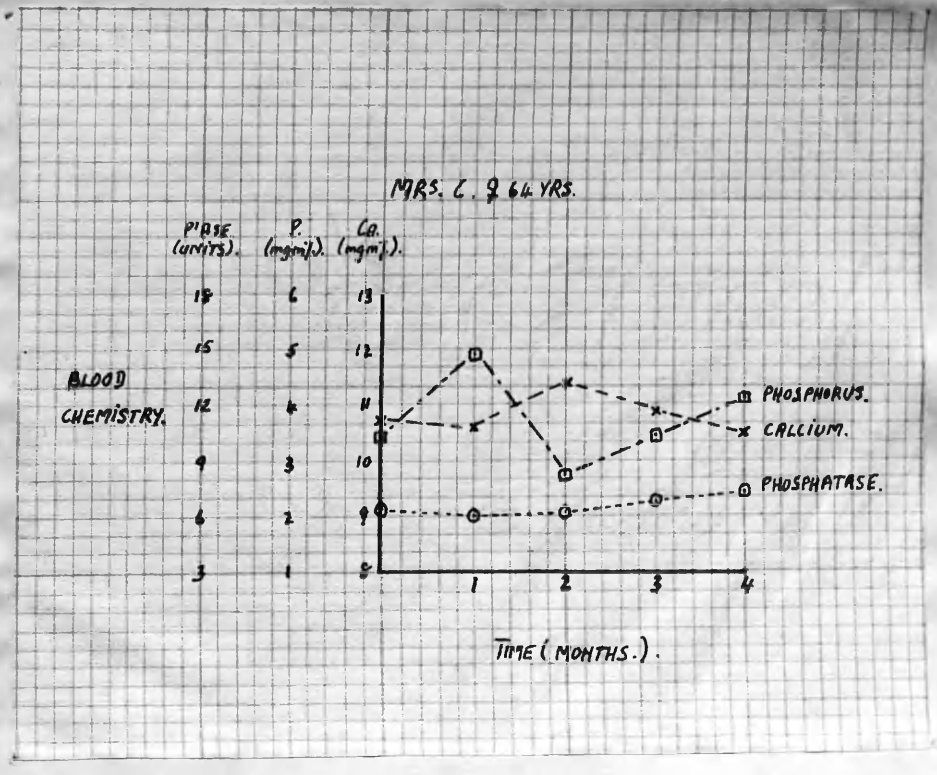
MRS. K. ♀ 88 YRS.

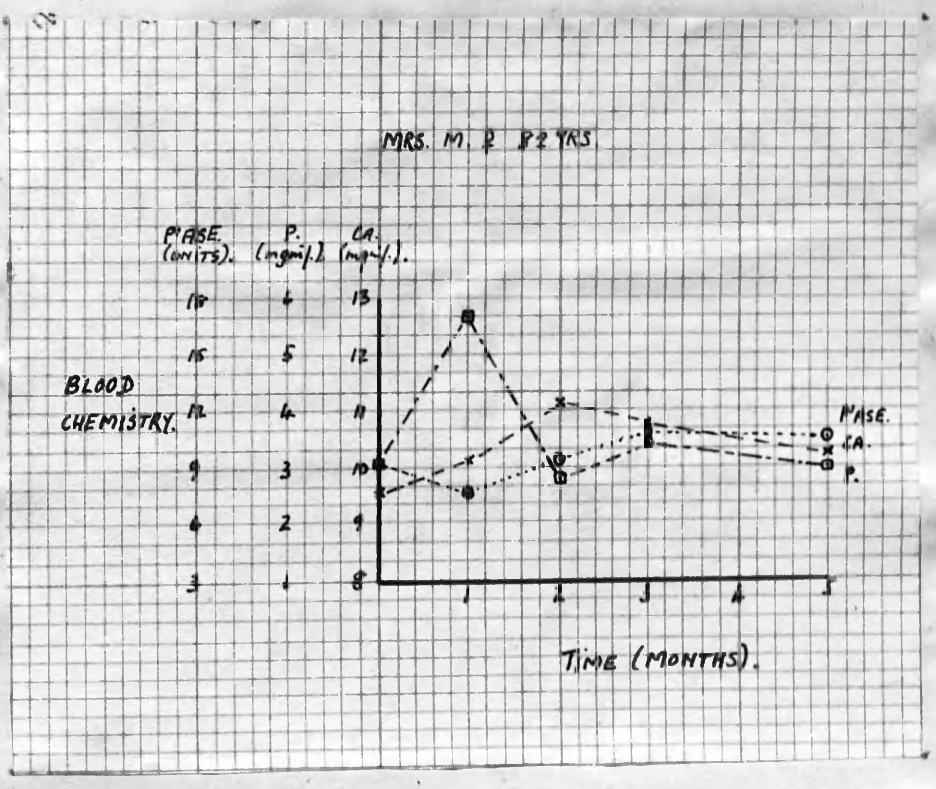


MRS. M. C. ♀ 44 YRS.




Miss B. ♀ 49 YRS.
PHASE (UNITS)
P (mgm%).
CA. (mgm%).
BLOOD CHEMISTRY
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
TIME (MONTHS).


MRS. C. ♀ 64 YRS.
PHASE (UNITS).
P. (mgm%).
Ca. (mgm%).
BLOOD CHEMISTRY.
18
15
12
9
6
3
6
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
TIME (MONTHS.).
PHOSPHORUS.
CALLIUM.
PHOSPHATASE.


MRS. M. P. 82 YRS.
BLOOD CHEMISTRY.
P'ASE. (UNITS).
P. (mgms/l.)
CA. (mgms/l.)
18
15
12
9
6
3
4
5
4
3
2
1
13
12
11
10
9
8
1
2
3
4
5
TIME (MONTHS).
P'ASE.
CA.
P.

No appreciable constant alteration in the serum calcium, inorganic phosphorus or phosphatase is observed. As the dosage used, namely stilboestrol mgm 2 daily, is a therapeutic one, it may be concluded that the oral administration of synthetic oestrogen in reasonable dosage has no appreciable effect on the calcium metabolism of older females as judged by the blood chemistry. The above patients were x-rayed before, during and after this course of treatment. The duration of treatment is shown below and as has been mentioned, generalised osteoporosis was present in 8 while 3 were normal:-

Initials	Age	Duration of Treatment (months)	X-ray
M.F.	77	1½	0
Mrs.J.	77	2	0
Mrs.McI.	77	2½	0
Mrs.McC.	74	5	0
Mrs.L.	72	6	0
Mrs.F.	81	6	0
Mrs.K.	88	6	0
Mrs.M.C.	77	6	0
Miss B.	49	2½	N
Mrs.C.	64	4	N
Mrs.M.	82	6	N

In no case was there detected a change in the x-ray appearance which finding suggests that deficiency of oestrin is probably not a factor in the production of

senile osteoporosis. It may be wondered if treatment thus with stilboestrol produces toxic effects of any kind. None were observed in either series of males. This corresponds with the findings of Finch (69) who treated a series of 9 males aged 65 to 78 years with a dosage of 5 mgm per day and found no toxic effects. Remarkably few toxic effects were detected in the female series. The following case, however, is of especial interest:-

Miss B, 49 years of age, was a nurse by profession and was allowed to know the nature of the medicine which was being administered. She had read about the toxic effects of stilboestrol, and complained of nausea, although she did not vomit, shortly after the treatment was begun. The nausea persisted for the few days during which the tablets were given but all symptoms vanished when the patient was led to believe that the stilboestrol was discontinued, when in actual fact the same dosage of stilboestrol was still administered in a mixture containing infusion of gentian. The stilboestrol was continued in this way for $2\frac{1}{2}$ months without any further upset. This case provides another illustration of the pyschological factor which must always be reckoned with when judging the effects of drug therapy.

One case showed toxic effects in the form of haemorrhage per vaginam. Mrs.C. 64 years, began staining per vaginam after $3\frac{1}{2}$ months treatment and this very gradually became worse. Treatment had to be discontinued at the end of 4 months and the bleeding stopped within a few days. Two cases exhibited with-

drawal bleeding when the drug was discontinued, Mrs.J. 77 years after, and M.F. 77 years after 1½ months treatment. In both cases the bleeding ceased within one week, and in neither was it profuse. Bleeding per vaginam indeed was the only toxic effect observed.

CONCLUSIONS

There is little evidence that post-menopausal disturbance is of importance in the aetiology of generalised osteoporosis, apart from the higher incidence in females. There is no significant correlation between multiparity and the incidence of generalised senile osteoporosis. The administration of synthetic oestrogen, viz. stilboestrol mgm 10 daily orally for 14 days in males over 40 years of age, has no appreciable effect on the serum calcium, serum inorganic phosphorus or serum phosphatase. One case treated for 3 months showed little or no alteration in the blood chemistry. Treatment with stilboestrol mgm 2 daily, orally, in females over 40 years of age, for as long as 5 months, has also no appreciable effect on the blood chemistry. No change is demonstrable on x-ray examination of the bones of normal and osteoporotic females treated thus for as long as 6 months , and no change was detected on x-ray in a normal male treated with stilboestrol mgm 10 for 3 months. Only one toxic effect namely bleeding per vaginam was observed in 11 females, all over 40 years of age, 9 being over 65 years, when undergoing treatment with stilboestrol. No evidence was found to connect oestrin and calcium metabolism and post-menopausal disturbance does not appear to play a

significant part in the aetiology of generalised senile osteoporosis.

2. Hyperthyroidism

Aub et al. (14) found that in hyperthyroidism there is an increased excretion of calcium both in the urine and faeces and that marked osteoporosis may be associated with prolonged hyperthyroidism. They detected no abnormality of the serum calcium or phosphorus. These findings are now generally accepted (13)(12). Demineralisation in cases of hyperthyroidism was found on x-ray by Kummer in 1917 (70) and has been noted by other observers since then (13). There was no evidence of hyperthyroidism either circulatory (tachycardia etc.), metabolic (basal metabolic rate) or biochemical (lowered blood cholesterol) in the cases of generalised osteoporosis observed during the course of this work.

3. Hyperparathyroidism

It is generally accepted that hypersecretion of the parathyroid hormone is the cause of the demineralisation found in generalised osteitis fibrosa. The demineralisation found in this condition may be differentiated from the generalised osteoporosis which was the subject of this investigation, radiologically and by the increase in serum calcium and phosphatase and by the marked increase in urinary excretion of calcium and phosphorus. Black et alii (17 found no abnormality of the parathyroid glands in 3 cases of senile osteoporosis in which they were explored.

4.Pituitary basophilism

Generalised osteoporosis may be associated with this condition (15). The clinical syndrome of obesity, hypertension, hirsutism and changes in the sex characteristics, provides adequate means of differentiating the aetiology of this generalised osteoporosis from that of senile patients. No evidence of pituitary upset was detected in the present investigation.

5.Suprarenal disease

Generalised osteoporosis may be found in disorders of the adrenals (5)(17) but no evidence of adrenal disease was found in the present series.

CHAPTER V

PROGNOSIS AND THERAPEUTICS

The prognosis in generalised osteoporosis depends, of course, on the cause of the condition. Where the aetiology is known and the cause can be removed the condition can be cured: thus for example in osteomalacia suitable treatment with vitamin D and high calcium intake leads to rapid re-calcification of the bones. Similarly where the cause is vasomotor disturbance, disuse, or endocrine imbalance, the osteoporosis may be cured by suitable treatment. The prognosis in the cases of generalised osteoporosis investigated above is not so satisfactory. A cure for the condition has not been found; therefore at the moment the best result to be expected is to prevent the condition from progressing and to prevent complications in the form of fractures and deformities. Provided the condition is detected the prognosis is fairly good as the incidence of serious complications such as fractures is not very high. In the majority of cases, however, the condition will not be diagnosed until a complication appears and the prognosis in these is therefore correspondingly worse. Treatment in cases where the cause is not known consists of:-

1. Relief of symptoms.
2. Prevention of complications or of further deformities if these are already present.
3. Attempt to induce recalcification.

1. Relief of symptoms

Rest in bed may actually be sufficient to produce relief but acute pain may require analgesics, or the local application of heat. Massage may also be of assistance in the less acute stages. The oral administration of a suitable calcium salt such as calcium gluconate may also prove of value.

2. Prevention of complications or of further deformities if these are already present.

If the condition be diagnosed before complications are present the patient may be warned of the dangers of sudden jolts and jars. The addition of calcium gluconate or calcium and phosphorus to the diet may prevent the condition from progressing and thereby lessen the chances of fractures and deformities appearing. If a deformity such as scoliosis be present or if there is a fracture of a vertebra a spinal support might prove of value in addition to the measures already outlined.

3. Attempt to induce recalcification

In the light of our present knowledge it is advisable to give a balanced diet containing high amounts of calcium and phosphorus and an adequate amount of vitamin D. Foods such as milk, cheese and eggs are of especial value. The addition of suitable salts of calcium and phosphorus to supplement the diet may also be of value. While treatment thus has so far not been proved to promote recalcification

it might do so if continued over very long periods. It at least may prevent the condition progressing by preventing excess resorption of calcium from the bones.

Toxic Effects.

Are there any toxic effects from prolonged high intake of calcium? Harris et al. (63) suggest that there is a danger of causing calcification in the arteries thus. As has been pointed out previously, no evidence of this was found in the above investigation. No deleterious effect on the haemoglobin level was observed. No gastro-intestinal disturbance was detected. Three cases treated with calcium gluconate and vitamin D developed a dermatitis of the hands and wrists. The records are as follows.

1. Mrs.W. 72 years had no previous history of skin trouble. One month after treatment was begun she developed a dermatitis of both hands which responded to local therapy although the administration of the calcium and vitamin D was continued. This suggests that the dermatitis was not connected with the drugs.

2. W.M. male 62 years had a history of recurrent dermatitis of the hands for the past 17 years. It was present slightly when treatment with calciuma and vitamin D was begun and flared up about $1\frac{1}{2}$ months later. This also responded to local therapy while the calcium gluconate and vitamin D was continued.

3. Mrs.B. 62 years had a history of dermatitis of the hands and wrists on and off for 6 months. It recurred whilst she

was on treatment with calcium gluconate and vitamin D and also responded to local therapy although these drugs were continued.

It is striking that these three cases should have a dermatitis in the same situation, but, as two of these had a previous history of this, it is likely that the cause of the skin lesion in these two at least, was not related to the drug therapy. The possibility of the dermatitis being aggravated by this treatment cannot, however, be entirely disregarded. The response to local therapy while the calcium gluconate and vitamin D were continued, militates against any causal relationship. On the whole, therefore, it is doubtful if the dermatitis was a toxic effect of the treatment. No other possible toxic effects were observed, and it seems reasonable to conclude that it is safe to administer calcium gluconate in high dosage over a prolonged period. This probably applies also to the other calcium salts which may be employed therapeutically.

CHAPTER VI

GENERAL SUMMARY

A. Diagnosis

1. Generalised osteoporosis is diagnosed essentially by x-ray examination of the skeleton, localised osteoporosis being excluded by detecting the condition in several regions of the body, for example in one lower limb, one upper limb and in the spine.

2. The criteria of osteoporosis are:-

   (1) Absorption of the transverse trabeculae and in severe cases of the longitudinal trabeculae.

   (2) A diminution in the density of the bone shadows, which may be obtained by comparison with "normal" films.

3. Osteoporosis is found most markedly in the feet, hands and spine.

4. The x-ray appearance of the vertebrae in generalised senile osteoporosis is very characteristic and consists of diffuse osteoporosis, ballooning of the intervertebral discs and compression of the bone resulting in "fish-tail" vertebrae or even in true compression fractures. Kyphosis is commonly seen in these older patients.

B. Clinical Manifestations.

Symptoms and signs may be of some assistance in the diagnosis of generalised osteoporosis but as they are found in a relatively small proportion of cases their value is correspondingly limited. They are found characteristically

in senile osteoporosis, are usually related to the spine and consist of back-ache which may be very acute, stiffness and weakness of the back, tenderness and spasm of the erectores spinae. These symptoms and signs are probably due to complications of the osteoporosis per se.

C. Blood chemistry

The blood chemistry provides negative evidence in diagnosis, as it is essentially normal, but there is a tendency to high normal readings of the serum alkaline phosphatase in generalised osteoporosis including the senile type. A significant correlation between the height of the phosphatase value and the incidence of generalised osteoporosis was detected in the 70-79 age-group but in no other. The main use of estimating the serum calcium, inorganic phosphorus and alkaline phosphatase is to exclude conditions such as hyperparathyroidism or osteitis deformans.

D. Autopsy findings.

Post-mortem examination can provide conclusive evidence of generalised osteoporosis. The ribs of subjects over 40 years of age who exhibited generalised osteoporosis, contain smaller absolute amounts of calcium and phosphorus than normal ones although the ratio of calcium: phosphorus is unchanged.

E. Incidence

1. Age.

Generalised osteoporosis is a pathological condition and

may be found at all ages of life but there is an increasing incidence with increasing age which appears to be significant statistically. There is no evidence to suggest that the generalised osteoporosis found in patients between 40 and 65 years of age, differs in any way from senile osteoporosis. The incidence in patients over 40 years of age is about 40%. In a series of x-rays of the spine obtained over three years the incidence of spinal osteoporosis was found to be 31%.

2. Sex.

Generalised osteoporosis is much more common in females, being found between 3 and 4 times in females for every male affected.

F. Aetiology

1. Treatment with a good diet plus calcium gluconate and vitamin D in adequate amounts over periods of several months gives relief of symptoms but does not cure the condition as estimated by x-ray examination. While this evidence does not support the view that prolonged deficient intake of calcium is the cause of generalised osteoporosis especially senile osteoporosis, it does not exlude this possibility as the condition either may be one which would be cured very gradually over a period of years or may be an irreversible process. Prolonged treatment as outlined above, has little effect on the blood chemistry although there is a tendency for a slight rise in the serum calcium and the inorganic phosphorus and a fall in the serum alkaline phosphatase which, however, usually fall within the normal ranges for these estimations.

2. Senile patients are capable of absorbing and retaining calcium and phosphorus if given higher intakes than those to which they are accustomed, their calcium metabolism being no different from younger adults in that respect. There is little possibility of deficient absorption and retention being factors in the production of generalised senile osteoporosis.

3. Generalised osteoporosis may be produced by disuse provided the degree of disuse is great enough. This factor probably only plays an ancillary part in the production of generalised senile osteoporosis.

4. There is no connection between generalised osteoporosis and generalised vascular disease such as arteriosclerosis. Anaemia is also not a significant factor in the aetiology of generalised osteoporosis. Prolonged treatment with a good diet plus calcium gluconate and vitamin D in adequate doses does not induce calcification of the arteries and has no deleterious effect on the haemoglobin level but may even tend to have a beneficial effect. It is very doubtful if there are any toxic effects at all from this treatment.

5. Hormonal disturbance such as hyperthyroidism or pituitary basophilism are known to produce generalised osteoporosis. There is little evidence to suggest that post-menopausal upset may also have this effect. Generalised senile osteoporosis is not connected with any recognised hormonal disturbance: no evidence of this was found in a series of

osteoporotic patients over 40 years of age. The administration of stilboestrol in therapeutic doses for 5 months had no appreciable effect on the blood chemistry in either sex, and had also no effect in generalised osteoporosis as judged by x-ray examinations after 6 months treatment in females over 40 years of age.

F. Prognosis and Treatment.

The prognosis in generalised osteoporosis depends on the cause. Generally speaking if the cause is known a cure is obtainable but in the majority of cases the cause is not known. The complications which may be found are either fractures or deformities such as kyphosis and scoliosis. Rest and a diet containing a good supply of minerals will relieve symptoms and may help to prevent complications but a cure of the condition by dietetic treatment has not, as yet, been demonstrated.

G. General conclusion.

Further investigation is required to establish the aetiology of generalised senile osteoporosis. The theory that prolonged deficient intake of minerals is the cause still lacks confirmation but may well prove ultimately to be the main factor in the aetiology. The only other factor certainly connected with the origin is disuse but this is probably only of minor importance.

APPENDIX

BIOCHEMICAL METHODS

1. Blood Serum Estimations.

(a) Serum Calcium.

The Clark-Collip modification of the Kramer-Tisdall method.

(b) Serum inorganic phosphorus.

Youngburg's method.

(c) Serum 'Alkaline' phosphatase

Method of Kine et alii (1937)

2. Bones.

Specimens of ribs were obtained P.M. and the attached soft tissues were removed. The ribs were then dired, weighed and ashed in an electric muffle. The estimations performed were:-

(a) Calcium content.

Method of Shohl and Pedley.

(b) Inorganic phosphorus content.

Youngburg's method (see above).

3. Food and Excreta.

The food and faeces were dried, weighed and then ashed in an electric muffle. The volume of urine was recorded and then it was concentrated by evaporation and decolourised by means of charcoal and filtration.

Aliquot portions were examined for:-

(a) Calcium - method of Shohl and Pedley.

(b) Inorganic phosphorus - Youngburg's method.

REFERENCES.

(1a) Harris,H.A. Bone Growth in Health and Disease 1933 p.85.

(1b) " " " " p.82.

(1c) " " " " p.199.

(1d) " " " " p.181.

(2a) Brailsford,J.F. The Radiology of Bones and Joints 1934 p.31.

(2b) " " " " p.42.

(2c) " " " " p.30.

(2d) " " " " p.303.

(2e) " " " " p.396.

(2f) " " " " p.26.

(3) Todd

(4a) Price,F.W. A Textbook of the Practice of Medicine 6th Ed. 1941 p. 456.

(4b) " " " " p. 1381.

(4c) " " " " p. 1037.

(4d) " " " " p. 1378.

(5) Jung,M.A. Rev.Chir. 1937 56.473. quoted by (6).

(6) Annotation. The Lancet 1937 Dec.25.p.1500.

(7a) Tidy,H.L. Synopsis of Medicine 7th Ed. 1939 p.896.

(7b) " " " " p.893.

(7c) " " " " p.895.

(7d) " " " " p.894.

(8) Wright,S. Applied Physiology 7th Ed. 1941 p.295.

(9) Morris, N. Stevenson,M.M. Pedon,C.D. and Small,J.M.D. Arch.Dis.Childh. 1937.12.45.

(10) Purves-Stewart,Sir J. The Diagnosis of Nervous Diseases 8th Ed. pp.513-514.

(11a) Whitby,L.E.H. and Britton,C.J.C. Disorders of the Blood pp.278 and 345.

(11b) " " " p.124.

(12) Abeloff,A.J. Sobel,I.P.Bernhard,A. Amer.Journ.Dis.Child. 1933.45.105.

(13) Hunter,D. The Lancet 1930 May 3, p.947.

(14) Aub,J,C. Bauer,W.,Heath,C. Ropes,M. Journ.Clin.Inv.1929.7.97.

(15) Freyberg,R.H.,Grant,R.L. Arch.Int.Med. 1936.58.213.

(16) Albright,F.,Smith,P.H.,Richardson,A.M.,Journ,Amer.Med.Assoc. 1941.116.2465.

(17) Black,J.R.,Ghormley,R.K. and Camp,J.D. Journ.Amer.Med.Assoc. 1941.117.2144.

(18) Schmorl,G. Beits.Z.path.Anat.u.z. Path. 1931.87.585. quoted by (17).

(19) Meulengracht and Meyer Ungesky.Laeg.1936.98.961.quoted by (21)

(20) Leitch Nutrition.Absts.Rev. 1936-37.6.553. quoted by (21).

(21) Owen,E.C. The Bioch.Journ. 1939.33.22.

(22) Owen,E.C.,Irving,J.T. and Lyall, A. Acta Med.Scand.1939.103.235

(23) Wishart,G.M. The Brit.Dental Journ. 1938. Feb.1.

(24) Robertson, J.D. The Lancet, 1941.197.

(25) Adams, M. Boothby,W.M. and Snell,A.M. Amer.Journ.Phys. 1935-36.114.383.

(26) Ghormley,R.K.,Sutherland,C.G. and Pollock,G.A. Journ.Amer. Med.Assoc. 1937.109.2111.

(27) Albert,M. The Brit.Med.Journ. 1942 May 30 p.666.

(28) Beadle,C.A. Med.Res.Cncl.Sp.Rep.Ser. No.161.1931. quoted by (27).

(29) Light,R.F. and Frey,C.N. Proc.Soc.Exp.Biol.&Med.1941.48.256.

(30) Maxwell,J.P. Proc.Roy.Soc.Med. 1929-30.23.639.

(31) Meulengracht,E. Acta Med.Scand. 1939.101. Fasc.II-III.

(32) Vogt,J.H. Acta Med.Scand. 1941.106.16-25.

(33) Annotation. The Brit,Med.Journ. 1937. Dec.11 p.1176.

(34) Morris,N. and Peden,O.D. Quart.Journ.Med. 1937.30.211.

(35) Gutman,A.B.,Swenson,P.C. and Parsons,W.B. Journ.Amer. Med.Assoc. 1934.103.87.

(36) Bodansky,A. and Jaffe,H.L. Arch.Int.Med. 1934.54.88.

(37) Bodansky,A.,Jaffe,H.L. and Chandler,J.P. Proc.Soc.Exper. Biol.& Med. 1932.29.871.

(38) Cantarow,A. Internat.Clin.Philad. 1936.1.230.

(39) Hawk's Practical Physiological Chemistry 11th Ed.

(40) King,E.J.,Haslewood,G.A.D. and Delory,G.E. The Lancet, 1937.1.886.

(41) Peters,J.P. and Van Slyke,D.D. Quantitative Clinical Chemistry, London 1931.1.808 and 1097 quoted by (24).

(42) Schmorl,G. Die pathologische Anatomie der Wirbelsäule, Verhandl.d.deutsch.orthop.Gesellsch.1926.21.3.quoted by (17).

(43) Morris,N.,Ford,F.J. and Graham,S. Acta Paediatrica, 1935.18.50.

(44) McCrudden,F.H. Arch.Int.Med. 1910.5.596. quoted by (45).

(45) Hunter,D. and Turnbull,H.M. Brit.Journ.Surg. 1931-32.19.203.

(46) Miles,A. and Wilkie,D. Thomson and Miles' Manual of Surgery 9th Ed.1939.1.513.

(47) Bailey,H. and Love,R.J.M. A Short Practice of Surgery, 3rd Ed. 1936.774.

(48) Hume and Nirenstein. The Lancet, 1921.201.849. quoted by (21)

(49) Meulengracht. The Lancet, 1938.235.775. quoted by (21).

(50) Orr,J.B. Food, Health and Income. 2nd Ed. 1937. London.

(51) McGowan,J.P. The Brit.Med.Journ. 1933. Sept.30. 599.

(52) Jaffé,H.L.,Bodansky,A. and Chandler, J.P. Journ.Exp.Med. 1932.56.823. quoted by (22).

(53) Yamane, T. Mitteil Med.Acad.Kioto, 1932.6.2541.quoted by (22).

(54) Becker,R.B.,Neal,W.M. and Shealy,A.L. Journ.Diary Science, 1934.17.1. quoted by (22).

(55) Sherman,H.C. Chemistry of Food and Nutrition 1937 New York, quoted by (24).

(56) Hickmans,E. The Biochem.Journ. 1924.18.925.

(57) Schmidt,C.L.A. and Greenberg,D.M. Physiol.Rev. 1935.15.297. quoted by (17).

(58) Bridges,M.A. Food and Beverage Analysis, 1935 2nd Ed. London.

(59) Von Economo C Encephalitis Lethargica 1931 London.

(60) Hall,A.J. Epidemic Encephalitis 1924.

(61) Wimmer, A. Chronic Epidemic Encephalitis 1924.

(62) Leriche,R. and Policard,A. Les problèmes de la physiologie normal et pathologique de l'os. Paris 1936.quoted by (7).

(63) Harris,I.,Ireland,J.T. and James,G.V. The Brit.Med.Journ. 1941 Jan.11 49.

(64) Kletzien,S.W. Journ.Nutr. 1940.19.187.

(65) Tompsett,S.L. Biochem.Journ.1940.34.961.

(66) Barer et alii Journ.Lab.Cl.Med. 1940.26.351.

(67) Flock,E.V.and Bollman,J.L. Proc.Staff Meet.Mayo Clinic. 1941.16.783.

(68) Levin,L. and Smith,P.E. Endocrinology, 1938.22.315.

(69) Finch,J.W. Journ.Amer.Med.Assoc. 1942.119.400.

(70) Kummer,R.H. Revue Med. de la Suisse Romande 1917.37.439. quoted by (14).