T H E S I S

on

"The Serum Calcium in Rheumatoid Arthritis and Osteo-Arthritis and the Effect of Certain Types of Treatment thereon."

by

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September 1928.

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I N T R O D U C T I O N.

In a disease where the nomenclature is so varied, it is essential at the outset to define the scope of the term "chronic arthritis". As used in this investigation it is taken to include "the group of cases of arthritis which have as prominent features a tendency to chronicity and to more or less permanent change in the joints or structures about the joints, those forms of arthritis with a definite etiology being excluded"[1]. For all practical purposes this may be taken to mean the two diseases generally described as rheumatoid arthritis and osteo-arthritis in this country. It is into these two types that the cases investigated have been divided according to their clinical symptoms and their X-ray picture, the one showing chiefly periarticular changes, the other bony and cartilaginous.

The amount of crippling and discomfort due to chronic arthritis is too well known to reiterate: the too often disappointing results of all forms of treatment tried are equally well known, due in most cases to lack of exact knowledge of the etiology or to too long delayed appropriate treatment: in a certain proportion of cases the disease commences following some known chronic infection of low virulence but of great tenacity: if the focus of that infection is adequately re-

moved then the disease may clear up completely, though no actual organisms originating therefrom have been found in the joints affected. Treating the disease on the assumption that it is a chronic intoxication, in recent years protein shock therapy has been used and attended by successful results: this treatment, as reported by Campbell[2] consists of the administration of graduated doses of typhoid vaccine or similar protein: his results support the infective or rather toxic etiology of rheumatoid arthritis.

Whatever the cause of the disease, and whatever the type, there is almost always pathological change in the bone, either rarefaction of the cancellous tissue or the deposition of new bone around or in the joint, which fact would suggest possibly either excessive calls on, or perverted use of, the bone forming substances, which in turn may possibly be due to some definite abnormal functioning of the bony metabolism.

In other diseases showing pathological defects in the bony structure and metabolic changes, there have been demonstrated important abnormalities in the chemical composition of the blood: in rickets, for example, the blood chemistry has been the subject of much original work, which has helped materially in the elucidation of the etiology and in evolving a rational line of treatment. The calcium content of the blood was an important item in these investigations, being often, though not always, lowered both in ordinary rickets and in experimental rickets in animals.[3] In

another bone disease, osteitis fibrosa, Lambie[4] has shown the presence of a hypercal-caemia. In gout, a disease which some are inclined to compare to osteo-arthritis in certain ways Coates and Raiment[5] have recorded a marked rise in the calcium content of the blood. It was thus thought that the serum calcium in chronic arthritis might in some way vary from normal, and if so, might help to throw some light on part at least, of the changes in the bone metabolism taking place.

Upon consulting the literature upon the subject several scattered observations were found, but none involved a large series and in most cases dealt exclusively either with one or other of the types involved in this discussion. Mark[6] found a normal calcium in one case of "rheumatic arthritis" and a marked rise in the serum calcium in three cases of osteo-arthritis. Watchorn[7] reported a raised serum calcium in cases of rheumatoid arthritis especially where accompanied by fibrositis. Weil and others[8] record a raised serum calcium in "chronic rheumatism," while Horrowitz[9] gives similar results in "arthritis deformans". On the other hand Stewart and Percival found normal serum calcium in rheumatoid arthritis[10]

The present investigation, extending over a period of about 18 months, was suggested by the large number of cases seen alike in general practice and in medical wards, both of which contributed to the number of cases, though naturally hospital patients on the whole could be more thoroughly examined. Each case as

it came under observation was thoroughly investigated clinically; where possible radiograms of affected joints were taken, and any other examination suggested by the case carried out. The serum calcium was determined and where possible again calculated after treatment, and in suitable cases followed up; the method used will be described later: the results obtained were classified and compared with each other and with other data. As different workers have recorded different figures for the normal for serum calcium (vide postea) owing to slight variations in technique or personal factors, a preliminary series of twelve presumably healthy normal adults of ages corresponding as far as possible with that of the patients investigated, was examined, so as to give a relatively normal figure for comparison.

Several types of treatment were used, these being briefly as follows:-

(1) Local and general constitutional treatment such as radiant heat, massage, dieting, etc.

(2) Intramuscular injections of iodine, guaiacol and camphor in oil as recommended by Smith.[11]

(3) Protein shock - as already noted.

(4) Any method which might be suggested from any constant abnormality found in the serum calcium in the course of investigations. In osteo arthritic patients, following the finding of a constant hypercalcaemia the calcium intake was reduced and acid phosdil administered. This will be discussed later, but it was of interest at the close of the investigations to discover in Mark's original article[6] the results of somewhat similar treatment in a case of osteo-arthritis with hypercalcaemia.

If from the results obtained any type of treatment were

to show a return to or to an appreciable extent towards the normal level of serum calcium over a series of cases so treated and accompanied by a clinical improvement, then that treatment would seem to be the most rational in combating a disease at once worrying to the physician and crippling to the patient in all too many cases.

Origin and Chemistry of Serum Calcium.

The ultimate source of all calcium in the body is from the food - solid and liquid - ingested. Of this a large proportion is passed on through the bowel unabsorbed: the remainder, after absorption from the small bowel, is mostly got rid of by the large bowel in the faeces: that part of the calcium not excreted by the intestine, is got rid of by the kidneys. It has been suggested by Cushny[12] that the diffusible calcium is excreted by the kidney by simple filtration and the fixed calcium by the intestine by vital action.

In health and at most other times calcium has been demonstrated in the blood in very constant amount under varying conditions of intake, body requirement and of output. It is thus assumed that the calcium of the blood can be taken as an index of the calcium of the tissues in general (that this is so has been denied by some, and will be noted later). This constancy of the calcium content suggests that there is some calcium regulating process which is of great importance physiologically and pathologically. It is generally agreed that the

great bulk of the blood calcium is in the plasma, the cellular elements containing negligible quantities. Thus the plasma calcium content is a better guide to the body tissue calcium than the blood calcium owing to the liability to varying proportion of the red and white corpuscles to the blood volume. Plasma is difficult to obtain and it has been shown that though the blood serum contains 10-20% less calcium than the former, yet the proportion is fairly constant, so that the most easily calculated figure and the standard index of calcium concentration is the amount of calcium in the serum. This amount has by various investigators and by various methods been found to vary from 9 to 12 mg calcium per 100 ccs. serum, but on the whole those having fairly uniform results record it as being about 10 mg. per 100 ccs. The total calcium as demonstrated by several, is not all present in one form, but is generally split into a diffusible and a non diffusible part corresponding to crystalloid and colloid matter (Cushny) From observations which have been made (vide Postea) the diffusible part would seem to be divided still further into ionised and ionisable (but non-ionised) fractions. By different methods the following fairly constant results have been arrived at.

Vines[13] added enough ammonium oxalate to just precipitate total calcium present: this amount he says, only acts upon the "diffusible" calcium which is calculated in his usual way, and then given as a % of the total calcium.

Cushny[12] using a collodion filter under pressure for a certain time found that part of the serum calcium was kept back, only the diffusible fraction dialyzing through: his findings were:-

Diffusible	=	62-70%
Colloid	=	30-40%

Neuhausen and Marshall[14] state that by electrometric methods only 10-20% of the calcium is truly ionised, the remainder of the diffusible calcium being non-ionised.

Von Meysenburg[15] by dialyzing the serum against solutions of known strength found the diffusible to be 60-70% the non-diffusible to be 40-30%.

It is thus seen that there is 40-60% of the serum calcium which, though not ionised, is yet ionsable and potentially "active" or available for physiological requirements. As this proportion varies to some extent, it upsets the reliability of the serum calcium index to some extent as indicating exactly the amount of available calcium in the tissues.

The inactive or colloid calcium has been said by Salvesen and Linder[16] to be bound to the plasma proteins, as they found that in parathyroidectomy, where the diffusible calcium is decreased primarily, there is no change in the plasma proteins, while in nephritis with cardiac failure and consequent serous filtrates in abdomen, etc., there is lowered calcium content of the serous fluid accompanied by lowered plasma proteins. Thus it would seem that the non-diffusible calcium being

bound to protein is not so readily available to the tissues as the diffusible calcium.

The calcium of the serum is split up as follows:-

Ionised	10-20%)	Available
Diffusible but non-ionised	40-50% -)	
Indiffusible or colloid	30-40%	

The same proportions are present in plasma as is shown by "in vivo" experiments such as the analysis of the cerebro-spinal fluid.

Recently Holt, La Mer, and Chown[17] have shown the presence of $Ca_3 (PO_4)_2$ in supersaturated solution in the blood, the amount in solution being controlled by a balance between the calcium and (PO_4) ions can the $Ca_3 (PO_4)_2$ itself; excess of ions - product of Ca and PO_4 - causes deposition of $Ca_3 (PO_4)_2$ while a fall in the ion product causes rise in $Ca_3 (PO_4)_2$ by passage of Ca and PO_4 from the tissues. The above workers say that in their experiments the precipitation of $Ca_3 (PO_4)_2$ from serum on shaking with solid $Ca_3 (PO_4)_2$ is due to acceller-ation of equilibrium due to the presence of the solid phase.

This naturally leads to the theory that there is some control over the amount of calcium in the blood by a hypo-thetical substance which Holt suggests is itself controlled by the parathyroid hormone. Since the experiments of McCallum and Voegtlin[18] showing that the complete removal of the para-thyroids results in tetany with its lowering of blood calcium and increased metabolism, it has been held that the para-

thyroids, directly or indirectly, control the calcium metabolism of the body.

Koch[19] demonstrated the presence of guanidin and methyl-guanidin in the urine of parathyroidectomised dogs. This fact has been fully corroborated and its causal relationship amply demonstrated by Paton and his co-workers. The position of the relationship of the parathyroids to calcium and guanidin is fully detailed in a paper by Paton[20] where an account is given for the belief that the symptoms of tetany are not necessarily due to the lowered blood calcium but to the presence of guanidin and methyl-guanidin in excess: the administration of these substances has given the same symptoms as tetany: it has also been shown by Anderson and Graham[21] that latent tetany may occur in infants without fall in calcium, and that blood calcium may be low when no tetany is present (advanced acidosis). Also in hyperpnoea tetany the blood calcium is not lowered. In tetany ionised calcium is lowered: the same effect has been found from guanidin poisoning. Paton comes to the conclusion that if the parathyroid hormone controls metabolism of muscle tone, it is possibly by maintaining a relative balance between guanidin and calcium: when parathroid is out of action there is a rise in guanidin and a fall in calcium, which together produce tetany. In this connection and in the treatment of tetany it is important to note that Burns and Watson[22] found that the paraly-

sing action of guanidin on vagal endings was removed by administering calcium.

Vines[13] considers that the parathyroids act directly to detoxicate guanidin. Hence the parathyroids may be considered as detoxicating organs whose want of functioning is accompanied by lowered serum calcium.

Since the preparation by Collip[23] of a physiologically active extract of the parathyroids much work has been done upon the action of this substance both in hypocalcaemic subjects and in those whose blood calcium is normal, and in determining its mode of action, and the source of the increase of blood calcium after its administration. Collip believes that the parathyroids control calcium metabolism by controlling the blood calcium: the administration of his extract removed tetany symptoms from parathyroidectomised dogs, in which the blood calcium increased in proportion to the clinical improvement. He also found an increase in normal adults following a dose of the extract. These results have been confirmed by Stewart and Percival[24] who also found that intravenous injection of $NaHCO_3$ caused a fall in blood calcium in cats, and that the simultaneous administration of equivalent doses of $NaHCO_3$ and parathyroid extract balanced each other, suggesting that the action of parathyroid extract is to cause an acidosis when given in excess. They also found that the effect of the extract was unaffected by removal of brain, cord, liver, spleen, pancreas,

stomach, or bowel; this showed that the rise of blood calcium was not due to influence through any of these organs, nor was it due to an increased absorption of calcium: they also showed experimentally that there was no decrease, but rather a slight increase of excretion into an isolated loop of large bowel, following administration of extract, so that it does not act by hindering excretion, nor increasing retention. Thus it was assumed that the source of the increased calcium was the body tissues, which rendered diffusible calcium.

Greenwald[25] from his experiments comes to the conclusion that the parathyroid controls the solution of calcium phosphate from bone and other body tissues and at the same time delays its precipitation. His experimental animals received practically no calcium, but the serum calcium increased, which must have been at the expense of certain tissues, and he concludes that this amount could only have come from bone as no other tissues could have supplied such an amount as he found from actual "balance" experiments to have been lost. His theory is that want of parathyroid leads to loss of substance keeping $Ca_3(PO_4)_2$ in solution, thus causing precipitation: excess of parathyroid causes excessive mobilisation of $Ca_3(PO_4)_2$ from bones and increase of calcium and phosphorus in blood, the latter being promptly excreted by the kidneys. In further experiments over a long period Greenwald[26] found increased calcium and phosphorus

excretion, most in urine, but also in faeces, the amount confirming his belief that the calcium must come from bone, though possibly indirectly through the soft tissues. Percival and Stewart[24] are of the opinion that the parathyroids control the amount of diffusible calcium by producing a substance to retain excess of $Ca_3 (PO_4)_2$ in the blood. The same authors state[27] that the increase in serum calcium caused by giving parathyroid extract is accompanied by absolute and relative increase in the diffusible calcium. On the other hand Moritz found no constant changes in hypercalcaemia in the proportion of diffusible and fixed calcium. In the hypocalcaemia due to parathyroidectomy he found a more rapid fall in diffusible than in fixed calcium. Salvesen and Linder[16] came to the same conclusion by different methods.

The chief functions of calcium in the body are:-

1. Necessary for clotting of blood.
2. Essential for controlling neuro-muscular apparatus, the want of it causing hyper-excitability.
3. Essential for proper contraction of heart muscle.
4. Helps in maintaining ionic balance of blood

   $\frac{Na + k}{Mg + Ca}$ = constant (De Wesselow (Blood Chemistry)
5. Helps in maintaining pH of blood at proper level.
6. Ionic calcium along with (PO_4) radicle and $Ca_3 (PO_4)_2$ maintained in equilibrum in

blood by parathyroid hormone.

7. Supply of calcium for bony growth and maintenance .

There are thus obviously several factors co-ordinating in the control of the body calcium as reflected in the serum calcium: the availability of ingested calcium; the ability of the body to store and retain it; the reaction of the tissues and the proportion of the other basic and acid ions: the absorption of calcium has also been shown to be controlled by the presence or absence of vitamin D; lastly, as has been demonstrated here, the parathyroid hormone. That there is a delicate balance amongst these factors, is undoubted, and of them the most important controlling factor is the parathyroid. This balance is maintained with wonderful constancy, but in some diseases there is a fairly constant variation, as in the hypocalcaemia of certain tetanies (chiefly of parathyroidectomy) in acidoses of nephritis, and sometimes in rickets: all these have serious constitutional symptoms. On the other hand, in diseases where a hypercalcaemia has been found, such as osteitis fibrosa and chronic arthritis there are mostly local symptoms. Of the diseases mentioned the serum calcium can be controlled properly by parathyroid hormone only in tetany of parathyroid deficiency, so that there would appear to be other factors at work in the other diseases which cannot wholly be controlled by regulating the amount of parathyroid hormone in the blood.

Thus, in considering any change in the serum calcium in chronic arthritis, the etiological factor must be kept in mind and its bearing on the serum calcium given due consideration. From what has been said any error in calcium metabolism must be looked for in one or several of the following quarters:-

1. There may be an inability on the part of the body to assimilate calcium.

2. There may be a chronic acidosis calling upon the bases of the body to maintain the pH at normal level, which may in turn cause excessive excretion. If there is not enough available calcium in the tissue fluids, then the bony tissues might be called upon to supply the want.

3. A primary or secondary hyper function of the parathyroid glands; this action has not been fully studied nor is there any known pathological entity which has been shown to be due to it.

With these points in view the pathology and biochemistry of rheumatoid arthritis and osteo-arthritis will be considered in a later part of this thesis. It has to be borne in mind, however, that, no matter what is the value of a serum calcium reading, it bears no indication of the proportion of diffusible to fixed calcium, nor is it any indication of the amount of ionised calcium. Thus an abnormal serum calcium may have normal proportions of the different types of calcium, but, on the other hand there may be great relative variations of these forms, whose separate functions are at present little understood; hence the upset of the normal ratio amongst these factors

may in itself have profound pathological results without there being any marked deviation from the normal serum calcium. It is known, however, regarding these forms of calcium that they have a mutual equilibrium which, if one is altered materially, is maintained by a readjustment of the whole system to regain the normal balance.

Methods of Estimating Serum Calcium.

The reasons for taking serum calcium as an index of the calcium content of the blood have already been discussed. The older methods of ashing the serum and estimating the calcium gravimetrically have been superseded by those whose principle lies in precipitating and separating the calcium as oxalate and titrating against potassium permanganate of known strength. Another method is that of Vines[30] who claims for it simplicity and a minimum required of blood. It acts by recalcifying oxalated blood by addition of material to be tested and comparison of the action of the latter with that of calcium chloride solutions of known strength in causing clotting.

The two best known methods are those of Kramer and Tisdall and of Clark and Collip. In the former[31] 1-2c.cs serum are added to a graduated 15c.c. centrifuge tube, 1c.c. saturated ammonium oxalate is added and mixed and the whole allowed to stand for half an hour.

The volume is made up to 6c.cs with distilled water and again mixed, then centrifuged for 10 minutes, when the super-

natant fluid is syphoned off. 4c,cs 2% NH_4 OH are added and centrifuged for 5 minutes: this process is repeated twice, the supernatant fluid being syphoned off each time. The final residue is dissolved in approximately normal H_2SO_4 heated to about 70°C in a water-bath and titrated against $^N/_{100}$ $K_2Mn_2O_8$ (fresh) from a micro burette. This $^N/_{100}$ $K_2Mn_2O_8$ should be standardised against $^N/_{100}$ sodium oxalate. The amount of permanganate required, less that required for a blank experiment multiplied by 5 or 10 as 1 or 2c.cs serum were used gives the number of mgs calcium per 100 c cs. serum.

Tisdall[32] later modified this method by adding at first 2c.cs serum, 2c.cs distilled water, 1c.c saturated ammonium oxalate, and commencing centrifuging after half an hour, and completing as before.

Clark and Collip[33] in modifying Tisdall's process add 2c.cs serum, 2c.cs distilled water, and 1cc 4% ammonium oxalate to graduated 15c.cs centrifugal tube: allow to stand for 30 minutes and centrifuge for 5 minutes, the supernatant fluid being decanted and the tube inverted and drained over blotting paper for 5 minutes. The tube is now washed down with 3c.cs 2% NH_4OH, when it is again centrifuged for five minutes and drained. The precipitate is dissolved in 2c.cs normal H_2SO_4 the tube placed on a water-bath at about 70°C and the contents when dissolved titrated to a definite pink colour persisting for one minute with $^N/_{100}$ $K_2Mn_2O_8$. The calculation is as

as before. The advantage of this method lies in the draining, as only about 0·02 c.cs mother liquor is left as compared with 0·1 cc if not drained. Thus in this washing there remains ammonium oxalate equivalent to 0·2% of calcium present in 2c.cs serum (·02 cc = 0·2% of 5c.cs mixture containing 2c.cs serum). This however is balanced by the slight loss of calcium oxalate owing to its very slight solubility, which is stated by Clark and Collip to be reduced by oxalate ions already present in solution. The $^{N}/_{100}$ $K_2Mn_2O_8$; is also standardised against $^{N}/_{100}$ $Na_2C_2O_4$; it is kept as $^{N}/_{10}$ solution and diluted with distilled water to $^{N}/_{100}$ as required.

Calculation

The combining weight of calcium is 40 and it is divalent and so equivalent to 2 atoms of hydrogen. Hence 1 litre of $^{N}/_{1}$ $K_2Mn_2O_8$ is equivalent to 20gms calcium, that is to say 1 c.c. $^{N}/_{100}$ $K_2Mn_2O_8$ is equivalent to 0·2 mg calcium. Therefore if x c.cs $^{N}/_{100}$ $K_2Mn_2O_8$ are required to titrate calcium in 2c.cs serum Then there are 50 x o·2 x x mg calcium in 100 c.cs serum or, when due allowance is made for the amount of potassium permanganate required to give coloration in a calcium free experiment then 50 x $0^2$2 x (x - blank) is number of mgs calcium in 100c.cs serum, or, more simply, ten times (x - blank.)

The method is used in the present series of cases was that of Clark and Collip.

In addition to the facts already noted regarding this

method, special care was taken to have all the re-agents calcium free, making them up with distilled water: in the same way needle, syringe, and test tube were washed with distilled water and dried before use. The blood was allowed to stand for 8-12 hours and the clear serum decanted ready for estimation. About 10ccs of blood were withdrawn from the basilic vein, this giving ample serum for a repeat estimation if necessary.

As already stated, owing to the slight variation in the reports of individual observers using different techniques, a separate series of presumably normal adults was examined for serum calcium. These included a number of subjects of ages corresponding to the elderly patients of osteo-arthritis, so as to eliminate any possibilty of confusion with arterio sclerosis in which a rise of serum calcium has been reported.

Examples of the normal serum calcium as reported by various observers are:-

	Mg per 100 ccs.
Myers[34]	10·0
Salvesen & Linder[16]	10·1
Kramer & Tisdall[31]	10·0
Pericyal & Stewart[10]	9·6
Vines[30]	10·7
Brockbank[35]	10·1

The results obtained are given in detail with the other results later, but on the average agree with the above figures, having if anything a slightly wider range of value, possibly

owing to the varied type taken as a "normal" adult.

PATHOLOGY and BIOCHEMISTRY as applied to ETIOLOGY and TREATMENT.

In the introduction it was stated that the definition of arthritis deformans in Osler and McCrae's System of Medicine was taken as covering the cases examined: that does not mean however, that they are all included as one disease. McCrae himself only supports that theory by the statement that there are cases showing characteristics of both diseases involved - rheumatoid arthritis and osteo-arthritis - but gives no common etiology. The terminology of these diseases is an old vexing question and has undergone many changes since the days of early medicine, and still there exists great confusion.[36] The two groups examined have been separated into their appropriate categories from the following characters.

Rheumatoid Arthritis.

Polyarthritis, often beginning in the smaller joints, sometimes with temperature at onset or during acute exacerbations: the pathological changes are mostly periarticular and bilateral, and often accompanied by fibrositis; patients usually have a pale toxic look: the majority are females and the onset often in early adult life though a certain proportion begin at the menopause.

Osteo-arthritis.

Gradual onset later in life than in rheumatoid arthritis: a-febrile course: it may be confined to one large joint, or at most to several where distribution is asymmetrical: the essential joint changes are in the cartilage and bone.

Llewellyn Jones (1909) emphasised "the essential distinctness of the two diseases - rheumatoid and osteo-arthritis". Stockman[37] distinguishes between the two: rheumatoid arthritis is primarily a chronic infection of the white connective tissues of the body, but mostly affecting the joint fibrous tissues, while osteo arthritis he considers of unknown etiology and not amenable to treatment: in it the connective tissues are not involved. This division of these diseases is the commonly accepted one and was supported by Rolleston.[38]

Joint Pathology.

In two such widely differing types of joint condition a separate brief description of each may be given.

Rheumatoid Arthritis.

Unless where there is an acute onset the joints gradually swell and give the fingers, which are usually first involved, their characteristic fusiform shape. The swelling is soft with absent or negligible effusion, the initial change being in the white connective tissues and the consequent affection of the synovial membrane causing it to become reddened, thickened, and inflamed. In the later stages the bone becomes

locally atrophied, either owing to the disease itself or to disuse, while all the fibrous tissues round the joint become thickened and fibrosed, which, with the additional important factor of contractures of wasted muscles, causes the typical joint deformities. The articular cartilages may roughen and become worn and atrophied till the bone is laid bare, when, aided by the fibrous ankylosis of the capsule, there may take place bony ankylosis. The bones, the changes in which are the most important from the point of view of calcium metabolism, become, aided by disuse, more atrophic than before: the trabeculæ of the spongy bone become thinner and fewer and more easily penetrated by X rays: in a typical example examined by Stockman, the dried atrophied metacarpals were found to have a specific gravity of 0·562 as compared with the normal of about 0·875

Osteo Arthritis.

The first change is a degeneration of the joint cartilage, which is usually accompanied by fibrous degeneration of the under-lying bone. The cartilaginous matrix is fibrillated, with active cell proliferation going on: the articular cartilages are dulled in appearance and little swellings, appear on the surface and may ulcerate from pressure: the swellings appearing at the periphery proliferate, as there is no pressure, and become ossified, forming osteophytes giving rise to the characteristic lipping of joint edges and to grating upon movement. In the centre of the joint the cartilage is worn

away till hard eburnated bone is laid bare. Along with these changes atrophy of the underlying bone takes place, the bony trabeculae being changed into fibrous tissue.[37] The final result is empty spaces lined with fine fibrous tissue: while this is taking place new bone is laid down at the joint edge. Ankylosis, fibrous or bony, never takes place, nor does the synovial membrane form adhesions, but there may be enough deposition of bone in the joint structures to cause fixation.

It is thus seen that the two types of arthritis differ widely in pathology except in that there is rarefaction of bone in the one and fibrosis in the other, each involving a loss of calcium from its substance to be used elsewhere for some unusual purpose: possibly in osteo arthritis to be deposited as osteophytic outgrowths.

The villous type of arthritis, of which there is one clinical example in the series under review, may be taken as a form of rheumatoid arthritis with excessive proliferation of the synovial membrane, though several observers have attempted to show that it is due to a specific organism.[37]

Biochemical Changes.

Investigations along these paths have greatly increased of recent years, and as will be shown, again demonstrate dissimilarity between the two diseases, though in some findings they do resemble each other.

Quoting from the literature on the subject and assembled

under the appropriate headings the chief data are as follow

Basal Metabolism. In 400 cases Pemberton[39] found that in 20% of these (undifferentiated) the basal metabolic rate was definitely lowered, the remaining 80% being normal, none over normal.

Pemberton and others[40] in their series found little alteration, but where there was any change then it was to lower metabolism.

Swain and Spear[41] found that in definitely infective (focal sepsis) type about 20% were slightly over normal. In "atrophic" (presumably rheumatoid) type 17% were slightly lowered: in hypertrophic (osteo-arthritis) about 30% were lowered: it is difficult to estimate the definite proportions for these figures, owing to the nomenclature used.

Blood pH. In 178 cases examined by Race[36] this was found normal, showing no uncompensated acidosis nor alkalosis. Pemberton[39] found the same to be the case.

Serum Calcium. Mark[6] found in 3 cases of "arthritis deformans" the following values - 20·35, 18·5 and 27·4 mg Ca per 100 ccs, while in a single case of "rheumatic arthritis" he found 10·95 mg Ca per 100 ccs.

Pemberton[39] found the blood calcium in fasting conditions to be within normal limits, but did not determine the serum calcium, so that there is room for discrepancy.

McMillan[36] found normal serum calcium in osteo arthritis and fibrositis.

Weil and Guillaumin[8] in a series of 11 cases mostly coming under the heading of "rheumatisme chronique ankylosant generalisé" found an average reading of 14·2 mg Ca per 100 ccs the values ranging from 17.8 to 11.1 mg.

Horrowitz[9] found a raised serum calcium in five out of fourteen cases of "arthritis deformans" while the others were about the upper border or slightly over normal.

Watchorn[7] in a series of five cases of fibrositis or rheumatoid arthritis or both, found one case of rheumatoid arthritis normal: one 12.11 mg ca per 100 c.cs, two cases of combined rheumatoid arthritis and fibrositis 11.72 and 12.7, and one case of fibrositis 14·29. This combination is of interest in view of Stockman's description of the pathology of rheumatoid arthritis.

Stewart and Percival[10] found normal serum calcium in four cases of rheumatoid arthritis.

Uric Acid.

This was found to be increased in the blood in 69% of cases of osteo arthritis by Race,[36] while Glover[36] reports a similar rise in eight out of fifteen cases of rheumatoid arthritis.

Creatin. Pemberton[39] found an extra high blood creatin in 50% of 40 cases (type unspecified) examined for this. He also found a clinical improvement coincident with a return of the blood creatin to the normal value.

Urinary output.

The urinary excretion of calcium is increased 31-64%.[36] in the same report there was an increase in the output of magnesium and chloride. Cawadias[42] found the sulphur excretion increased in about the same proportion as the calcium is above. He surmised this to be due to deficient oxidation, but later changed his opinion to saying[43] that sulphur oxidation was normal, but that there was an increased katabolism of sulphur or a decreased thiopexy. The increased sulphur excretion was confirmed by Pemberton.[40]

Sugar Tolerance.

Pemberton[39] found a lowered sugar tolerance, roughly proportional to the activity of the arthritis. He noted a return towards normal in recovery especially after removal of foci of infection. These results are confirmed by Pringle and Miller.[44]

Pemberton[40] found the glucose tolerance impaired and the blood sugar curves to resemble those of true diabetics.

The existence of lowered sugar tolerance in chronic sepsis and its return to normal upon removal of infective focus as in similar treatment of rheumatoid arthritis has been demonstrated.[45] Thus the lowered sugar tolerance is not the cause of rheumatoid arthritis, but is secondary to the causal factors of the latter. Possibly the toxic element is acting by altering the endocrine balance.

Achlorhydria.

Hurst[46] reviewing the incidence of this factor in rheumatoid arthritis quotes Faber's statistics of fifteen cases of achlorhydria in 65 cases of arthritis, and lays emphasis on the fact that in cases which do not recover when focal sepsis is removed 40% have congenital achlorhydria, and stresses the fact that in these cases it may be a predisposing cause.

Pemberton[40] in his series found 65% with hypochlorhydria and 50% with achlorhydria (rheumatoid arthritis)

Douthwaite[47] found hypochlorhydria in only a few cases of his series of rheumatoid arthritis: there was marked gastric atony and slowness in emptying of the stomach.

Hepatic Function.

Pemberton[40] found the hepatic efficiency to be doubtful, and the blood laevulose tolerance curves showed a decided abnormality in his series.

Leucocytosis.

Munro[48] in 171 cases of rheumatoid arthritis gives the following results - 57% leucocytosis of 9,000 - 20,000 with relative lymphocytosis and 21% leucopenia; this suggests infective origin. He reports a still larger proportion of cases of osteo-arthritis (24 out of 25) in which there is a definite leucocytosis.

Red Cells.

In rheumatoid arthritis there is sometimes a slight anaemia, usually much less than the appearance of the patient

would suggest. It has been suggested that the half million fewer red corpuscles in women than in men accounts for the high female incidence: but why should this apply only to rheumatoid arthritis?

In osteo-arthritis the red count is usually normal. With the pathological and biochemical findings before us it is possible to discuss briefly the etiological factors with a view to treatment, keeping in mind the while the abnormal serum calcium which has been found by several observers. The generally accepted cause, as regards rheumatoid arthritis by almost all, and as regards osteo arthritis by some, is chronic toxic absorption from some local septic focus. The relationship of focal sepsis to rheumatoid arthritis is fully discussed by Rolleston.[38] Dental sepsis, chronic sepsis of tonsils, antral post nasal catarrh, in the upper respiratory tract are all recognised causes; alimentary toxaemia has been blamed, and in this connection the achlorhydria which is present may favour intestinal intoxication, but the fact that it is only present in a proportion of cases, seems to indicate that it is not a primary cause, though possibly a predisposing one: on this point it is of interest that Pemberton,[40] who found low gastric HCl fairly common in his series of cases, also found a questionable hepatic efficiency, which he suggests may be due to a toxic absorption to the body in general through the portal system. Infections of the urogenital tracts in both sexes have been found to be causal-agents, especially cervical in-

fections of the uterus.

The incidence of pulmonary tuberculosis, as favoured in France varies in different series of cases and may be taken, when found, as being a coincident infection. The lowered serum calcium often found in tuberculosis is opposed to the frequently raised serum calcium in rheumatoid arthritis.

The theory that chronic arthritis is directly due to an endocrine imbalance has strong advocates, but how much of this possible imbalance is primary and how much secondary to toxaemia it is difficult to say, but with all facts considered, it is most likely secondary. Goldthwaite has divided individuals into a slender "carnivorous" or hyperthyroid type, liable to suffer from rheumatoid arthritis, and a robust "herbivorous" or hypothroid type, liable to osteo-arthritis, and benefitted by the giving of thyroid. There has also been noted a corresponding geographical distribution of endemic goitre (hypothyroidism) and of rheumatoid arthritis.[49]

Vines[13] gives his reasons for the antagonistic action of thyroid and parathyroid, so that if there is hypothyroidism, the action of the parathyroids will be increased. He also discusses the action of the parathyroids as detoxicating. organs as well as calcium regulators. He considers that in infective diseases that the action of the toxins is to subdue the parathyroids, but it is quite conceivable that a long continued intoxication will stimulate to hyperfunction

the glands so irritated. Thus he quotes Brown and Pearce (p89) who consider that in infections both thyroid and parathyroid overact, both presenting signs of overactivity in which one or the other may gain the upper hand. In Watchorn's series of cases of chronic sepsis[7] mostly in antral or nasal origin the raised serum calcium favours an over-action of the parathyroids.

There is no record as far as I can find of the guanidin of the blood in cases of this disease: taking a line through the raising of the guanidin content when there is a hypo-calcaemia, one might expect a lowered amount of guanidin in the blood in hyper-calcaemia. The blood creatin has been found to be increased in rheumatoid arthritis[39] (Pemberton) with a fall corresponding to clinical inprovement. Paton[20] has shown that guanidin may be detoxicated by conversion to creatin, so that this raises the question of whether in rheumatoid arthritis when a hyper calcaemia occurs the guanidin is lowered correspondingly by its conversion into creatin, with a lessening of the amount converted as the clinical state returns to normal.

Cumberbatch and Robinson[50] describe cases of arthritis occurring at either end of menstrual life when no infection could be traced: these they think possibly due to a deficiency of ovarian hormone setting up endocrine imbalance.

On the whole the evidence given and the conclusions

most widely accepted are that rheumatoid arthritis at least, if not osteo arthritis, is generally of the nature of a chronic toxaemia (not a joint infection) which acts on the joints, possibly due to their hypersensitiveness from previous disease or injury, and at the same time accompanied by general metabolic changes which are not at present too well understood: there is also the effect of the toxaemia on the endocrine system, through whose effects the upset of metabolism may be caused, by the dysfunction chiefly of the parathyroids, the thyroid, and possibly the pancreas and the ovaries in some cases.

Barr[51] suggested that rheumatoid arthritis is due to a mild acidosis of toxic origin and that to compensate this additional base in the form of calcium is mobilised from the bones. The chemical findings are in keeping with a mild compensated acidosis: both Ca and (SO_4) are increased in the urinary output, while there is retention of chloride in about half the cases by the gastric mucosa, which may possibly call for still more calcium. This excessive requirement of calcium might lead to the raising of the serum calcium, in which case the rise would occur in the diffusible portion and leave the fixed part unaffected: this increased call upon calcium supply might be made good from increased absorption or by increased mobilisation from bones; but certainly not by increased retention, as the output has been shown to be increased. In any theory of acidosis there arises the ques-

tion - why is compensation not brought about in the usual way by eliminating CO_2 by lungs and (PO_4) by the kidneys? The lowered basal metabolism might to some extent be the cause of this. Pemberton[40] has shown that there is no renal inefficiency so that there is presumably no retention of phosphates. The fact that (SO_4) excretion is increased and that sulphur metabolism is upset points to the possibility of the acidosis being due to an increase in the (SO_4) radicle. It has also been experimentally shown by King & Goto[52] that bone may be decalcified by prolonged administration of acid, by using up the basic radicle. The acidosis of rheumatoid arthritis is not due to an excessive protein katabolism as the urea output is not disturbed to any extent,[36] but may be considered to be due to the chronic toxaemia.

In support of the toxic etiology (and this holds equally in rheumatoid arthritis and osteo arthritis) is the fact that, generally speaking, there is a leucocytosis or leucopenia in rheumatoid arthritis, and practically always a leucocytosis in osteo-arthritis. If the hypercalcaemia when present in chronic arthritis, is due directly to the infection, then there should be a fairly well marked relationship between the calcium and the leucocytosis or leucopenia: in a number of cases in the present series a leucocyte count was done and a comparison made with the serum calcium: the results are given in the appropriate

section.

Crowe[53] believes both diseases to be due to direct infection and from his work and successful results concludes definitely that osteo arthritis and non-articular rheumatism are due to streptococci of numerous strains, while rheumatoid arthritis is due to staphylococci: mixed types also exist. He has isolated a micrococcus albus or deformans, cultivated it from the joints, and obtained agglutinin reactions with the blood of patients: he has also isolated it from the urine.

The similarity of the blood sugar curves in rheumatoid arthritis and diabetes suggests a toxaemia affecting the pancreas as this is a known cause of glycosuria: this is one fact against a hyperparathyroidism, as the parathyroids are similar in action to the pancreas in as far as they are antagonistic to the thyroid and other "sympathetic" glands.

To sum up - at present the following facts have been garnered: rheumatoid arthritis is of infective origin - a toxaemia, which acts both on joints, causing the typical clinical picture, and on general metabolism, causing an imbalance of the endocrine system, and possibly a mild chronic acidosis, which in itself may cause a decalcification of the skeletal structures: the serum calcium is often raised, either by compensating the acidosis present, or from hyperparathyroidism due to compensatory mobilising of calcium or

to stimulation by the chronic toxic irritation. The fact that possibly some of the normal amount of guanidin present in the blood has been changed to creatin to give a raised blood creatin, would, if demonstrated, support in theory at least, a hyperparathryoidism: it would therefore be interesting to know the guanidin content of the blood in this disease.

Osteo arthritis is said to belong to the hypothyroid type, but beyond that not much has been observed in addition to the bone pathology, a definite leucocytosis, a raised blood uric acid, in some cases a lowered basal metabolism, and the hypercalcaemia found by Mark and Horrowitz. The disease is mostly described as a degenerative change owing to its liability to occur in elderly patients and in joints exposed to trauma, though toxic infection is supported by some.

Taking into consideration pathology and the blood condition it will be noticed that there is a certain resemblance between osteo arthritis and osteitis fibrosa. In both there is a local replacement of the bony trabeculae by fibrous tissue, though at different situations and definitely encysted in osteitis fibrosa: in both there is a raised serum calcium. Lambie[4] describes fully a case of osteitis fibrosa, which he suggests is due to abnormal functioning of the parathyroids, and in which there was hyperplasia of these glands; 17 mg calcium per 100 c.cs serum: otherwise the blood was fairly

normal; the urinary output of calcium was normal, but the faecal output was raised, resulting in a negative calcium balance, such as was found in osteo-arthritis by Mark.[6]

Hoffheinz[54] gives a summary of 45 cases of enlargement of the parathyroids; of these 27 cases were associated with bone disease, including 17 of osteitis fibrosa, 8 of osteo malacia, and 2 of rickets, but none of osteo arthritis nor rheumatoid arthritis; neither is there any record of osteo-arthritis and osteitis fibrosa occurring in the same individual, possibly owing to the essential difference that new bone is not laid down in osteitis fibrosa, while it is characteristic of osteo arthritis.

The morbid anatomy of the parathyroids has not been made a matter of routine examination, with the result that rarely have they been examined, and then only when abnormal size or some special clinical symptom called for further knowledge.

Few changes beyond hypertrophy - parenchymatous or glandular - and fatty degeneration in acute diseases have been recorded. Luce[55] found that rats fed on a diet deficient in calcium showed a consistent enlargement of the parathyroids due to hyperplasia and not to hypertrophy of cells: evidently the hyperplasia was compensatory, to mobilise calcium from the bones; it would be of interest to know the serum calcium in such cases. De Wesselow[56] noted a case considered clinically to be hyperplasia of the parathyroids in which there was hyper-

calcaemia.

As far as I can find there is no record of examination of the parathyroids post-mortem in osteo arthritis or rheumatoid arthritis; it would be essential to know the results of some such examinations to throw any further light on what at present can at best be only a hypothesis, namely, that some at least of the symptoms and findings of rheumatoid arthritis and osteo arthritis are caused by hyper-activity of the parathyroids due either to the toxaemia or to compensation calls on the calcium of the bones, to make good requirements in the general tissue fluids.

In this respect the coincidence of chronic sepsis, fibrositis and rheumatoid arthritis with a hypercalcaemia in Watchorn's cases[7] is of interest.

Similarity between osteo arthritis and gout has been suggested by some, owing to the fact that in both diseases there is a laying down of calcareous deposit, an increased uric acid and calcium in the blood. Coates and Raiment[5] found an average serum calcium of 18.87 in six gouty persons, while Horrowitz[9] found a hypercalcaemia in acute gout but not in the resting stage. The parathyroids have not been found abnormal in gout.

While there is no disease entity at present which is considered to be due to hyperparathyroidism, in the same way as Grave's disease is due to hyperthyroidism, yet the possibility

that this underlies, in part at least, the etiology of some bone diseases must be borne in mind. Following the conclusions of Stewart and Percival[24] and Greenwald[26] that prolonged administration of parathyroid hormone in normal animals causes a drain on the osseous calcium, then pathological hyperparathyroidism may cause a similar condition with rarefaction of bones. This action of the parathyroids is confirmed by Lehman and Col[57] who found from experiments on rats that there is a tendency to delay in healing when parathyroid is administered in fractures, and that when healed the strength of a naturally healed control is greater then that of one treated with parathyroid.

Hence the fact that rarefaction of bones may be caused by continued hyperparathyroidism is a possibility, and it is interesting and important to note in such cases any other evidence of excessive functioning of the parathyroids.

In both osteo arthritis and rheumatoid arthritis rarefaction of bone occurs, though it is said by some to be secondary in the latter; in both there has been noted by several observers a hypercalcaemia.

The findings in experimental hypercalcaemia induced by parathyroid administration, as noted by Collip[58] in his original experiments are applicable to dogs which are very sensitive to parathyroid hormone, and give rise to a train of events far too acute to compare with the chronicity of the diseases under

review; possibly experiments with smaller dosage on more immune animals would give more information if spread over a long time; in these one could note if there were any bony or joint changes typical of arthritis especially in any joints which had been the victims of previous trauma or joint disease. The symptoms found by Collip were; hypercalcaemia: vomiting and diarrhoea with melaena and depression: a rise in the blood phosphates: decreased blood volume with decreased clotting time: blood urea increased: stoppage of kidney function: all symptoms pointing to an acute acidosis with retention of phosphates which does not occur in chronic arthritis.

Thus the only points of similarity between chronic arthritis and hyperparathyroidism that have been found are the hypercalcaemia, the rarefaction or decalcification of the bones, and an acidosis, mild and compensated in the former, acute and uncompensated as has been produced in the latter in dogs. It is to be noted that Lambie, who suggests causal relationship between hyperparathyroidism and osteitis fibrosa, found no signs of an acute acidosis in the blood in that disease. In addition to these facts Vines[13] found a marked leucocytosis following administration of parathyroid: this occurs also in both rheumatoid arthritis and osteo arthritis. Taking the lowered basal metabolism of chronic arthritis into consideration, M^{c}Callum and Voegtlin[18] found that the loss of

parathyroids caused increased metabolism, from which they concluded that the parathyroids lessened metabolism: this would constitute another point of similarity.

Another disease in which it has been suggested that the parathyroids overact is myositis ossificans. In a case described by Healey[59] myositis ossificans and spondylitis deformans (osteo arthritis of the vertebral column) existed in the same patient; the serum calcium, which has been said to be raised in this disease, he found to be normal. In a case of my own of traumatic myositis ossificans, the serum calcium was about the upper border of normal, namely 11.2 mg per 100 c.cs.

The connection between the parathyroids and these bony diseases must remain a hypothesis until the pathology of the glands in connection with the latter has been studied, and until cause and relationship of these two can be proved experimentally. If the parathyroids do overact, then it is either from stimulation by the toxaemia or from the necessity of mobilising calcium to maintain the physiological balance of the tissue fluids, as for example in the acidosis of rheumatoid arthritis, or, if for any reason a greater proportion of the blood calcium became fixed than is normally the case.

The desirability of applying calcium therapy depends on what causes the hypercalcaemia; if there is a lowering of the free calcium or a call for more of it for any reason, then the

administration of calcium orally, or preferably, intravenously or intramuscularly would benefit the condition. In this connection it should be noted that in a recent paper Loew[60] states that a lack of lime in certain organs is sometimes coincident with a hypercalcaemia, as it is by the blood that the calcium is transferred from the bones to the part deficient in lime. From this he infers that in certain diseases showing a high serum calcium the administration of calcium is indicated and has good therapeutic results: for this purpose he advises the use of the double salt of calcium and sodium lactate since it favours retention, owing to its oxidation to the carbonate. Rheumatoid arthritis and osteo arthritis may possibly come into this category, especially if the hypercalcaemia is due to the compensation of acidosis.

The administration of parathyroid as suggested by Vines[13] would further increase the rarefaction of the already affected bone and possibly have no effect on the pathological deposits: at the same time it would increase the already present hypercalcaemia. The giving of parathyroid as suggested by Barr[51] to cause calcium retention and so stop decalcification has been shown to be of no practical use by Stewart and Percival[24] who showed that the administration of parathyroid extract caused, if anything, a slight increase in the calcium output.

If, on the other hand, the hypercalcaemia is directly due to hyperparathyroidism, whatever its cause, then the disease

takes a similar place to hyperthyroidism and measures to depress the hormonic secretion are called for. Rest, of course, is the first essential: then benefit would accrue from use of thyroid extract, by suppressing the parathyroid action, and from the giving of iodine, as in the iodine, guaiacol and camphor injections, where the iodine stimulates the thyroid.

It is questionable if the witholding of calcium in the food will help. Mark[6] found that by this means he could reduce the serum calcium by an appreciable amount, but not nearly to normal. Stewart and Percival[24] found that in the hypercalcaemia of hyperparathyroidism (artifically induced) the intravenous injection of $NaHCO_3$ brought the blood calcium to normal. This treatment was not tried in the present series, but Mark[6] by giving alkali orally found a slight lowering of the blood calcium. He found a similar effect from the administration of HCl orally, but this was followed by a rise of serum calcium.

In their observations on the serum calcium Stewart and Percival[10] showed that in a case of rheumatoid arthritis of normal serum calcium, protein shock treatment caused a distinct fall for some time of the serum calcium, in spite of the coincident administration of parathyroid extract: thus this type of treatment would seem to be of benefit in a hypercalcaemic arthritis.

Another factor upon which a great deal regarding both etiology and treatment depends and upon which a great deal of

work remains to be done, is which form or forms of the serum calcium is altered in the diseases in question: and whether the serum calcium is affected as a whole when its value becomes pathological in any disease.

The points of similarity between osteo arthritis and rheumatoid arthritis, osteitis fibrosa and hyperparathyroidism (induced) are briefly shown in tabular form.

TABLE 1.

Disease	Rheumatoid arthritis	Osteo-arthritis	Osteitis fibrosa	Hyper-parathyroidism
Bone affection	Rarefaction of affected bones.	Fibrosis & rarefaction plus osteophytes in affected parts,	Fibrosis (encysted) of bones.	Decalcification. ? rarefaction.
Acidosis	Mild chronic.	Has not been demonstrated.	Has not been demonstrated.	Present: varies with dosage and animal.
Serum Calcium	Often increased	Increased.	Increased.	Increased.
Calcium excretion.	Increased	Normal.	Increased.	Increased.
Calcium balance.	?	Negative.	Negative.	Negative.

Table 1 contd.

Disease	Rheumatoid arthritis	Osteo arthritis	Osteitis fibrosa	Hyper-para-thyroidism
Leucocyte count.	Leucocytos-is or leuco-penia.	Leucocyto-sis.	No ob-serva-tion.	Leucocytosis.
Basal meta-bolism.	Sometimes lowered.	Sometimes lowered.	No ob-serva-tion.	Probably lowered.
Thyroid Function.	Question-able whether af-flicted & in what way.	Decreas-ed.	No ob-serva-tion.	Decreased.

In summing up regarding treatment, parathyroid administration would seem to be contra-indicated on account of the rarefaction of bone. The giving of calcium is a point still to be settled, according as whether the hypercalcaemia is compensatory or due to hyperparathyroidism. Additional treatment which may be attempted along with routine therapy includes thyroid extract, iodine, intravenous alkalis, the giving of a calcium deficient diet, and protein shock therapy: all these are with a view to causing a return of the serum calcium to normal.

Clinical Reports and Results of Treatment.

The technique of the examination of the blood serum for calcium has already been described. The following is a

table of the normals and controls estimated, with a brief clinical note of each regarding blood pressure, evidence of focal sepsis, age, and any other clinical abnormality of special consequence.

TABLE 11.

Name	Age	Blood pressure mm.Hg.	Focal Sepsis	Clinical Notes	Serum calcium mg. per 100c.cs.
1.Campbell	48	Normal.	Slight pyorrhoea.	Vertigo ? Endarteritis obliticans Wassermann negative Urine normal.	9.2.
2.Self	27	125	None.	Normal.	10.6
3.Phillips	21	120	Slight pharyngitis	Convalescent encephalitis lethargica. Athletic type normal otherwise.	11.2
4.Cosgrove	34	Normal	None	Peripheral neuritis Wassermann negative Urine normal.Kidney normal.	10.3

Table 11 contd.

Name	Age	Blood Pressure mm.Hg.	Focal sepsis	Clinical notes	Serum calcium mg.per 100c.cs.
5 Hamilton	53	135	None found at time of examination	Has twice had broncho pneumonia & pleurisy in two yrs. Wassermann positive.	10·2
6 Johnstone	56	140	carious teeth Xray shows no abscesses.	Trigeminal neuralgia tonsils & pharynx normal. Urine normal	10·7
7 Jameson	31	Normal	None	Normal	10·8
8 Brown	61	136	None	Arterio sclerosis.Urine normal. Otherwise normal.	11·1
9 Murray	62	210	None	Hyperpiesia arterio sclerosis slight: severe headaches	11·9

Table 11 contd.

Name	Age	Blood pressure mm.Hg.	Fosal sepsis	Clinical notes	Serum calcium mg.per 100c.cs.
10 Carey	26	Normal	None	Myositis ossificans (traumatic) following fall 9 months ago. Confirmed by Xray examination.	11·2
11 Robertson	28	Normal	None	Normal	9·8
12 Wilson	36	Normal	None	Normal: Female menses & no leucorrhoea.	10·0

The series examined were eleven males and one female, ranging from 26 to 62 years of age, and of the various types noted: the serum calcium values range from 9.2 to 11·9 mg calcium per 100 c.cs serum, the highest being in a case of hyperpiesia with moderate arterio sclerosis, but even that is not much above the accepted average of 9-11 mg. From the present figures and for the technique used in the estimation the normal for the purpose of this investigation was taken as

ranging from 9·2 - 11·2 mg calcium per 100 c.cs; due allowance should be made for any rise of blood pressure of marked extent. Of the controls several (Nos. 1-3-6) showed a possibility of septic foci but no hypercalcaemia. The case of myositis ossificans was included as normal.

One other case examined might be included in the series: it was a case of Paget's disease with typically curved tibiae and xray findings, accompanied by great general weakness, which eventually ended fatally: his serum calcium was found to be 9·2 mg per 100 c.cs serum.

Taking the cases which lie between 9·2 and 11·2 mg calcium per 100 c.cs serum, the average is found to be 10·35 mg calcium, which agrees well with other published series, though a little higher than the usual 10.0 mg.

Investigation of Cases.

Special attention was paid to:- History of progress, with duration of disease: any etiological factors: mode of onset: joints in which disease began, and if any spread, then to which points. Any signs of chronic sepsis anywhere e.g. nasopharynx, tonsils, teeth, chest, alimentary tract, genito-urinary tract etc., condition of circulatory system.

X Ray Photos were taken of the affected joints where possible for diagnosis or confirmation of clinical signs: in later cases of the series a leucocyte count was also taken. In all cases the serum calcium was estimated once at least, and sometimes

twice or oftener.

TABLE 111.

SERIES 1. RHEUMATOID ARTHRITIS.

Name	Age	Sex	Clinical Notes	Etiology	Calcium	Leucocytes	Degree
1 Lyon	65	Male	15 yrs duration: polyarticular: has resisted all treatment at home & in hospital during that time: ankylosis of knees.	ex-posure.	10.8	-	Severe
2 Lauchland	26	female	3 yrs duration: gradual onset: fingers, wrists & ankles. Bronchitis: leucorrhoea ? chronic appendicitis; cardiac irregularity.	Septic foci	12.6	8.960	Severe
3 Sloan	21	female	3 yrs duration: polyarticular, with marked limitation of movement of knees & wrists. Previous treatment by removal of teeth & protein shock: irregular mensturation & leucorrhoea.	Septic focus in teeth and possibly in uterus.	13.8	5.000	Severe

Table 111 contd.

Name	Age	Sex	Clinical Notes	Etiology	Calcium	Leucocytis	Degree
4 Green	70	Male	5 yrs duration: monarticular swelling fibrositis: atheroma & raised blood pressure. Farm labourer & has always been exposed to weather No septic foci found.	Exposure	10.8	-	Slight
5 Reid (1)	26	Female	20 months duration: slow onset: teeth removed: naso-pharyngeal catarrh. Periarticular swelling of hands, wrists & knees.	Septic	13.9	10.000	Severe
6 Spark	51	Male	10 yrs duration in wrists: pyorrhoea: auricular fibrillation. Rheumatic fever as a boy	Septic focus & ?Rheumatism	11.3	6.200	Slight
7 Hunter	67	Female	16 yrs duration very gradual onset; wrists, fingers & ankles. has also fibrositis & was once seen with auricular fibrillation following severe chill. No signs of septic focus	Menopause	10.9	8.650	Severe

Table 111 contd.

Name	Age	Sex	Clinical Notes	Etiology	Calcium	Leucocytes	Degree
8 Calderwood	27	Female	5 months duration:polyarticular; septic tonsils; trace of albumen in urine,but renal function normal.	Septic focus	13.7	9.480	Severe
9 Ferguson	48	Fe-	8 mths duration; both knees affected: synovial hypertrophy easily palpable. ? Villous arthritis.Achlorhydria. No septic focus.	Menopause	12.2		Slight
10 Noble	56	Fe-	Early arthritis of right wrist: slight periarticular swelling but no limitation of movement. No septic foci:but has had many recurrent attacks of influenza. Bottle washer.	?Menopause or exposure	10.3	-	Slight
11 McCutcheon	49	Male	History of trauma years previously to joints involved. Acute onset resembling rheumatic fever. Asthma & bronchitis for years. Teeth	Septic focus & old trauma	12.4	-	Severe but clear-up well

Table 111 contd.

Name	Age	Sex	Clinical Notes	Etiology	Calcium	Leucocytis	Degree
11 McCutcheon. contd:	49	male	septic & were removed. Both ankles, right wrist & left knee involved; was improving when died from pneumonia.	Septic etc.	12.4	-	Severe etc.
12 Calder	36	Female	6 yrs duration: multipara began following mild puerperal sepsis: knees, ankles & temporomandibular joints involved: was steadily getting worse.	Septic focus	12.1	8,460	Severe
13 Lamont	51	Female	2 yrs duration: knees, elbows & wrists involved with marked limitation of movement: leucorrhoea. Teeth already removed.	Septic or menopause.	11.3	7,120	Severe
14 Reid (2)	28	Female	Polyarticular arthritis: wrists, fingers & elbows: pyorrhoea & carious teeth: only seen once.	Septic focus	12.1	9,280	Moderately severe

This gives 14 cases, 10 in females and 4 in males giving percentages of 71·4 in females
28·6 in males.

Of the females only 4 or 28.6% were possibly due to menopause so that this does not account for the whole preponderance.

The average calcium value for the whole series is

12.0 mg Calcium per 100 c.cs serum.

In only one case was there albuminuria and in it the serum calcium was not different from the other cases: similarly, in the only case with a markedly raised blood pressure, there was no corresponding change in the serum calcium.

In two cases auricular fibrillation was noted.

From the table the following facts have been noted under the appropriate headings.

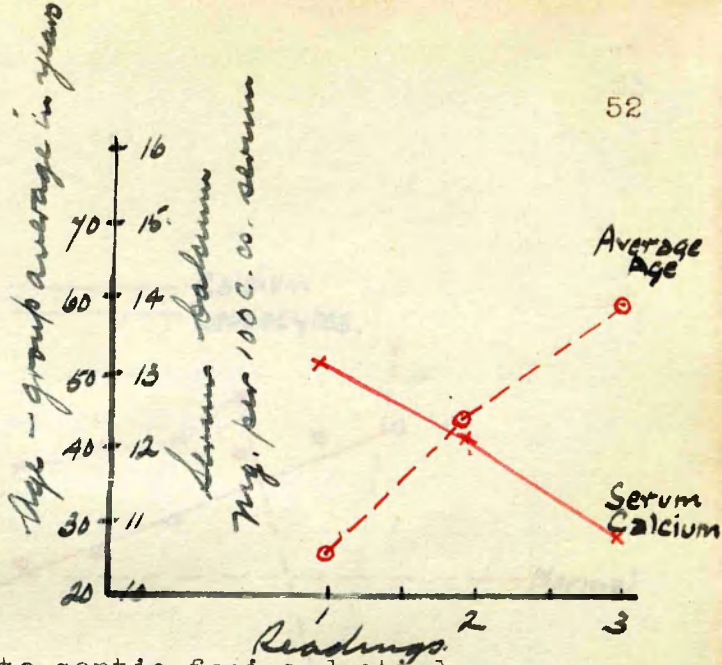
1. Relationship between Age and Serum Calcium. The cases were divided into three age groups;

(a) 21 - 35
(b) 36 - 50
(c) 51 - 67

the average for each group was calculated when it was found that as the age increased the serum calcium decreased, which is the opposite of what is believed to be the case in normal adults. The results are shown graphically in figure 1.

Figure 1.

Age	Calcium
21 - 35	13.2
36 - 50	12.2
51 - 67	10.9



11. Relationship of calcium to septic foci and etiology.

Type and number in each class		Calcium
Number of cases due to sepsis	9 or 64.3%	12.7
Number of cases due to menopause	4 or 28.6%	11.2
Number of cases due to exposure	3 or 21.4%	10.6

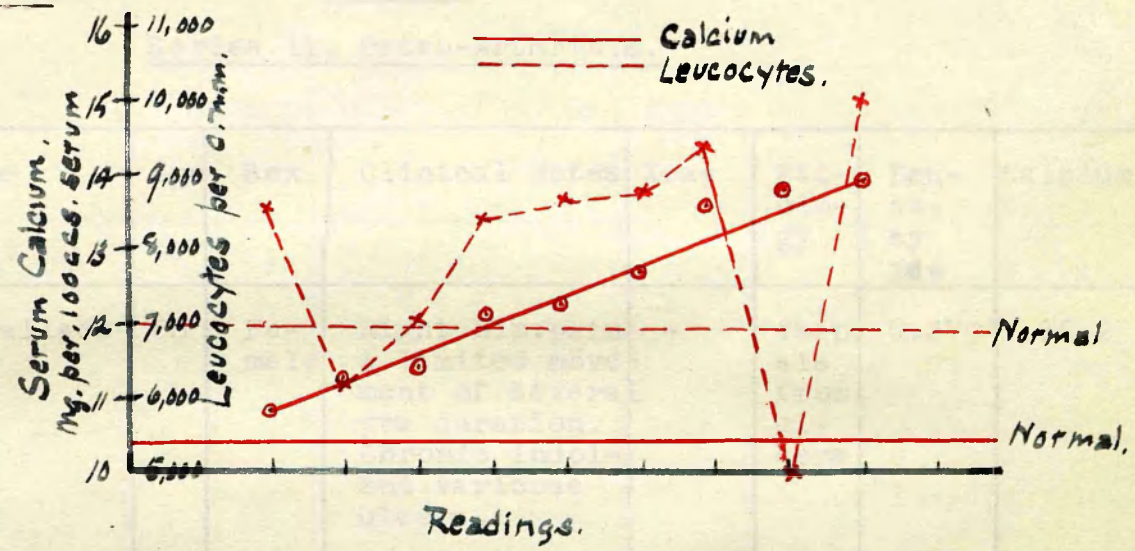
Thus it is seen that the average calcium value for cases due to the menopause or exposure falls within the normal limits though at the upper border. In those cases of septic origin the average is well over the normal figure. It is also seen that the fall in the serum calcium previously noted as the age of the patient rises is due to the fact that the cases occurring in this class are in the present series practically all due to menopause or exposure.

111. There is no relationship between the duration of the disease and the serum calcium.

IV. Relationship between Calcium and the Leucocyte count.

The figures for the serum calcium were taken in order from the lowest upwards and these and the corresponding leucocyte values charted and compared.

Figure 2.



While there is a general rise with the serum calcium yet there is no definite relationship.

V. Relationship between Calcium and the Severity of the disease

Ten cases were severe and crippling: their average serum calcium was 12.36 mg per 100 c.cs.

Four cases were slight or moderate i.e. did not absolutely incapacitate the patient. Their average serum calcium was 11.13 mg.per 100 c.cs.

Hence the serum calcium was higher in severe than in slight or moderate cases.

TABLE IV.

Series 11. Osteo-Arthritis.

Name	Age	Sex	Clinical Notes	Xray	Etiology	Leucocytes	Calcium
15 Wallace	63	Female	Right hip:pain & limited movement of several yrs duration. Chronic indolent varicose ulcers.	-	?sepsis from ulcers	9.370	12.2
16 McWilliams	58	Male	Pain & weakness in left side: 5 mths duration from first symptom poker spine.	Spondylitis cervical upper dorsal & lumbar vertebrae.	Nervous shock	7.470	17.7
17 Radcliffe	58	Male	Trauma year before:sciatica: no limitation of movement.	Osteo arthritis of hip.	? Injury	-	15.0
18 Hill	70	Male	5 yrs duration:stiffness & pain & limitation of movement in both elbows: increasing disability.Outdoor labourer.	Marked bony over growth round joint rarefaction of bones.	? Exposure.	8,420	16.1

Table IV contd.

Name	Age	Sex	Clinical Notes	Xray	Etiology	Leucocytis	Calcium
19 McKenzie	58	Female	2 yrs duration pain & stiffness in right knee: cardiac irregularity & tachycardia Hyperthyroid symptoms of long standing.	slight osteo arthritis & rare faction of bones.	-	-	15.2
20 Young	65	Male	Stiffness in hips. Recurrent fistula in ano: teeth bad b.p.230: no albuminuria. Hemiplegia with fatal termination.	-	? Sepsis	-	18.6
21 Campbell	78	Female	8 yrs duration knees semi-fixed but able to move about a little. Teeth bad: b.p. raised urine normal.	Osteo arth- of both knees.	-	-	15.9
22 Currie	67	Male	7 yrs duration: movements of hips practically nil; sciatic pain: gradually becoming worse.	Advanced osteo arthritis of both hips; rarefaction in bones.	-	-	15.2

Table IV contd.

Name	Age	Sex	Clinical Notes	X Ray	Etiology.	Leucocytis.	Calcium
23 Page	59	Male	Osteo arthritis of right knee of 3 yrs duration: arteriosclerosis b.p. 180	-	Exposure.	-	17.8
24 Morton	58	Female	Stiffness & pain in knee for a year Stout build & panniculitis.	Early osteo arthritis with rarefaction of bones	?Menopause	-	15.8
25 McCartney	54	Male	History of trauma: rapid-advancing osteo arthritis of rt hip:sciatic pain & shortening: septic teeth.	Advanced osteo arthritis.	Trauma & predisposition.	6.850	16.0
26 Cosgrove	60	Male	12 yrs duration began in knee: now in both knees,& shoulders,septic teeth labourer.	Osteo arthritis of knees cartilage partly destroyed.	?sepsis & exposure.	-	16.5

Table IV contd.

Name	Age	Sex	Clinical Notes	X ray	Etiology.	Leucocytis.	Calcium
27 Watson	63	Female	5 yrs gradually becoming worse:pain & limitation of movement in left hip:slight shortening of thigh.	Mushroomed head of femur: rarefaction of neck and shaft of femur	-	7,500	15.7
28 Hunter	72	Female	Pains & stiffness of back: tenderness over spine: clinical spondylitis.	nil	-	6,890	10.1
29 Breckenridge	56	Male	For 3 yrs had been becoming shortened in rt.leg but paid no attention to it.Pain in front of thigh:shortening of femur & bulging over trochanter.Limited movement.	Advanced osteo arthritis. joint line intact. Rarefaction of shaft of femur.	? Strain of work; joiner.	-	13.1

Table IV contd.

Name	Age	Sex	Clinical Notes	XRay	Etiology.	Leucocytis.	Calcium
30 Holmes	70	Male	Swelling, pain of elbows & limitation of movement. 4 yrs duration.	Confirms clinical diagnosis.	-	-	15.9
31 McCallum	57	Male	Pain & stiffness of left knee: lipping of ends of bones: grating on movement.	Osteo arthritis with rarefaction of bone.	-	8,190	15.6
32 Mason	46	Female	Fibrositis: stiff spine with tenderness over mid-line. Pain down arms, septic teeth, which have been removed with successful result.	Spondylitis upper dorsal vertebrae.	Sepsis	7,360	17.5
33 Fitchell	54	Male	Convalescent from cerebral thrombosis BP normal. Urine normal: genu-valgum of rt. knee & osteo arthritis with lipping of upper end of tibia; long duration; teeth artificial. Slight	Confirms clinical diagnosis Typical appearance.	-	6,800	16.7

Table IV contd.

Name	Age	Sex	Clinical Notes	XRay	Etiology.	Leucocytis.	Calcium
33 contd			similar condition of metacarpo-phalangeal joints.				
34 McGill	63	Male	Osteo arthritis of left knee: pain: limitation of movement & grating. No sepsis BP.145 Labourer with very heavy work.	Confirms diagnosis. Lipping at edges; much osseous deposition rarefaction.	Exposure and strain at work.	7,890	12.9
35 Farquhar	56	Male	Osteo arthritis of both knees of 16 yrs duration and slow onset. No septic foci. B.P. normal.	-	-	-	13.5

In this series there are 21 cases, of which 15 or 71.4% are males, and 6 or 28.6% are females. The average calcium

value is 15.24 mg per 100 c.cs; age varied from 46 to 78 years.

The following observations were made:-

1. Relationship of Calcium to Age.

The cases were divided into groups -

a. 46 - 58 years
b. 59 - 68 "
c. 69 - 78 "

46 - 58 years - 10 cases - average = 15.61 mg calcium.

59 - 68 " - 7 " - " = 15.56 mg "

69 - 78 " - 4 " - " = 14.50 mg "

Hence age has no effect on the serum calcium.

11. Relationship of Calcium to Etiology.

Etiology at best in this disease is tentative, so that the observations given here are speculative.

a. Sepsis: 5 cases possibly due to this: average calcium is 15.6 mg.

b. Exposure & Trauma may be taken together as predisposing causes: these were present in 6 cases whose average calcium was 15.15.mg

c. Nervous strain: only one case in the series was thought to be caused by this factor: in it the calcium value was 17.7 mg.

The etiological factor has therefore no effect on the level of the serum calcium.

111. Relationship of Calcium to Duration of Disease.

No relationship was noted to the duration.

LV. Relationship of Calcium to raised Blood Pressure.

There was hyper-tension in relation to age in 5 cases,

whose average serum calcium was 15.7 mg, but this was lowered by the presence of one reading of 10.1 The average for the other four was 17.05 so that possibly a high blood pressure gives a slightly higher calcium when present.

V. Relationship of Calcium to Leucocyte count.

These figures are contrasted graphically as in rheumatoid arthritis, and shown below

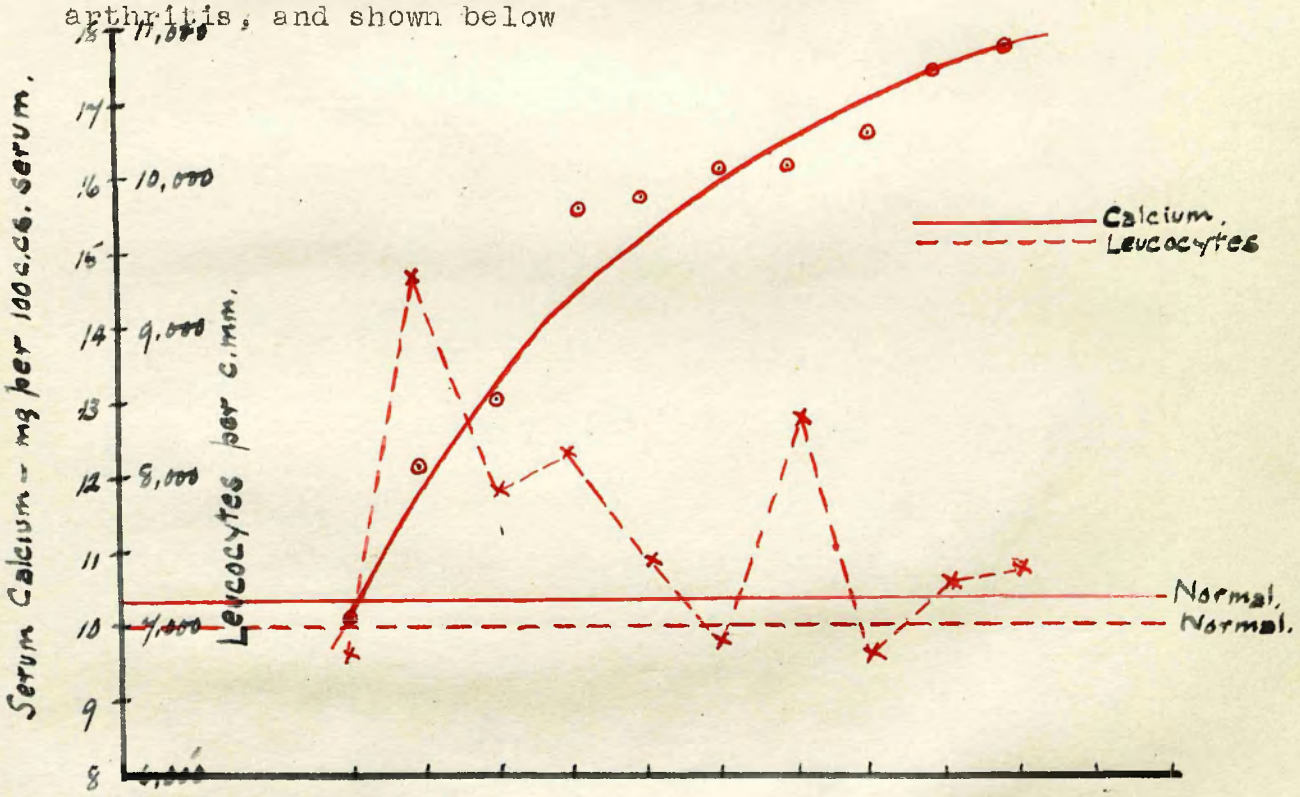


Figure 3

This shows that there is no relationship between leucocyte count and calcium.

VI. Relationship of Calcium to Severity of Disease.

5 Cases might be considered as comparatively slight, (23, 24, 28, 32, 33) from clinical symptoms; their average serum calcium is 15.58 so that the degree of involvement has no effect on the calcium content of the serum.

TREATMENT and its EFFECT on the SERUM CALCIUM.

1. Rheumatoid Arthritis.

In all cases, unless the joints were acutely inflamed, radiant heat, massage, and passive movements, were used. In addition to this, rest in bed and generous diet were given; also, depending on the type of case and the indications, either protein shock therapy or intramuscular injections of iodine, guaiacol and camphor in oil, were given.

(1) Protein shock therapy is described by Campbell[2]: the patient received intravenous doses of typhoid vaccine at intervals of six days, graduated as follows - 50 million, 100 million, 150 million, and 3 doses of 200 million. In each case a typical febrile reaction was obtained.

(2) Injections of Iodine, guaiacol and camphor in oil are recommended by Smith[11] for persistent painful cases especially. They should be combined with local treatment, liberal diet and laxatives as in the treatment outlined above. The preparation is 10% iodine, 10% guaiacol, and 5% camphor made up in oil and given by a wide bore needle intramuscularly. These injections were given daily for three to four weeks: generally there was little local reaction, and, on the whole there was some clinical improve-

ment as regards comfort of the patient.

The following cases, which are now more fully described, were treated by one, or both, of these methods.

(2) Mrs. L. aet 26 years: multipara: 2 children, younger 2 years old. Onset of the disease was 3 years ago: it was insidious, beginning in the finger with pain, stiffness, and slight swelling of the first interphalangeal joints: later wrists and knees became similarly affected. She was first seen in August, 1927, for pleurisy and bronchitis, at which time she was semi-crippled with the joint condition.

On admission to hospital in October 1927 her condition was as follows: In the chest she had a flat note and diminished respiratory murmur over the upper anterior and proterior aspects of the left lung, with slight râles and scanty muco-purulent sputum which contained pneumococci but no T.B. Temperature normal: the pulse was normal in rate but irregularly irregular in character. Transverse cardiac dulness was $3\frac{3}{4}$" extending from mid-sternum. There was a question of a V.S. at the apex. The urine was normal: nervous system normal. She was anaemic looking: tongue, teeth and mouth in good condition: her appetite was fair, and the abdomen normal.

A Leucorrhoeal discharge had been present for 4 years: it contained no pathogenic organisms but diphtheroid bacilli and staphylococus albus. The joints showed a widespread affection: the first interphalangeal joints of all fingers showed a fusiform soft swelling with limited movement: there was a similar condition of the wrists; the knees were scarcely affected at all though painful on movement. There was synoveal swelling of the ankles with pain and grating and limitation of movement: there was also atrophy of the muscles of the affected parts.

Treatment. Pneumococcal vaccine: this gave no reaction: iodine, guaiacol and camphor injections with local and general treatment. There was clinical improvements and increased mobility: when dismissed her pain was gone and she was able to walk fairly well.

February, 1928, she was seen for an attack of acute abdominal pain, which was settling when examined and cleared up quickly: the history and clinical signs were of acute appendicits or possibly an acute attack occurring in a chronic appendicitis. No operation was performed on account of the cardiac condition. She was later given a series of protein shock injections at home: these caused a typical reaction

followed by still further improvement, which was maintained by massage.

At present her condition is remaining improved and she is able to do her household duties: she has had no recurrence of appendix colic.

In this case the difficulty lay in deciding which septic focus was at fault, chest, uterus or appendix.

(3) Sloan: aet 23 years, single. Bondworker. Admitted complaining of pain and stiffness in joints. She had good health up to 3 years ago when she had swelling and stiffness in proximal interphalangeal joint of right index finger: for this she had her upper diseased teeth removed, retaining lower and comparatively good ones. Six months later her shoulder and temporo - mandibular joints became stiff and painful: her knees next became affected with soft periarticular swelling with limitation of movement, which prevented straightening of legs. About this time she was in the Western Infirmary, Glasgow, where she had protein shock treatment and massage, which resulted in straightened legs and ability to walk, when she was dismissed as cured. She failed to keep up massage at home with a resultant recurrence, since when she has been trying all sorts of "cures" with no change except for the worse: the elbow movement be-

came markedly limited. The pain and stiffness returned to the temporo-mandibular joint, but cleared up spontaneously 3 months ago.

Her remaining teeth were extracted about a year ago. Since a little before the onset of the disease till just after admission to hospital she had a profuse leucorrhoea between the menses. No other abnormality was found except for the joints. There is a periarticular swelling of the first interphalangeal joints, with a slight swelling of the wrists. There is marked swelling of the elbows with much limitation of movement, which is increased by muscular spasm. A similar condition exists in the knee joints: the ankles are slightly affected.

The X ray findings are as follow:-

The right elbow shows advanced rheumatoid arthritic changes, erosion of cartilage, and rarefaction of bone.

Both knees show similar changes with very indistinct joint line and scarcely any space between the bones, which show marked rarefaction.

Photo (1) Sloan: Right Knee, lateral view.

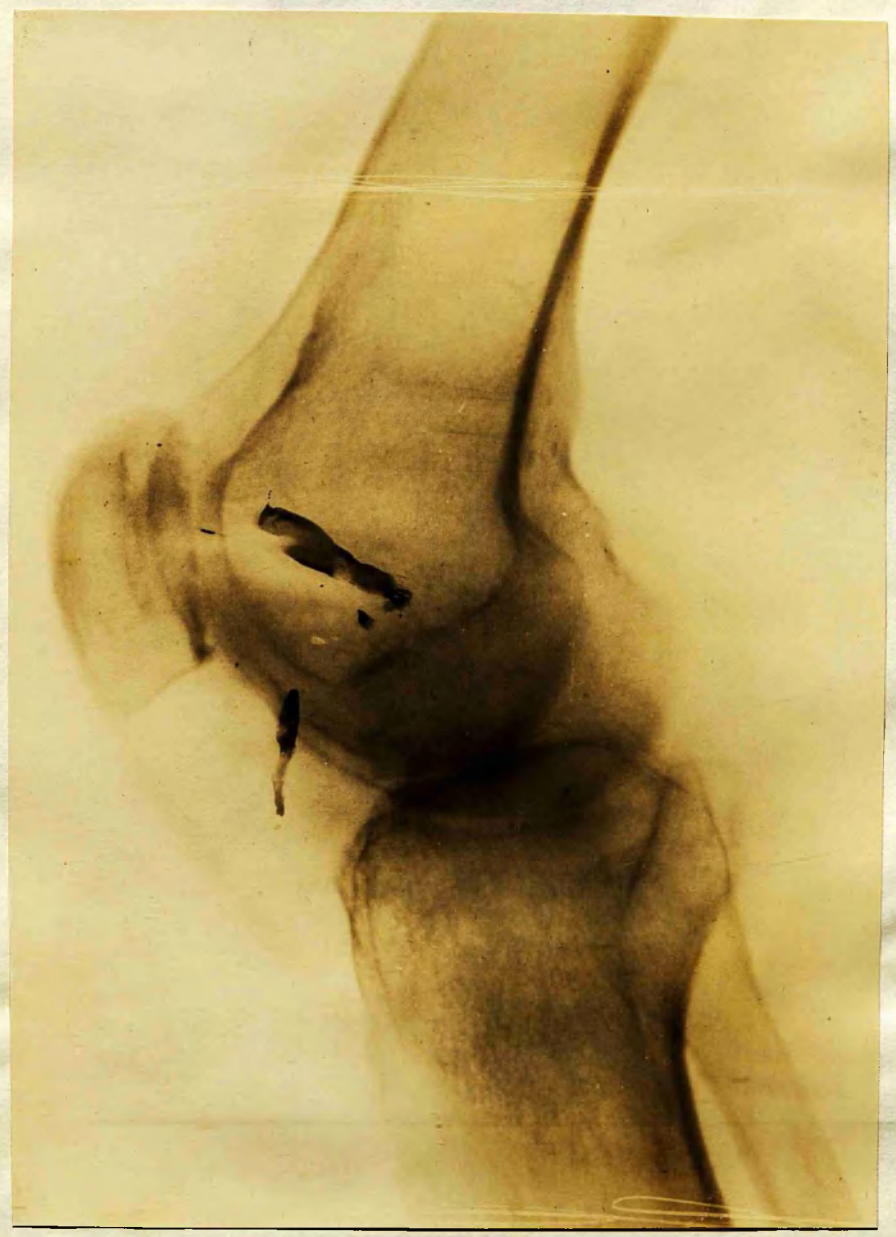
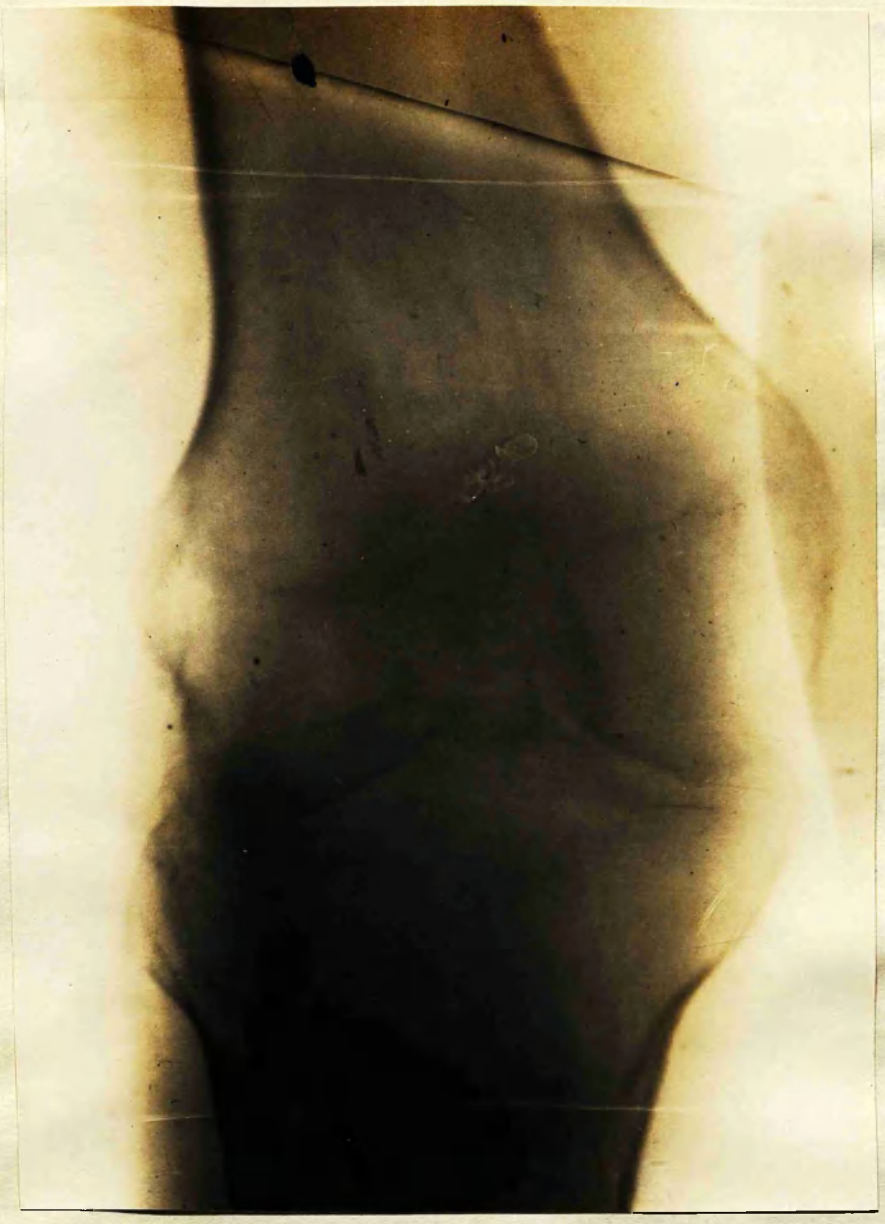


Photo (2) Sloan: Right Knee Antero posterior view.



Treatment. Massage: radiant heat and iodine, guaiacol, and camphor injections: a uterine curettage has been advised: she is still under treatment, and, though progress has been made, it is difficult to give a prognosis as there are such advanced periarticular, ankylosing, and bone changes.

(5) Reid. Aet 26 years: single: domestic servant. Admitted suffering from pain and swelling of wrists and knees.

Up till 20 months ago was healthy with no known previous illness. At that time she had pain in her left shoulder, which she was told was chronic rheumatism, and for which she had her teeth removed, presumably owing to their septic condition. Her pain disappeared, only to reappear, however, in her fingers which became swollen and painful. For this she had hospital treatment in Aberdeen - radiant heat, massage, etc. This again helped her, but six months ago she had another recurrence, this time affecting her wrists and knees, and which gradually became worse.

On admission she was thoroughly examined for septic foci, but none were found except a mild but chronic naso-pharyngeal catarrh: apart from her joints. the physical condition was normal. The joints affected were: the metacarpo-phalangeal joints of the ii and iii digits of both hands, in which there was periarticular swelling,

but not much limitation of movement: there was swelling of both wrists with slight limitation of movement and soft crepitus on moving. Periarticular swelling was present in both knees, in which movement was normal but caused pain and grating.

Treatment. First of all put on ordinary treatment and injections of iodine, guaiacol, and camphor for a month: on this she made practically no headway. She was then given a series of protein shock injections, which caused good reactions and great improvement of the joints, both as regards movement and comfort. She is now able to be up and move about freely, though at present her leg muscles are weak owing to her having been months in bed. Whether this improvement is permanent or not remains to be seen: her massage is being continued.

(12) Mrs.Calder: aet 36 yrs, multipara.

Admitted with swelling and ankylosis of knees, swelling of ankles and elbows: pain in all these on attempted movement.

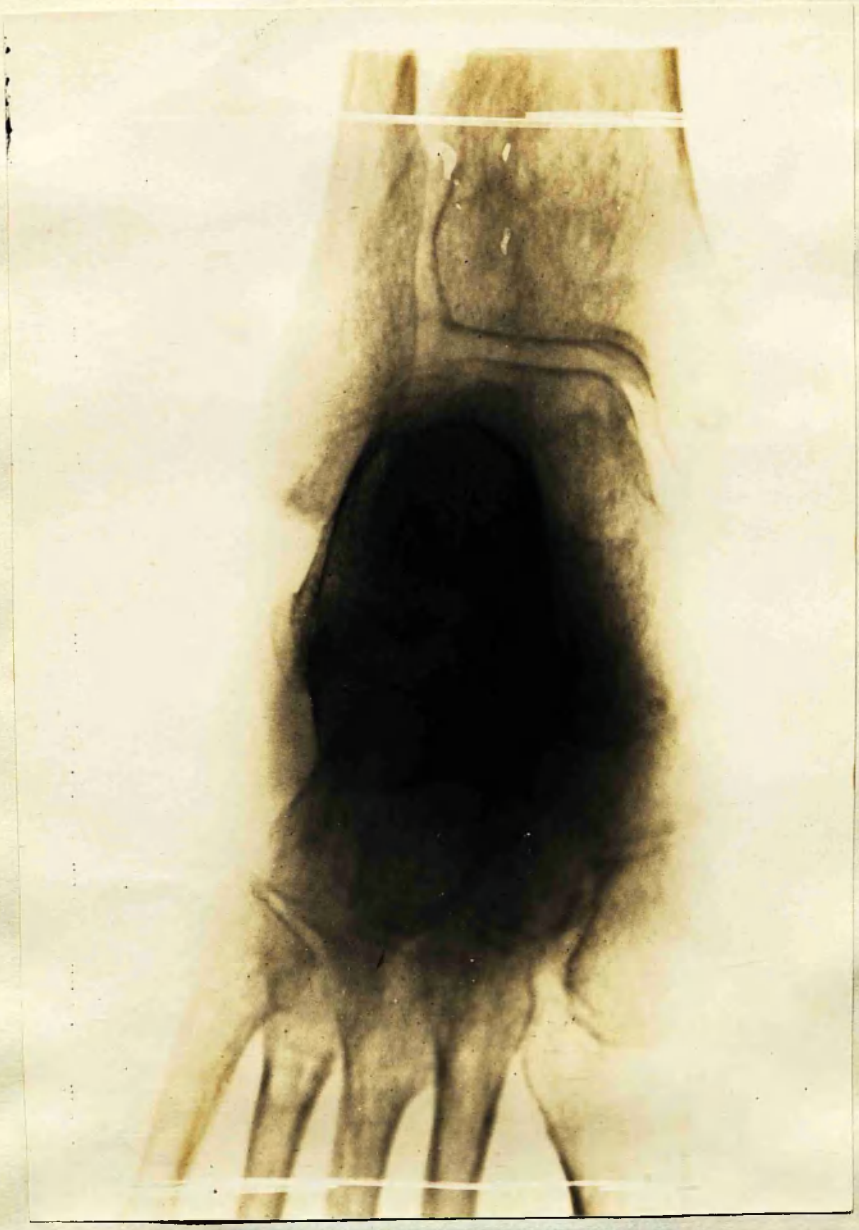
Was always healthy up to six years ago when postpartum she had some cervical or vaginal infection of moderate intensity, but followed by leucorrhoea of long duration: at that time she had pain in both knees but can give no definite history of any swelling: two months later she had pain in ankles, this time accom-

panied by swelling: a similar condition followed in the knees and wrists, fingers and elbows, in that order. With this involvement - slight in most joints - she was able to go about, but since her last confinement 2½ years ago, the condition has become steadily worse, causing her to be confined to bed for the past 9 months. Two years ago she had protein shock treatment in Western Infirmary, Glasgow, but she states that it did her no good, but admits that she refused to persevere with massage, etc.

On admission she had periarticular swelling and moderate stiffness of the ankles, with fair movement. Her knees were both swollen, ankylosed, and painful on attempted movement. Pain and slight swelling of the right temporo-mandibular joint: the elbows were swollen and movement limited. There was very slight involvement of wrist and fingers. No evidence could be found of any septic foci: the only history of one found was the puerperal condition, which immediately preceded the onset of the desease.

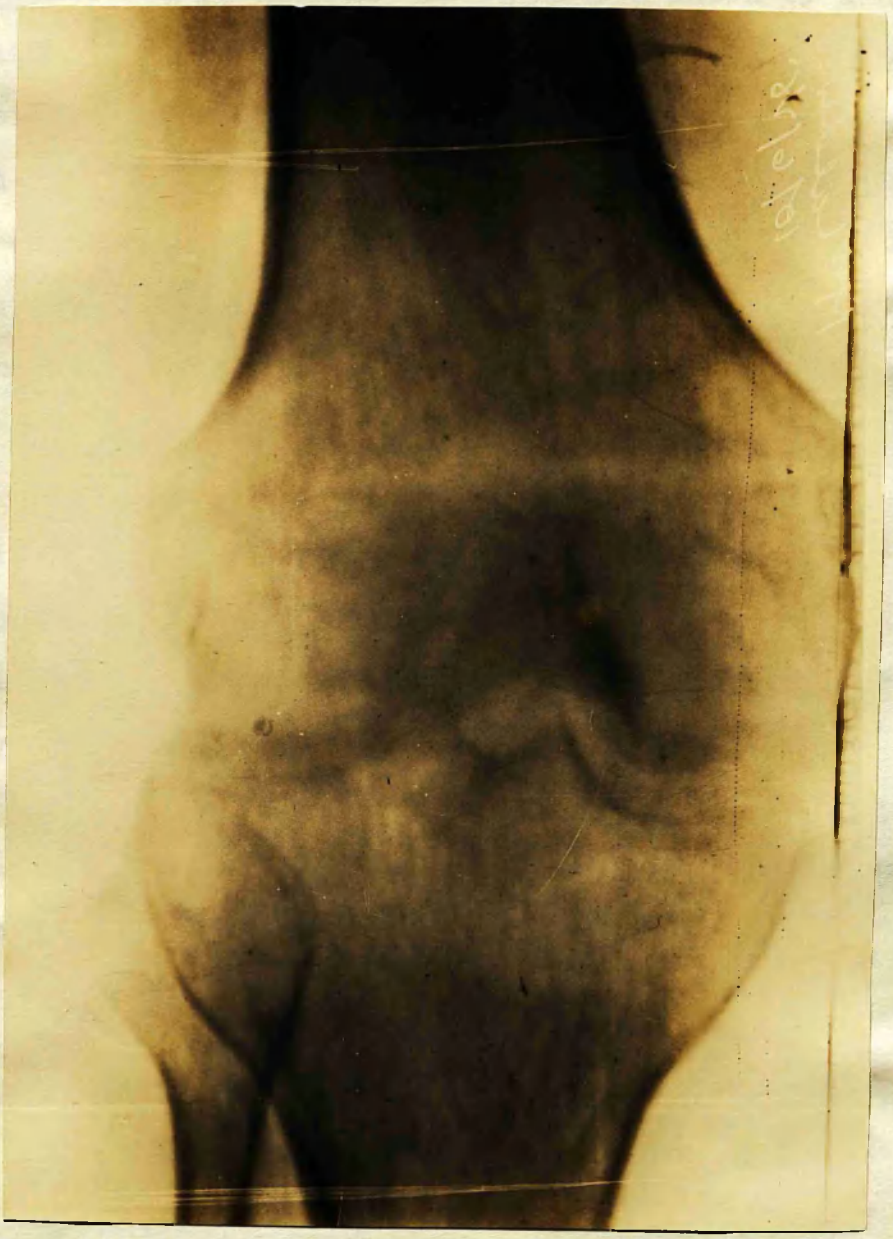
X Rays (see Photos overleaf)

Photo (3) Calder: Left Ankle: shows rarefaction of bones and loss of joint spaces.
Right shows osseous rarefaction.



Left Ankle - A-P view

Photo (4) Calder: Right Knee, Antero-posterior view. Shows completely eroded cartilages with possible bony ankylosis: much osseous rarefaction. Left shows erosion of cartilages & slight osseous rarefaction.



Right Knee - A-P view

The cardio vascular system, the respiratory, alimentary, and nervous systems showed no abnormality. There was marked wasting of the muscles corresponding to the affected joints. Leucocyte count was 8,460.

Treatment. On account of the condition shown by X Ray, the duration, and the refusal of the patient to submit to them, protein shock injections were not given. Treatment was confined to local applications and massage to the joints combined with gradual steady extension of the knees by weights: the knees were fixed at an angle of about 115°. Injections of iodine, guaiacol and camphor were also given. The result was that the knees were slightly extended, showing that complete bony ankylosis had not taken place, and the pains except those due to the extension practically disappeared. There was slight improvement in her general condition. She would not, however, persist in treatment, and went home of her own accord in practically status quo.

The results obtained from treatment in these cases as regards the serum calcium are now given in tabular form and also expressed graphically.

TABLE V.

Iodine, Guaiacol, and Camphor Injections.

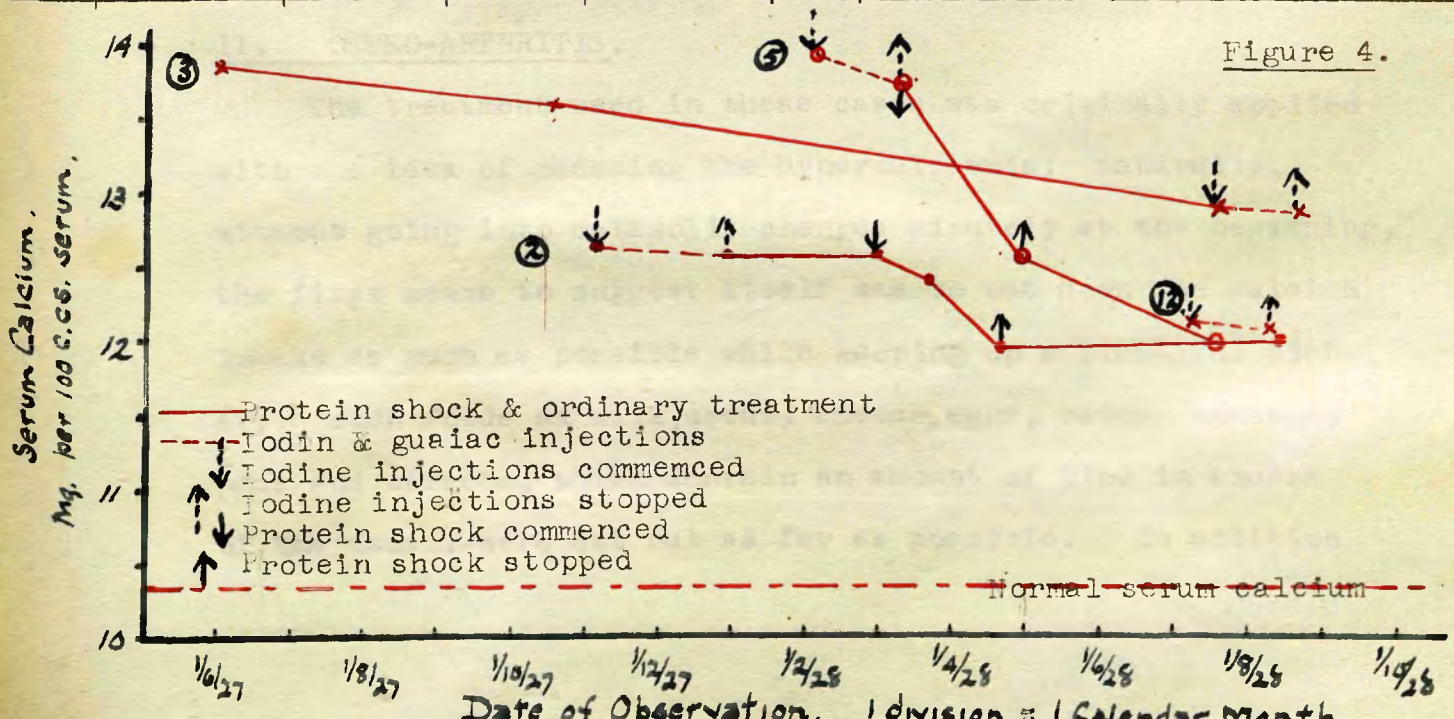
Case	Date	Initial Calcium	Date	Calcium	Date	Calcium	Date	Calcium	Result
2	31.10 27	12.6	31.12. 27	12.5					Marked Improve;
3	30. 5 27	13.8	17.10 27	13.6	17.7 28	12.8	16.8 28	12.8	Slight Improve:
5	11. 2 28	13.9	10. 3 28	13.7					Slight Improve:
12	11.7. 28	12.1	10. 8 28	12.0					No change

TABLE VI.

Protein Shock Therapy.

Case	Date	Initial Calcium	Date	Calcium	Date	Calcium	Date	Calcium	Result
2	1.3.28	12.5	15.3 28	12.3	12.4 28	11.8	14.8 28	11.9	Marked Improve:
5	10.3. 28	13.7	21.4 28	12.5	19.7 28	11.9			Marked Improve:

Figure 4.



Results of Treatment of Rheumatoid Arthritis.

From these results it is seen that the iodine injections relieve pain and cause some clinical improvement, but no appreciable change in the serum calcium: this improvement is probably due to the massage and other treatment. Protein shock therapy causes a fall in the serum calcium, but not to normal: it coincides with marked clinical improvement, which in one case has lasted 4½ months: cases would need to be followed up over a longer period of time.

The clinical improvement in (2) with iodine and guaiacol injections was not accompanied by a fall in serum calcium, which was markedly lowered with protein shock.

In (3) there has been a slight continuous fall from the first observation during home treatment, while the joint condition has been stationary: there has been no increased rate of fall with the clinical improvement since hospital treatment and iodine and guaiacol injections.

11. OSTEO-ARTHRITIS.

The treatment used in these cases was originally applied with the idea of reducing the hypercalcaemia; naturally, without going into metabolic changes minutely at the beginning, the first means to suggest itself was to cut down the calcium intake as much as possible while keeping up a plentiful dietary: such foods as milk, cream, cheese, eggs, beans, cabbage, peas and carrots, which contain an amount of lime in excess of the usual, were cut out as far as possible. In addition

to this dilute phosphoric acid was given with the idea of preventing assimilation from the bowel by converting calcium to insoluble calcium phosphate: it is of interest to note that Binger[61] found that the injection of NaH_2PO_4 lowered the blood calcium in dogs. The dosage given was - ac-phos dil mxv combined with M viij of tr.nucis vom, thrice daily.

Later it was discovered that Mark[6] also tried a low calcium intake in osteo arthritis with hyper calcaemia, and, as will be seen, with much the same result. He also tried acid administration but in this case he used m x 10% HCl thrice daily, which would tend to act by decalcifying bones by withdrawing excessive base from them: in fact, he found it caused a slight rise in the serum calcium, probably, as he says, due to mobilisation of calcium to hold the acid.

The cases now to be described were put on this treatment and, where necessary given rest, passive movements or analgesics: the serum calcium was noted before and after treatment.

16. Mc.William, aet 58 years, Railway inspector.

Admitted to hospital 5/1/27 suffering from pain and slight loss of power on the left side, and from stiffness and limitation of movement of the back and neck. His symptoms suggested root pains possibly due to pressure; he had slight inco-ordination of arm and hand move-

ments: there was no incontinence and his cerebration was normal. Upon X ray examination there was found to be osteo arthritic changes of the upper dorsal, lower cervical and lower lumbar vertebrae, corresponding to the tender areas over the spine.

He had occasional minimal rises of temperature over normal, but no septic foci could be discovered, and, from routine examination he was fairly normal for his age: his blood pressure was 165, his arteries in good condition, leucocytes 7,470.

He dates the onset of his trouble to six months before admission, or shortly after the general strike, during which he suffered abuse, as the result of being a loyal worker. Previous to that he had never complained of ill health.

In addition to the treatment outlined above he had rest in bed and counter-irritation in the shape of emplast-cantharidin over the affected areas of the spine.

Since his discharge from hospital 3/9/27 he has steadily improved and feels the better of his low calcium diet and medicine; he is now able to walk about half a mile on the level,

though he has recurrent attacks of the root pains.

18. Hill. Aet 70 years; Labourer.
First seen for impacted fracture of the surgical neck of his right humerus. At that time his occupation was night watchman, owing to his inability to work because of stiffness of his elbows: this disability had been progressing for 5 years. There was bony and periarticular swelling of both elbows and marked limitation of movement: there was slight involvement of the shoulder joints, but no other joints were affected. His teeth were few in number and showed pyrrhoea and decay. Blood pressure was 150 mm mercury, and his arteries and heart normal for his age: urine was normal; no signs of other septic foci. Leucocytes 8,240 per c.mm. X ray confirmed the clinical condition, showing osseous hypertrophy round joint margins, which caused the limitation of movement.

In addition to the usual treatment he was given a course of iodolysin injections, but unfortunately readings of his serum calcium could not be taken before and after this. There has been slight improvement with his range of movement resulting in his ability to take his food with ease: he

is still unable to touch the back of his head or neck: his pain has also disappeared except on forced movement. No change has taken place in the swelling of the elbows themselves.

21. Campbell. Aet 78 years: female: housewife: previously had done charing with a great deal of floor scrubbing.

Eight years duration: pain and stiffness in knees: 4 years ago had evidently become semi-ankylosed, and they were straightened under anaesthesia: recurrence about 2 years ago, accompanied by swelling. She now complained of inability to walk, owing to the knees being slightly flexed and almost fixed; osseous hypertrophy round the joint edges; the slight movement possible was accompanied by grating: there was also slight stiffness, pain and limitation of movement of hip joints. Her other joints were normal for her age. She gave a history of nervous irritability and insomnia. Her general condition was poor: she possessed only two teeth - incisors: there was quite marked myocardial weakness: blood pressure was 155: urine normal. Her appetite was fair and the bowels regular. Her pain was

chiefly in the knees and down the front of the legs and the dorsum of the foot. There was marked local muscular wasting.

Treatment, including rest and passive movement; showed no clinical improvement, and the pains were unchanged.

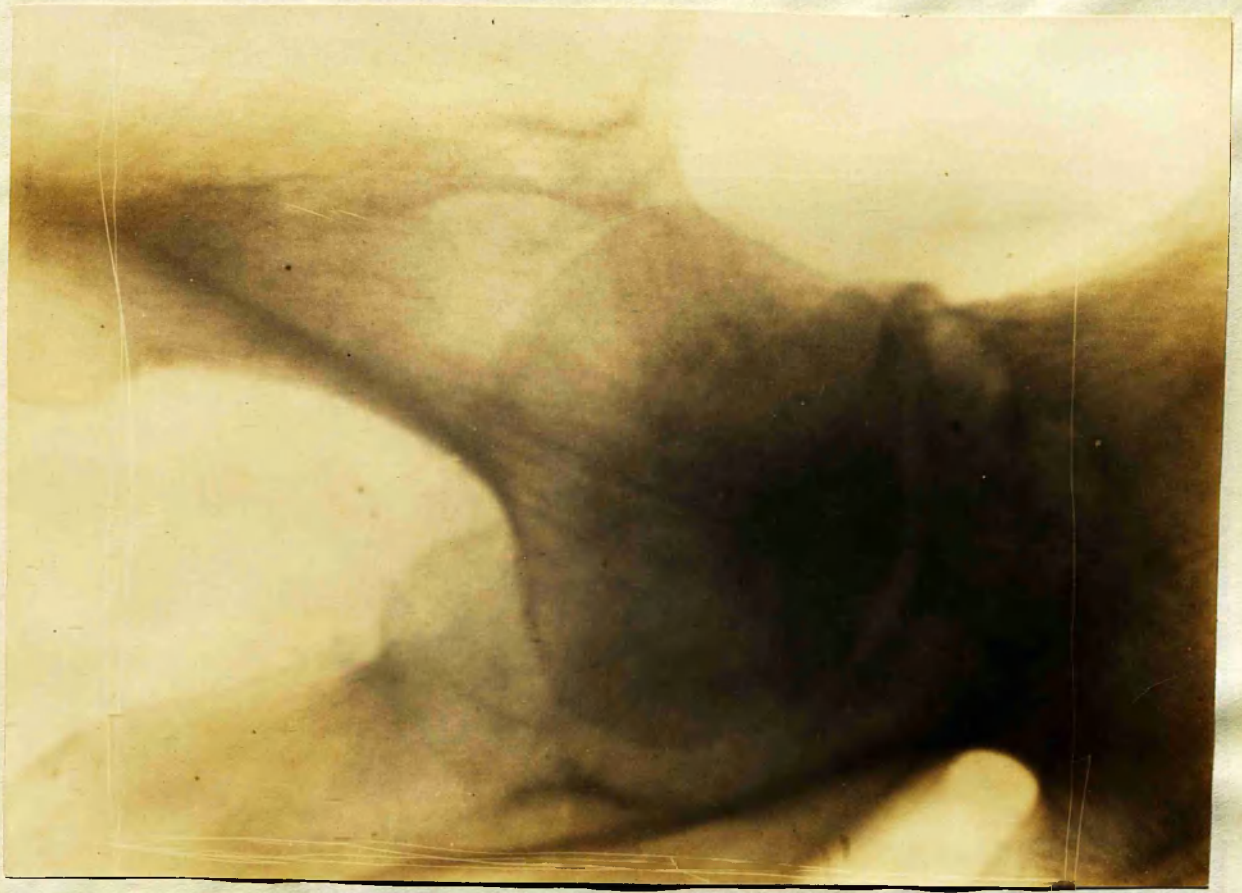
A few months after the second calcium determination her myocardial weakness became more apparent, and she died of heart failure with oedema of legs and passive pneumonia.

25. McCartney. Aet 54 years: Agricultural labourer. Was first seen 2 years ago for accident in which he sustained a stellate fracture of his right patella, which healed with excessive formation of callus and new bone. At that time his right ankle was noticed to be swollen owing to hypertrophy of the bones and peri-articular structures: there was only slight disability: this he said appeared following an accident years ago.

Four months after his patellar injury, when the latter was healed and his knee movements were normal except for some limitation of flexion, he complained of pain in the right leg: this was of sciatic distribution and type: for this he was kept in bed at rest with blister-

ing and anodynes : some improvement was effected. As soon as possible the joint was X rayed when osteo arthritis as shown in photo (5) was found: the head of the femur was flattened and typical osteoarthritis changes were seen; the joint cavity was intact; rarefaction of the femur was noted; at this time his serum calcium was 16.0

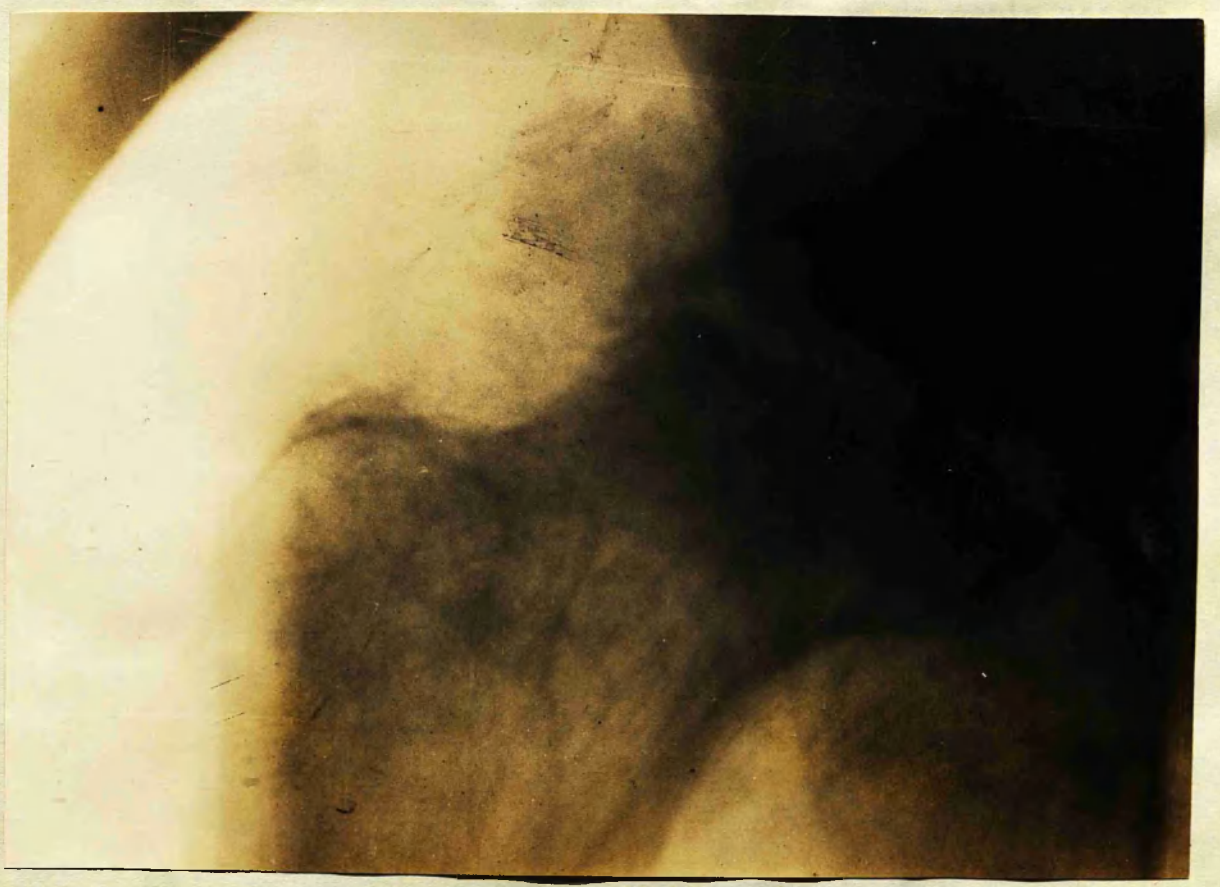
Photo (5) McCartney: Right hip joint.



Apart from this nothing else abnormal was found: his leucocyte count was within normal limits - 6,850.

For the next 6 months he was put on the usual treatment with rest anda little movement. During this time his chief complaint was of pain in the knee and not in the hip. In spite of care taken the leg became obviously shorter and on examination by X rays showed a much more advanced condition as shown in photo (6); the head of the femur is practically gone and movements very limited on account of osseous hypertrophy round the joint: the serum calcium was now 15.2.

Photo (6) McCartney: Right Hip showing shortening.



Since this plate was taken the condition, judging from the clinical signs, appears to have become stationary, while the patient is much more comfortable and any pain seems to be due to the presence of osteophytes in the right knee. The present serum calcium is 15.8.

33. Fitchell. Aet 54 years. Iron turner.

Was first seen at the beginning of March, 1928. for cerebral thrombosis or endarteritis, when he lay in a stuperose condition for several weeks. From that condition he has made a good recovery and has just started work again with cerebration and nervous system practically normal. At the onset his blood pressure was 135: he had no evidence of atheroma, nor were there any changes in the retinae or optic nerves: his urine showed no abnormality and there was no incontinence: there was slight paresis of the right arm and leg, and the left side of the face: no complaint of headache nor diplobia: he never had sickness nor vomiting.

During convalescence he complained of pain in his right knee which was worse on movement: on examination there was found to be genu-valgum, present since childhood, and in addi-

tion marked lipping and grating on movement. Up to the present illness he had enjoyed good health. In addition to the knee condition there was also slight ulnar deviation of the fingers of the right hand, with osseous lipping of the edges of the joints: these changes had previously been noted. The pain in the knee and leg may have been due to the after effects of the paresis. X ray examination confirmed the presence of osteo-arthritis. The leucocyte count was 6,800.

After two months treatment the pain and stiffness have disappeared to some extent but of course the bony deformity remains.

26. Cosgrove. Aet 60 years. Labourer .

This case presented features both of osteo-arthritis and of rheumatoid arthritis: he was treated by low calcium diet etc., and in addition had a series of intramuscular injections of yatren-casein i.e. mild protein shock. These injections caused no general reaction and only slight local reaction.

His complaint dates back to 12 or 13 years ago, when he had pain and swelling of the left knee. He was advised to have his teeth, which

were septic, removed, but did not have it done. Since then his condition has gradually become worse till a couple of years ago: since then his condition has been stationary. His complaint is of difficulty in walking and pain in the affected joints - both knees, shoulders and wrists: the knees present clinical features of both rheumatoid and osteo-arthritis: the wrists resemble rheumatoid arthritis. No septic focus beyond the teeth could be found and otherwise no abnormal condition, except some evidence of fibrositis in that his pains are always worse with a change of weather.

Treatment resulted in no clinical improvement.

TABLE VII.

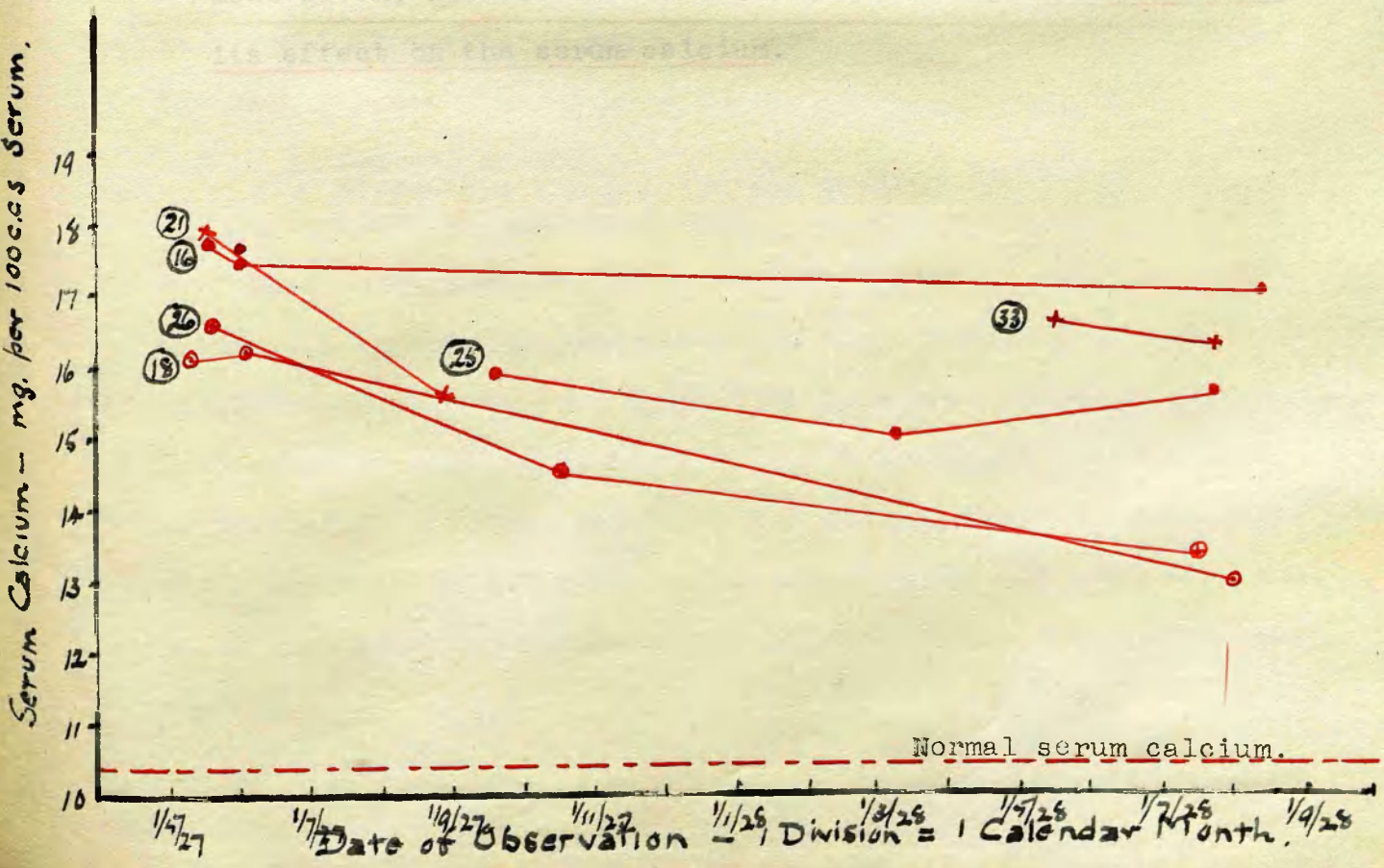
Results of Treatment.

Case	Date	Initial Calciam	Date	Calcium	Date	Calcium	Clinical Notes.
16	16.5.27	17.7	30.5.27	17.4	16.8.28	17.1	Improved greatly.
18	10.5.27	16.1	4.6.27	16.2	30.7.28	13.1	Pain gone & slight increase in movement.
21	20.5.27	17.9	21.8 27	15.7			No improvement marked.

Table VII contd.

Case	Date	Initial Calcium	Date	Calcium	Date	Calcium	Clinical Notes.
25	13.9.27	16.0	6.3.28	15.2	28.7.28	15.8	Marked advance of desease followed by stabilising.
33	13.5.28	16.7	28.7.28	16.5			No improvement, except relief from pain.
26	20.5.27	16.5	14.10.27	14.5.	16.7.28	13.5	No improvement.

Figure 5. Results of Treatment on Serum Calcium in Osteo-Arthritis.



From these results it is seen that in all cases there was a fall, sometimes very slight, as a result of this treatment. The clinical improvement was found to bear no relation to the fall in the serum calcium: in fact, in case 25 while the serum calcium was falling the condition was getting worse, and later, when the calcium was rising again the condition was becoming stationary: this raises the question of whether the hypercalcaemia is an attempt by nature to remedy the pathological condition: if so, then the giving of calcium instead of the with-holding of it is advisable. In two cases (21,26) showing the most marked fall in serum calcium, there was no corresponding improvement: in fact, they are the two recorded as showing no improvement, while that showing most improvement, shows a remarkedly constant serum calcium. Hence, the treatment given, when it is beneficial, evidently does not act by its effect on the serum calcium.

S U M M A R Y.

The scope of the cases examined is defined: from analogy with other diseases affecting the bony skeleton is pointed out the desirability for investigating the serum calcium; results which have been published already in similar series are given.

The origin of calcium of the body from the ingestion of food, and its uses in the body have been detailed. Its constancy in health and most diseases has been noted, and its distribution in the elements of the blood given. Reasons are given for the serum calcium being taken as an index of the body calcium; the average varies from 9 to 11 mg calcium per 100 c.cs. serum but is usually round about 10 mg. This calcium is present in several forms: these are discussed and the average findings for them given:-

Ionised 10-20%
Diffusible but not ionised 40-50%) 60-70%
Fixed or colloid 30-40%

The recent theories of the precipitation of calcium or of holding it in solution are given and the connection of the parathyroids with calcium metabolism gone into, showing the inverse ratio of calcium to guanidin in the blood and the interdependence of calcium, guanidin, and the parathyroid hormone in the body: this relationship is specially important with reference to the detoxicating action of the parathyroids. The most recent theory/

theory and that supported by most experimental work, is that the parathyroids control the calcium balance of the body and that excessive action causes a drain on the calcium of the bones: it is also said that excess parathyroid retains more calcium dissolved in the blood, possibly by raising the percentage of diffuse calcium.

The chief functions of calcium, namely, clotting of blood, controlling the neuro-muscular activity, stimulating cardiac contraction, maintaining the acid-base and the ionic balance, and formation of bone are enumerated. From these it is noted that the calcium level may be upset in several ways: by disturbing the acid-base balance or the ionic balance, or by dysfunction of the parathyroids, or by want of calcium assimilation. That the parathyroid is the controller is shown that in any of these pathological conditions the calcium balance is restored if the former is functioning properly.

The methods of estimating serum calcium are mentioned and that of Clark and Collip, which was the one used, is described fully and its advantages discussed. The technique of collecting the blood, etc. is gone into in detail. Examples of published normal cases are given.

The pathology and biochemistry are discussed with a view to finding any relationship, hypothetical or otherwise, of the serum calcium to the etiology: if any is noted then it would be applied to treatment. The essential points of difference and similarity between osteo-arthritis and rheumatoid arthritis are noted/

noted, the similarity consisting in the occurrence of rarefaction and fibrosis of bones. The chief biochemical findings in the literature are given under the proper headings: it is noted in which disease the figures are taken, as far as the terminology of the authors allowed.

The well known chief etiological factor of absorption from a septic focus and its relation to hypercalcaemia is discussed: the possibility of an involvement of the endocrine organs is also noted, and the reasons for supposing the parathyroids to be at fault are given. It is also suggested that the guanidin level in the blood might furnish further knowledge as to whether the parathyroids are affected or not. It is pointed out that there is also a mild chronic acidosis in rheumatoid arthritis, and its possible effect on the serum calcium discussed especially in connection with the abnormal sulphur metabolism present. The conclusion come to is that rheumatoid arthritis is usually primarily a disease of toxic origin and that the joint condition and the biochemical changes are secondary, being probably effected through the endocrine system or by causing acidosis.

In osteo arthritis no fresh suggestions can be made. Its resemblance, however, to osteitis fibrosa is noted: the latter has been blamed on hyperparathyroidism. There is want of pathological observations on the parathyroids in health and disease. The pathological cases which have been noted are discussed and especially the effect of a low calcium diet in rats.

It has been attempted to compare osteo arthritis and osteitis fibrosa/

fibrosa with hyperparathyroidism , but the latter is too vague an entity even in its experimental form to come to any definite conclusions. The chief findings in induced hyperparathyroidism are given. The points of similarity between rheumatoid arthritis osteo-arthritis, osteitis fibrosa and hyperparathyroidism are given in tabular form.

The desirability of giving or witholding calcium is discussed, but no definite conclusion come to, as the metabolic changes are not perfectly understood: parathyroid is contraindicated and the reasons for this are given. Other factors in treatment such as thyroid extract, iodine, alkalis and acids are briefly mentioned. It is also noted that a lowering of the serum calcium has been observed following protein shock.

In the clinical section the series of cases in which the serum calcium was estimated to give control values is reviewed, especially as regards any salient features. The reasons for giving such types is stated. Separate tables for rheumatoid arthritis and osteo-arthritis have been drawn up stating briefly the age of the patient, duration of disease, etiology, especially regarding sepsis, X-ray reports, leucocyte count and other clinical features of note, and the serum calcium value. These findings are discussed for their bearing on the relationship of the serum calcium to age, etiology, duration of disease, leucocyte count and severity: tables and charts of these comparisons are given: in osteo-arthritis, the relation of the serum calcium to the blood pressure is also discussed.

The/

The treatment given is detailed, use being made of rest, radiant heat, massage, injection of iodine, guaiacol and camphor in oil, and protein shock therapy in rheumatoid arthritis: of rest, slight movement and low calcium diet combined with phosphoric acid in osteo-arthritis. Cases specially observed are fully reported, including some radiograms of cases to illustrate certain points. Serum calcium estimations were made at intervals and these results given in tabular form and charted: the results and conclusions are then given regarding the appropriate diseases.

Conclusions.

The conclusions come to in this series have the disadvantage of being drawn from a comparatively small number of cases, but such as they are and for what they are worth they are as follows:-

(1) The average serum calcium in twelve comparatively normal people was 10·35 mg calcium per 100 c.cs serum, the actual values ranging from 9·2 to 11·9 mg.

(2) In 14 cases of rheumatoid arthritis the average serum calcium was 12·0 mg. calcium per 100c.cs serum.

(3) In cases of septic origin the average was 12·7 mg calcium per 100 c.cs serum: in those due to the menopause or exposure the average value fell within normal limits: this caused the serum calcium to fall as the age of the patient increased.

(4) In/

(4) In Rheumatoid-arthritis there was no relationship between the serum calcium and the leucocyte count or the duration of the disease.

(5) The serum calcium was higher in severe cases of rheumatoid-arthritis than in moderate or mild ones.

(6) In 21 cases of osteo-arthritis the average serum calcium was 15·24 mg. calcium per 100 c.cs serum.

(7) The serum calcium in osteo-arthritis had no relationship to age, etiology, duration, leucocyte count, or severity of the case.

(8) A raised blood pressure in relation to the age of the patient tended to raise the serum calcium still higher in osteo-arthritis.

(9) Injections of iodine, guaiacol and camphor in oil caused some clinical improvement in rheumatoid arthritis but no appreciable change in the serum calcium, in 4 cases thus treated.

(10) In 2 cases of rheumatoid arthritis protein shock therapy caused a fall in the serum calcium but not to normal: it coincided with marked clinical improvement and, as far as they have been followed the fall is persistent.

(11) The beneficial effect of treatment of osteo-arthritis by low calcium diet was very doubtful: in most cases it caused a moderate fall in the serum calcium, but this did not coincide with any clinical improvement.

(12) Any change of osteo-arthritis for the better was not due to a reduction of the serum calcium.

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