ACTA ORTHOPAEDICA SCANDINAVICA
SUPPLEMENTUM No. 62

FROM THE CLINIC FOR ORTHOPAEDICS AND TRAUMATOLOGY,
UNIVERSITY OF HELSINKI, (HEAD: PROFESSOR K. E. KALLIO)

THE EFFECT OF GROWTH HORMONE AND THYROTROPIN ON HUMAN FRACTURE HEALING

A CLINICAL, QUANTITATIVE RADIOGRAPHIC AND METABOLIC STUDY

BY

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MUNKSGAARD
COPENHAGEN 1963

Printed in Finland
Helsinki 1963
MERCATORIN KIRJAPAINO

To my Wife

CONTENTS

I INTRODUCTION

Bone repair and the factors affecting its course constitute one of the most prominent considerations in fracture treatment. The continuous increase of bone fractures, and of traumatic injuries on the whole, has given rise to problems, which are being approached from new points of view. More clearly than before, the bone is understood to be a living tissue with its peculiar modes of reaction and with its individual metabolism. Not only several investigations concerning the healing of fractures but also the research work pursued on the subjects of osteoporosis, bone transplantation and antigen factors, to mention only a few, has contributed toward the crystallization of these ideas.

Well aware of the fundamental prerequisites which are necessary and essential for instituting an adequate orthopaedic therapy and to achieve successful repair of the fracture, it has been shown, particularly in recent experimental and clinical studies, that hormonal factors possess significance in respect of the course of the reparative process in the bone and that it is possible to control it under the effect of certain hormones. Striking hormonal influences are well-known from the spontaneous fractures, which have become common and problematic with the general use of prolonged corticoid therapy. The profound effect of the corticoid hormone on the entire organism, on the connective tissue and the bone is undisputed, and its delaying influence on fracture healing has been convincingly established in several investigations (e.g. *Albright et al.* 1941, *Albright* 1947, *Irvin et al.* 1954, *Reifenstein* 1956, 1957).

On the other hand, the literature reveals that the opinions concerning the influence of different so-called anabolic hormones on bone repair are variable; the reported results are found to be controversial in many cases when subjected to critical assessment. In part this may be due, especially

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A preliminary report of the work described in this paper was presented by the author as invited speaker at the Gordon Research Conference on the Chemistry, Physiology and Structure of Bones and Teeth in Meriden, N.H., U.S.A., July 9—13, 1962.

as regards growth hormone, to the fact that only in a few recent years so-called pure hormone preparations have been available, while the products employed previously used to contain other fractions which could actually exert an influence opposite to that intended with the hormone administration. This was true, for instance, with the hormones of the anterior pituitary, such preparations containing growth hormone and also ACTH, which are antagonistic in their effects in numerous respects.

Since *Evans* and *Long* (1921) succeeded in demonstrating that lack of the anterior pituitary growth hormone isolated by them stimulated the growth of mammal animals, which fact was later attributed to the effect of the hormone on the epiphyses of the long bones, attention has become essentially concentrated on the bone growth-stimulating effect of this hormone and on its use in cases where such an effect is desired.

This substance, growth hormone or STH, stimulates the protein synthesis and retards the decomposition of protein. According to *Li et al.* (1945), among its most essential physiological effects there are mentioned: increase of the serum's alkaline phosphatase activity and of its inorganic phosphorus content, and increase of the nucleic acid content in liver and thymus. Nitrogen is stored and the excretion of phosphorus, sodium and potassium in the urine is reduced. It has frequently been observed that the urinary calcium excretion is paradoxically increased. *Henneman et al.* (1960) explain this peculiarity by pointing out that growth hormone promotes the absorption of calcium and if the incremental calcium cannot rapidly by deposited in new bone substance, it appears in the urine. Growth hormone is thus seen to be a metabolic hormone presenting remarkable anabolic activity.

Thyrotropic hormone affects the thyroid gland and produces its own well-known metabolic effects. As regards the skeletal system in particular, it has been found to possess an effect promoting the maturation of bone. This term relates to the times of appearance of epiphyseal centres of ossification and the times of cessation of epiphyseal bone growth which is marked by the disappearance of the epiphyseal plates (*Sissons* 1956).

In recent years some valuable papers have been published, concerning the significance of growth hormone in respect of the growth of bone and its maturation on the whole, which places them in close connection with the present subject. Without commenting on them in detail, the investigation carried out by *Asling* and *Evans* (1956) may be mentioned which revealed that the bone growth of experimental animals, after having been stopped by hypophysectomy, could be restored to normal or even stimulated to excess

by administration of growth hormone together with thyrotropin. No other hormone had this capacity. The effect was markedly augmented through the synergetic action of the thyrotropic hormone.

The effect of hormonal factors on fracture repair has been investigated e.g. by *Shepanek* (1953), who found that growth hormone expands the epiphyseal line and promotes greater growth. *Blunt et al.* (1950) and *Sissons* and *Hadfield* (1952) noted that cortisone had a delaying effect on the repair of fractures. According to *Fontaine et al.* (1954) thyroxine accelerated the osteogenesis in experimental fractures, which was on the other hand depressed by desoxycorticosterone and corticotrophine. *Moffat* and *Francis* (1955) observed that sex hormones possess significance in the bony repair of fractures. Recently, *Williamson* (1960) reported that the profit derived from the use of gonadal hormones cannot be assessed before statistically significant results have been obtained with the aid of a control series.

In clinical practice favourable results have been obtained with growth hormone in stunted growth caused by endocrine disorders (e.g. *Henneman et al.* 1960), which has been one of the most important indications for the use of human growth hormones. *Hernberg* (1960) has reported diabetogenic effects produced with human growth hormone. *Prudden et al.* (1956) observed that the use of growth hormone had remarkable significance in the treatment of burns. The evaluation of nitrogen, potassium and calcium was enhanced when hormone was given in sufficiently high dosage. Clinical applications in the treatment of fractures have been reported e.g. by *Laborit* (1953), who was able to record positive results of growth hormone therapy in cases with deficient callus formation and in surgical infections. *Cordebar* and *Guilleman* (1956) have achieved more rapid osseous consolidation with growth hormone than without it in fracture of various types with conservatively and operatively treated patients. Quite recently, *Galio* and *Peria* (1958) reported that local application of growth hormone aided the healing of comminuted fractures.

Previous investigations concerning the effect of growth hormone on fracture repair in human patients are scanty and based on quite small series without appropriate control series, which are indispensable if it is required to obtain an accurate idea of the effect, if any, and of its character. Since the question is one of investigating endocrine actions, also metabolic aspects play an important part and the investigation should not be based merely on results recorded on the clinical level, which can only furnish a partial answer. There is even greater reason for such an investigation as now a growth hormone preparation is available, which has already in previous

investigations proved effective in man (*Frandsen* 1955, *Carstensen et al.* 1954, *Nordström et al.* 1955, *Paulsen* 1961) in contrast to the variable results obtained with the preparations containing impurities that were used before.

In an earlier experimental investigation concerning the repair of fractures, a favourable effect of growth hormone and of growth hormone plus thyrotropin on the fracture repair process was noted (*Koskinen* 1959, 1962). Among other things, the present writer observed that with combined growth hormone and TSH treatment there were similar but even stronger changes indicative of osteogenetic stimulation as in the growth hormone experiments. This was evident from the very earliest stages of reconstruction onward as a stronger trabecular formation of new bone, the quantity of which increased continuously at a high rate throughout the period of observation. Clinical stabilization and roentgenological consolidation of the fracture took place more than twice as rapidly as in the controls. The results of autoradiography were consistent with the abundant and early formation of new bone established by the histological line sampling method of *Uotila* (1940, 1952).

The present work is an investigation on the effects of growth hormone and thyrotropin on the healing of clinical bone injuries in augmentation of proper, conservative or operative, therapy as compared with a control series. In this investigation attention has mainly been paid to clinical and roentgenological consolidation of the fracture, in addition to which a combined radiologic and quantitative planimetric study of the callus formation was carried out, the latter reflecting the actual quantity of callus during the progress of bone repair; all observations being compared with a control series as reference. Simultaneusly, the calcium and phosphorus contents of the serum were determined and the quantity of calcium and phosphorus excreted with the urine was followed, as well as the alkaline phosphatase activity of the serum. These quantities reflecting the metabolic effect during the repair of bone were also related to an appropriate control series.

II MATERIAL

The material on which this investigation is based comprises 60 patients from the Clinic for Orthopaedics and Traumatology, Central University Hospital of Helsinki (Chief: Prof. K. E. Kallio, M. D.). All examinations and treatment of these patients took place in the Clinic during the period 1960—1962, which was sufficient in length for adequate observation of each case and for follow-up examinations. Particulars of the cases have been compiled in Table 1 A. This hormonal treatment series consists of altogether 64 cases, of which 40 cases were recent fractures of an extremity, 21 were cases of non-union or delayed union and three cases of malunion. 29 of the recent fractures were of closed type, most of them comminuted, while in 11 cases there was a compound fracture. Four patients were bilaterally injured. A considerable part of the injuries were serious ones, as can be inferred also from the relatively high number of compound fractures. In addition, 30 patients treated in the same Clinic for injuries of the same kind (without hormonal treatment) served as controls (Table 1 B).

For the study involving quantitative determination of the callus size by planimetry of radiograms, 20 cases of the hormonal treatment series and 20 of the controls were employed. All these patients had a fracture of the femur. Ten cases of each series were treated conservatively and ten cases by intramedullary nailing.

An analytic study of metabolic values was carried out with a series of 50 patients from the hormonal treatment series and 13 cases of conforming distribution by types of injury from the controls.

The age of the patients in the hormonal treatment series varied between 18 and 78 years, mean age 46 years, and in the control series between 17 and 76 years, mean age 44 years.

TABLE 1. MATERIAL WITH CLINICAL RESULTS, ESTABLISHED BY RADIOGRAPHY.
Assessments of radiographic appearance: — Poor callus, + Slight callus, ++ Fair callus, +++ Solid, firm callus.

A. Hormonal Treatment Series

Case No. Age, Sex	Type and Site of Injury	Surgical Treatment	Hormonal Treatment		Radiographic Appearance after months:			Comments and Clinical Result
			Duration, days	Started, days after trauma or operation	2	4	6	
	Fractures of Femur							
1. 62 M	Transverse Middle 3rd	Conservative	37	41	+	++	+++	Solid osseous union in 5 months.
2. 43 M	Oblique Upper 3rd	Conservative	56	67	+	+++	+++	Osseous union in 4 months.
3. 66 M	Oblique Lower 3rd	Conservative	44	12	++	+++	+++	Osseous union in 3 months.
4. 65 F	Oblique Lower 3rd, Bilateral	Conservative	49	41	—	+++	+++	Osteogenesis imperfecta. Osseous union in 3 months.
5. 41 M	Transverse Lower 3rd, Compound	Conservative	30	42	++	+++	+++	Consolidation in 3 months.
6. 74 F	Transverse Middle 3rd	Conservative	64	41	++	+++	+++	Consolidation in 4 months.
7. 70 F	Oblique Upper 3rd	Conservative	64	13	++	++	+++	Diabetes. — Obvious partial soft part interposition, but consolidation in 6 months.
8. 36 M	Transverse Lower 3rd, Compound	Conservative	51	14	++	+++	+++	Consolidation in 4 months. Soft callus initially, but osseous union after 4 months.
9. 57 M	Oblique Lower 3rd, Compound	Conservative	18	16	+	+++	+++	Consolidation in 4 months. Callus remained about equal in size as at 2 months, but gained in firmness.
10. 56 R	Transverse Lower 3rd, Compound Bilateral	Conservative	44	43	++	+++	+++	Fracture of right femur consolidated in 4 months. Fracture of left femur united in 5 months.
11. 52 M	Transverse Middle 3rd	Nailing	26	32	++	+++	+++	Consolidation in 3 months.
12. 18 M	Transverse Middle 3rd, Compound; and tibial fracture	Nailing	43	19	+++	+++	+++	Osseous union in 2 months. Extensive callus developed during 4 months and subsequently decreased. Tibial fracture consolidated in 3 months.
13. 57 M	Oblique Boundary of M and L 3rds	Nailing	16	14	+	+++	+++	Solid union in 4 months. Callus increased only slightly in size but gained firm solidity.

14. 26 M	Transverse Middle 3rd	Nailing	29	20	++	+++	+++	Osseous consolidation in 3 months.
15. 40 M	Transverse Middle 3rd, Comminuted; Supracond. fr. of humerus	Nailing	47	14	++	+++	+++	Rapid osseous callus formation in 2 months, increasing up to 4 months; subsequent decrease. Supracondylar fracture consolidated in 6 weeks.
16. 66 M	Transverse Middle 3rd,	Nailing	23	26	++	++	+++	Consolidation in 4 months.
17. 45 M	Transverse Middle 3rd	Nailing	15	66	+	++	+++	Osseous union in 5 months.
18. 18 M	Transverse Middle 3rd; and tibial fracture	Nailing	22	43	++	+++	+++	Firm callus formation and consolidation in 3 months. Tibial fracture consolidated in 5 months.
19. 19 M	Transverse Middle 3rd	Nailing	26	30	++	+++	+++	Osseous union in 3 months.
20. 20 M	Transverse Middle 3rd, Compound	Nailing	39	24	++	+++	+++	Osseous union in 3 months.
Non-union or Delayed Union of Femur								
21. 22 M	Middle 3rd	Nailing and Iliac Bone Grafting	56	6	++	+++	+++	Two previous operations, 2 and 3 years ago, which brought no result. Sound union in 3 months.
22. 63 M	Middle 3rd	Nailing and Iliac Bone Grafting	68	61	+	++	+++	Previous skin transplantations on account of extensive soft part damage. Solid union after 6 months.
23. 37 M	Lower 3rd	Trepanation and Sequestrectomy	62	70	—	++	++	Previous open reduction with screws; osteitis and non-union ensued. Solid osseous union after 8 months.
24. 48 M	Upper 3rd	Nailing and Iliac Bone Grafting	52	30	++	+++	+++	Previous collum fracture of the hip; 2 months later sustained subtroch. fracture. Solid osseous union of both fractures in 3 months.
25. 57 M	Upper 3rd	Screws and Iliac Bone Grafting	76	10	++	++	+++	Pathologic fracture. Lues and osteoporosis. Extensive callus formation. Clinically solid union in 5 months.
26. 19 M	Upper 3rd	Nailing and Iliac Bone Grafting	26	10	+	++	+++	Previously: Oblique fracture in upper 3rd, treated with screws; delayed union and refracture. Solid osseous union in 4 months.
27. 59 M	Middle 3rd	Iliac Bone Grafting	41	123	—	—	++	Delayed union after bone grafting. Poor callus formation. After 6 months bridge-like consolidation.
28. 65 M	Middle 3rd	Trepanation and Iliac Bone Grafting	60	3	+	++		Previously: Internal fixation with plate and screws; osteitis and refracture followed. Consolidation of the fracture was under way, but unfortunately patient expired due to cardiac attack, 5 months after operation.

Table 1, continued

Case No. Age, Sex	Type and Site of Injury	Surgical Treatment	Hormonal Treatment: Duration, days	Hormonal Treatment: Started, days after trauma or operation	Radiographic Appearance after months: 2	4	6	Comments and Clinical Result
29. 52 F	Middle 3rd	Nailing and Iliac Bone Grafting	53	6	++	+++	+++	Polytraumatic case with compound fracture of femur. No consolidation had occurred within 6 months after trauma; fragment ends rounded and sclerotic. After operation and start of hormonal treatment rapid callus formation ensued. Sound clinical union after 4 months.
30. 53 M	Upper 3rd	Nailing and Iliac Bone Grafting	21	6	+	++	+++	Delayed union. After 4 months fair osseous consolidation.
31. 73 M	Middle 3rd	Nailing and Iliac Bone Grafting	59	41	+	++	+++	Polytraumatic case; delayed union. Strong osseous consolidation after 5 months.
Fractures of Tibial Shaft								
32. 40 M	Transverse Middle 3rd, Compound	Conservative	26	31	+	++	+++	Solid osseous union in 6 months.
33. 40 M	Transverse Middle 3rd, Bilateral	Conservative	33	6	++	+++	+++	Osseous union of both fractures in 4 months.
34. 39 M	Transverse Middle 3rd,	Conservative	20	26	++	+++	+++	Solid union in 3 months.
35. 50 M	Lower 3rd, Compound	Open Reduction with Screw	12	5	++	+++	+++	Osseous union in 3 months.
36. 26 M	Lower and Upper 3rd, Bilateral	Conservative	18	17	+	++	+++	Osseous union in 4 months on right side, in 5 months on left side.
37. 46 M	Lower 3rd, Compound	Conservative	14	11	+	++	+++	Osseous union in 4 months.
38. 43 M	Lower 3rd, Compound	Conservative	23	25	+	++	+++	Osseous union in 4 months.
39. 66 M	Lower 3rd, Compound	Conservative	30	7	—	+	+	Failure of union in 6 months. Later bone grafting resulted in union
Non-union or Delayed Union of Tibia								
40. 22 M	Middle 3rd	Osteotomy of Fibula and Compression with Pins	55	36	—	+	++	Two years previously: Compound tibial fracture with osteitis of fragment ends. Solid osseous union, clinically and roentgenologically in 8 months; fistula closed.

41. 25 M	Middle 3rd	Osteotomy of Fibula and Compression with Pins	48	63	—	+	++	Compound tibial fracture, subsequent osteitis of fragments, and fistula. Osseous union in 7 months.
42. 23 M	Boundary of L and M 3rds	Iliac Bone Grafting	52	10	+	+++	+++	Five years previously: Compound fracture, which failed to unite. Solid osseous union in 4 months.
43. 62 M	Middle 3rd	Iliac Bone Grafting	29	22	+	++	++	Previous bone grafting operation with failure of union. Solid osseous union in 5 months.
Fractures of Humerus								
44. 54 M	Middle 3rd, Comminuted	Conservative	20	17	++	+++	+++	Osseous consolidation in 2 months.
45. 35 M	Transverse Middle 3rd	Conservative	16	3	++	+++	+++	Osseous union in 2 months.
Non-union of Humerus								
46. 33 M	Transverse Lower 3rd	Iliac Bone Grafting with Screws	21	4	++	+++	+++	Two years old non-union of humerus. Solid osseous union in 3 months.
47. 37 M	Transverse Middle 3rd	Iliac Bone Grafting with Screws	34	8	++	+++	+++	Osseous union in 3 months.
Fractures and Delayed Union or Non-union of Cancellous Bone								
48. 90 F	Fracture of Femoral Neck	Conservative	44	43	+	++	+++	Union in 4 months.
49. 49 M	Fracture of Femoral Neck	Nailing	21	14	+	++	+++	Osseous union in 3 months.
50. 75 M	Trochanteric Fracture	Conservative	58	48	++	+++	+++	Osseous union in 3 months.
51. 63 M	Trochanteric Fracture	Conservative	26	29	++	+++	+++	Solid osseous union in 3 months.
52. 44 M	Trochanteric Fracture	Conservative	29	6	++	+++	+++	Firm consolidation in 2 months.
53. 65 F	Fracture of Femoral Neck, Delayed Union	Conservative	38	112	—	+	+++	Osseous union in 5 months.
54. 58 F	Fracture of Femoral Neck, Delayed Union	Nailing	62	105	—	+	+++	Solid osseous union in 6 months.
55. 50 M	Fracture of Femoral Neck, Non-union	Intertroch. Osteotomy	30	16	+	++	+++	Solid osseous union in 4 months.
56. 55 F	Trochanteric Fracture, Non-union	Intertroch. Osteotomy	45	7	+	+++	+++	Osseous union in 4 months.

Table 1, continued

Case No. Age, Sex	Type and Site of Injury	Surgical Treatment	Hormonal Treatment: Duration, days	Hormonal Treatment: Started, days after trauma or operation	Radiographic Appearance after months: 2	4	6	Comments and Clinical Result
57. 32 M	Fracture of Femoral Neck and Head, Comminuted	Arthrodesis	35	40	+	++	+++	Osseous union in 5 months.
58. 41 M	Posttraumatic Arthrosis of Knee Joint	Arthrodesis	27	6	++	+++	+++	Osseous union in 2 months.
59. 61 M	Posttraumatic Arthrosis of Knee Joint	Arthrodesis	29	5	++	+++	+++	Osseous union in 2 months.
60. 33 M	Posttraumatic Arthrosis of Knee Joint	Arthrodesis	20	12	++	+++	+++	Osseous union in 2 months.

B. Controls

Case No. Age, Sex	Type and Site of Injury	Surgical Treatment	No Hormonal Treatment	Radiographic Appearance after months: 2	6	4	Comments and Clinical Result
	Fractures of Femur						
1. 41 M	Transverse Middle 3rd	Conservative		+	+	++	Osseous union in 5 months.
2. 63 F	Transverse Lower 3rd, Comminuted	Conservative		—	—	+	No osseous union within 10 months.
3. 60 F	Oblique Lower 3rd	Conservative		—	+	++	Union in 7 months.
4. 41 M	Transverse Lower 3rd, Compound	Conservative		—	+	++	Osseous union in 6 months.
5. 76 F	Oblique Lower 3rd	Conservative		—	+	+	No osseous union within 8 months.
6. 63 F	Oblique Lower 3rd	Conservative		++	++	+++	Osseous union in 5 months.
7. 52 F	Oblique Lower 3rd	Conservative		++	++	++	Solid osseous consolidation in 5 months.
8. 67 F	Oblique Middle 3rd, Comminuted	Conservative		+	++	+++	Osseous union in 5 months.
9. 47 M	Transverse Middle 3rd	Conservative		—	++	++	Polytraumatic case. Osseous consolidation within 8 months.
10. 31 M	Transverse Boundary of L and M 3rds	Conservative		+	++	++	Osseous union in 5 months.
11. 44 F	Transverse Upper 3rd	Nailing		—	+	+	Polytraumatic case. No osseous union in 8 months.

12. 70 F	Transverse Middle 3rd	Nailing		—	+	+ +	Osseous union in 6 months.
13. 18 M	Transverse Upper 3rd, Comminuted	Nailing		+ +	+ + +	+ + +	Solid osseous union in 4 months.
14. 20 F	Transverse Middle 3rd, Comminuted	Nailing		+ +	+ + +	+ + +	Solid union in 4 months.
15. 73 F	Transverse Lower 3rd, Comminuted	Nailing		+	+ +	+ +	Osseous union in 6 months.
16. 19 F	Transverse Middle 3rd	Nailing		+ +	+ +	+ + +	Osseous union in 4 months.
17. 49 M	Transverse Middle 3rd	Nailing		+	+ +	+ + +	Osseous union in 5 months.
18. 44 F	Transverse Middle 3rd	Nailing		+	+ +	+ + +	Osseous union in 6 months.
19. 17 M	Transverse Middle 3rd	Nailing		+	+ +	+ + +	Osseous union in 5 months.
20. 21 M	Oblique Middle 3rd, Comminuted	Nailing		+	+ +	+ +	Osseous union in 5 months.
Fractures of Tibial Shaft							
21. 37 F	Transverse Upper 3rd	Conservative		+	+ +	+ +	Osseous union in 4 months.
22. 60 F	Oblique Lower 3rd	Conservative		+	+ +	+ +	Osseous union in 5 months.
23. 56 M	Oblique Lower 3rd	Conservative		—	+	+	Osseous union in 7 months.
24. 49 F	Oblique Lower 3rd	Conservative		+	+	+ + +	Consolidation in 6 months.
25. 34 M	Lower 3rd, Compound Comminuted	Conservative		—	+	+	No osseous consolidation.
26. 21 N	Transverse Middle 3rd	Conservative		+	+ +	+ +	Osseous union in 6 months.
27. 46 M	Middle 3rd	Iliac Bone Grafting		+	+ +	+ +	Delayed union after compound fracture. Consolidation after bone graft operation in 6 months.
Fractures of Cancellous Bone							
28. 63 F	Fracture of Femoral Neck	Nailing		+	+	+ +	Osseous union in 7 months.
29. 48 M	Pertrochant. Fracture of Femur	Conservative		+	+ +	+ +	Osseous union in 4 months.
30. 61 F	Pertrochant. Fracture of Femur	Nailing		+	+ +	+ +	Osseous union in 5 months.

III METHODS

Hormonal Treatment

The treatment of all 60 patients concerned in this investigation included, in addition to appropriate orthopaedic care, intramuscular administration of 10 U.S.P. units growth hormone (Somatotropine, STH)[1] and 2 U.S.P. units thyrotropine (Thyroid Stimulating Hormone, TSH)[2] every second day. The STH was a chromatographically purified preparation derived from the pig's hypophysis and its above-mentioned dosis had an effect equivalent to 25 mg of *Li* and *Wilhelms*' preparation.

The usual period of hormone administration was 3—10 weeks. In cases with non-union or delayed union and compound fracture or osseous defect this treatment was longer.

Assessment of Osseous Union

For evaluation of the progress of osseous union, the development of callus was closely observed during the period of investigation in addition to the clinical examinations. Roentgenograms were taken of all patients at regular intervals, more frequently during the initial phases of repair, in order to check on the position of the fragments. At a later stage roentgenological examination took place approximately every second month; this was continued until the final result of the repair process was definitely seen. The roentgenologic criterion of bony consolidation was a bridgelike callus formation between the ends of the fragments; the fracture line could then still be visible, but without signs of sclerosis. If no callus formation was observable, no finding of osseous union was recorded; the assessment was in such cases deferred to the next examination until consolidation was positively established by the said criteria.

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[1] »Somacton»; Ferring, Malmö, Sweden.
[2] »Actyron»; Ferring, Malmö, Sweden.

Quantitative Callus Evaluation

In 20 cases of the investigation series proper, where fracture of the femur was involved, and in an equal number of similar cases belonging to the control series, roentgenograms were taken two months and four months after the trauma or surgical intervention and examined for the quantity of callus by the following procedure.

From each roentgenogram the outline of the callus was copied on tracing paper and the total area of the resulting figure was determined with the planimeter. The mathematical treatment of the values thus found will be described in connection with the results.

Laboratory Examinations

The calcium and inorganic phosphorus contents of the patients' blood serum and the alkaline phosphatase activity were determined, at intervals of one week and in a later phase of the hormonal treatment at intervals of two weeks. Similarly, the urinary calcium and phosphorus excretion were determined from the collected 24-hour urine. The calcium determinations were made by the EDTA titration method and the phosphorus determinations by Dryer's method. The alkaline phosphatase activity was evaluated in Bodansky units. — The patients were on a constant diet, and no milk, cheese or fish was given during period of three days prior to each sampling.[1]

[1] The dietetic and laboratory work was carried out under supervision of the Physician of the Clinic's Laboratory Department, University Lecturer R. Gordin, M.D.

IV RESULTS

Clinical Aspects

Hormonal Treatment Series

Of all 64 fractures, delayed unions, non-unions and malunions in the investigation series proper, 62 showed ultimate osseous union. In two instances no union was obtained. The results, proved by radiography and the time when osseous consolidation was established, are seen in Table 2, p. 38.

Table 1 shows in each individual case the age and sex of the patient, the type and site of the bone injury, the surgical treatment and the period during which hormonal treatment was applied. This treatment was continuous during the number of days given in the table. Moreover, the table gives the time interval that had passed since the trauma or surgical intervention before hormonal treatment was instituted, and reports on the radiographic appearance of the callus after 2, 4 and 6 months, and the ultimate clinical result.

The hormone administration was well tolerated by all patients and in many of them improvement of physical condition could be noted during the hormonal treatment. No allergic reactions or harmful effects occurred, except for slight hyperglycaemia in some cases.

Fractures of the Femoral Shaft

The investigation series proper contains altogether 22 fractures of the femur in twenty patients. Two of the fractures were located in the upper third of the femur, eleven in the middle third, and nine in the lower third or on the boundary between middle and lower thirds. In the case of twelve fractures the fragments could be brought into alignment and made to retain

their position satisfactorily by conservative therapy consisting of traction and reduction, while in ten instances medullary nailing was undertaken, in connection with which the point of the fracture was exposed. Medullary nailing was considered best and it was the method of choice unless contra-indication was present in the form of fractures in the upper or middle third of the femur. In the cases where a supracondylar or oblique fracture was concerned, conservative treatment was frequently applied.

The duration of combined STH and TSH hormonal treatment was, except for three cases with a shorter period of treatment, between 21 and 64 days; average time of treatment 37 days. The time interval from trauma or surgical intervention to commencement of hormonal therapy in the cases with femur fractures was between 12 and 67 days.

In all cases osseous union was achieved, proved radiologically and by clinical assessment. The time required to reach this was 2 months in two cases, 3 months in nine, 4 months in seven, 5 months in three and 6 months in one case.

The series includes one patient with osteogenesis imperfecta (Case No. 4), whose injury was bilateral low fracture of the femur. Combined STH and TSH administration was not commenced until 41 days after the trauma. Prior to this time the callus had developed very poorly in the initial stage. Roentgenograms taken after six weeks and after eight weeks show no evidence of consolidation. After three months, when the patient had received 25 mg STH every second day during four weeks and 28 U.S.P. units thyrotropin, a distinct periostal callus had formed, bridging the gap between the fragments. Bony consolidation of the fractures took place so that the patient could resume weight-bearing.

The observation emerges from the clinically recorded results that in conservative and operative treatment of femur fractures under STH and TSH therapy callus formation took place within 2—6 months, on an average within 3.5 months, resulting rapidly in osseous consolidation. The results also suggest that the effect on the callus formation was slighter with hormonal therapy of less than 3 weeks' duration (Cases No. 9, 13, 17) than when this therapy was continued more than 30 days. In all but two cases the hormonal treatment was started at an early phase during the first or second month when the callus formation was under development. Hormonal treatment given during this time seems to be optimal as regards callus formation and osseous consolidation.

The following case report presents an example of a case involving comminuted fracture of the femur with multiple trauma. The fracture was

Fig. 1. *Case No. 15.* — Roentgenograms of a case with comminuted fracture of the femur (*A*), treated by medullary nailing. Combined growth hormone and thyrotropin treatment applied during 47 days. — Rapid osseous callus formation ensued in 2 months (*B*); solid union completed after 5 months (*C*). The nail was removed after 6 months (*D*). — Cf. Fig. 2.

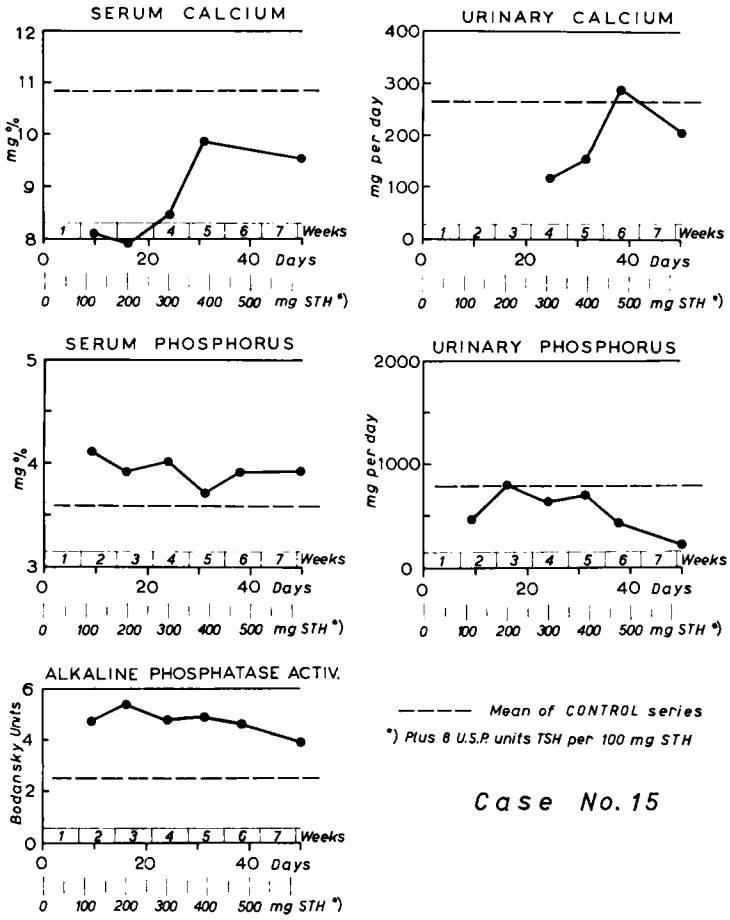

Fig. 2. *Case No. 15.* — Graphs showing the metabolic response to hormonal treatment of the case concerned in Fig. 1. Zero time corresponds to start of hormonal treatment (14 days after operation). — Low calcium content of serum; values of 8.1, 7.9 and 8.45 mg % being recorded during the first four weeks, and subsequent increase. Corresponding decrease of urinary calcium excretion, with values varying between 115 and 285 mg per day. — Elevated values of serum phosphorus content as well as alkaline phosphatase activity, values as high as 5.3 Bodansky units being recorded for the latter. Reduced urinary phosphorus excretion, lowest value 216 mg per day, indicating retention of phosphorus.

treated by medullary nailing and combined STH and TSH therapy was applied, with the result of rapid osseous consolidation within two months in the form of a solid osseous formation between the fragments (Figs. 1 and 2).

Case No. 15. — A mechanic, aged 40, sustained in an automobile accident comminuted fracture of the femur, fracture of the skull with cerebral injury, and supracondylar fracture of the humerus. Open retrograde medullary nailing was performed on the eighth day; combined STH and TSH therapy was applied during 47 days, beginning two weeks after the operation. Rapid osseous consolidation ensued between the ends of the fragments and the fracture gained firm stability in two months. The supracondylar fracture was repositioned and encased in plaster in anatomical position; this fracture was consolidated in six weeks.

The calcium content in the patient's blood serum was low: the values of 8.1, 7.9 and 8.45 mg % were recorded during the first four weeks. This was followed by an increase to 9.83, with the final value of 9.5 mg %. — The urinary calcium excretion showed a corresponding decrease, with values varying between 115 and 285 mg per day. — The serum phosphorus content presented increased values, as did the alkaline phosphatase activity; the highest value recorded for the latter being as high as 5.3 Bodansky units. — The urinary phosphorus excretion was reduced, indicating retention of phosphorus, with a lowest value of 216 mg per day.

Non-Union or Delayed Union of Femur

There were eleven cases in which non-union or delayed union of the femur had to be treated. In all cases an operation was performed, most frequently medullary nailing and transplantation of bone. In two cases (No. 23 and 28) the non-union was complicated by osteitis of the femur with a cutaneous fistula as a consequence of an earlier operation.

The duration of hormonal treatment in this group varied between 21 and 76 days. The average treatment period was 52 days, which is the highest among all different groups constituting the material of this investigation. Hormonal treatment was commenced at times between 3 and 70 days after the operation except for one case (No. 27), in which STH and TSH treatment was given exceptionally as late as four months after the operation, during a period of 41 days. In this case another bone graft operation was considered because no consolidation had taken place. The patient requested a postponement and was left under observation. Examination after two months revealed that the fracture had consolidated without further operative treatment.

All eleven cases in this group presented serious injuries which had already been treated previously but which had not responded to treatment or were complicated by refracture or osteitis. In ten of them osseous union proved by radiography was achieved, corresponding to 90 % successful recovery. The time required for consolidation to occur was 3 months in two cases, 4 months in three, 5 months in two, 6 months in two and 8 months

in one case; average 4.3 months. In one case with non-union and osteitis (Case No. 28) the infection abated and incipient consolidation could be observed, but the patient succumbed to a heart attack five months after trepanation and bone graft operation.

It can be noted that in the cases in which the hormonal treatment was started within 30 days after the operation and continued during a long period, up to 52—76 days, (Cases No. 21, 24, 25, 29) osseous consolidation took place sooner. In the cases in which hormonal treatment was instituted at a later stage, more than 40 days after the operation, (Cases No. 22, 23, 27, 31) and had a duration of 59—68 days, consolidation was obtained, but it took a correspondingly longer time. In the case with accompanying infection (Case No. 23) repair of the bone was very slow as compared with the aseptic cases, but bony consolidation was ultimately attained.

As an example of non-union of the femur, which did not respond favourably to two previous operations, Case No. 21 may be cited. In this case the effect of hormone administration is reflected by the decrease of the serum calcium content and the steep decline of urinary calcium excretion (Figs. 3 and 4).

Case No. 21. — An engine stoker, aged 22, sustained 23. VIII. 1958 in a traffic accident a fracture of the left femur. 28. VIII. 1958 osteosynthesis (Lane); 3. IV. 1959 trepanation and bone graft operation. Non-union and varus deformity developed, disabling the patient. 6. XI. 1960 osteotomy, intramedullary nailing and iliac bone graft operation were performed, and combined STH and TSH hormone treatment was applied during eight weeks. The bone fragments were sclerotic and avascular and the space between them was filled with abundant fibrous tissue. The bone graft applied at the preceding operation, which was calcified and had failed to unite, was removed. Recovery took place without complications; after three months (10. II. 1961), the gap between fragments and the bone sclerosis had disappeared, while at the point of non-union a dense but not excessive callus formation was noted. The patient was allowed to move freely and to resume weight-bearing. Complete osseous consolidation of the fracture and normal function ensued. — The serum calcium content decreased during the first three weeks from 10.1 to 9.3 mg %. Urinary calcium excretion fell abruptly to a low level (from 340 mg per day initially to 24 mg per day), which persisted throughout the period of hormone application. The serum phosphorus content displayed an increasing tendency; initial value 3.6 and highest value, 4.2 mg %. There were no marked changes in urinary phosphorus excretion or alkaline phosphatase activity.

Fig. 3. *Case No. 21.* — Roentgenograms illustrating osseous consolidation in a case of non-union and varus deformity following fracture of the femur (*A*, *B*). Combined growth hormone and thyrotropin treatment applied during eight weeks, starting 6 days after the operation. The surgical treatment was osteotomy and intramedullary nailing with bone grafting. — A firm, non-excessive callus formation can be seen after 3 months (*C*). End result after 6 months: complete osseous union with good anatomical position (*D*, *E*). — Cf. Fig. 4.

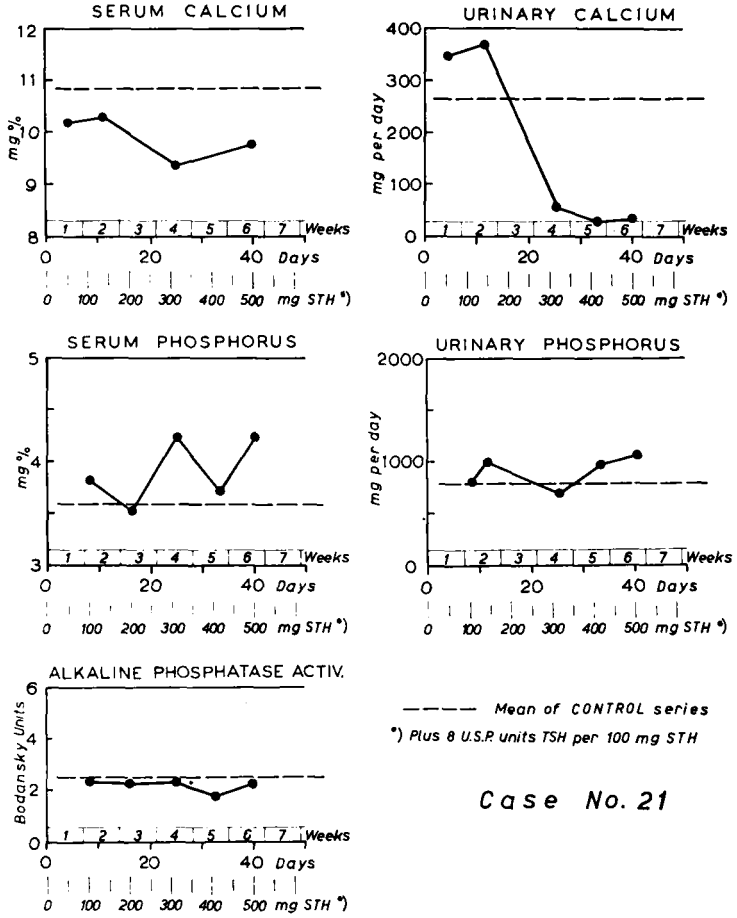

Fig. 4. *Case No. 21.* — Graphs showing the metabolic response to hormonal treatment of the case concerned in Fig. 3. Zero time corresponds to start of hormonal treatment (6 days after operation). — Decrease of serum calcium content during the first three weeks from 10.1 to 9.3 mg %. Abrupt decline of urinary calcium excretion to a low level (from 340 mg per day initially to 24 mg per day), persisting throughout the period of hormone administration. — Increasing tendency of serum phosphorus content; initial value 3.6 and highest value 4.2 mg %. — No marked changes in urinary phosphorus excretion or alkaline phosphatase activity.

In the next case an example is encountered of the refracture of osteoporotic bone in the subtrochanteric region, after nailing of the femoral neck. In this case, too, a distinct decrease in urinary calcium excretion was observed during the time of hormone administration. Also the urinary phosphorus excretion was seen to decrease, and the serum phosphorus content displayed fairly high values (Figs. 5 and 6).

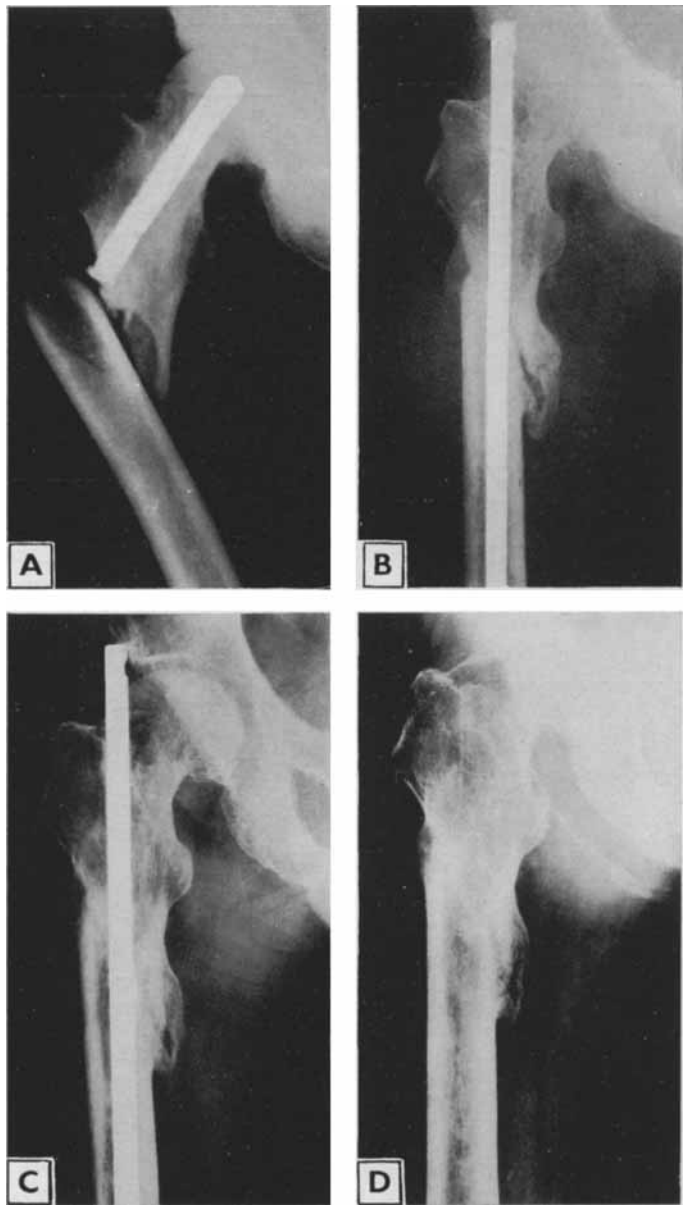

Fig. 5. *Case No. 24.* — Roentgenograms illustrating osseous consolidation in the case of a diabetic patient with a subtrochanteric fracture of the femur at the point of insertion of the nail applied two months previously owing to fracture of the femoral neck (*A*). Combined growth hormone and thyrotropin treatment applied during 52 days. The surgical treatment was intramedullary nailing and iliac bone grafting. — Some increase of blood sugar values occurred during the period of treatment, but no ketonuria. — Rapid callus formation ensued (*B* — 2 months, *C* — 4 months, *D* — 6 months after the operation), and good functional ability was restored. — Cf. Fig. 6.

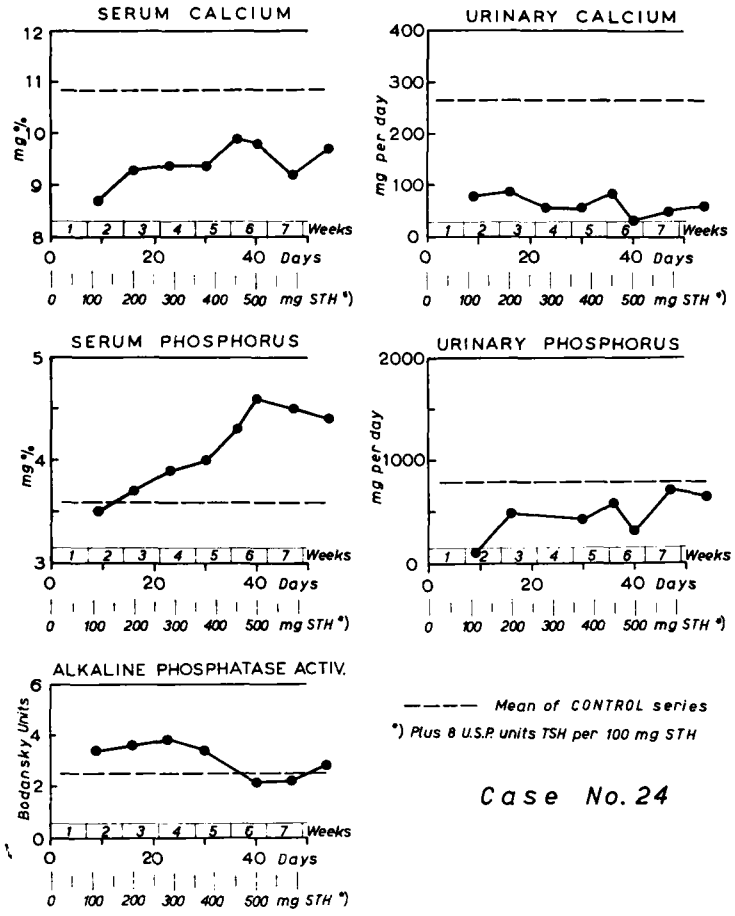

Fig. 6. *Case No. 24.* — Graphs showing the metabolic response to hormonal treatment of the case concerned in Fig. 5. Zero time corresponds to start of hormonal treatment. — Lowered serum calcium level. Urinary calcium excretion fell to 30 mg per day and maintained a low level throughout the period of hormonal treatment. — Elevated serum phosphorus content, with values up to 4.6 mg %, urinary phosphorus excretion mostly below 500 mg per day. Alkaline phosphatase activity showed increased values up to 3.8 Bodansky units.

Case No. 24. — A diabetic electrician, aged 48, sustained a fracture of the femoral neck, which was treated by nailing 25. X. 1960. After two months (28. XII. 1960) a subtrochanteric fracture occurred in the same leg at the point of entrance of the nail. Intramedullary nailing with iliac bone graft was performed and combined STH and TSH treatment was applied during 52 days, starting on the 30th postoperative day. At the same time 24 units insulin were given daily. The blood sugar values somewhat increased during hormonal treatment (218—264 mg% compared to previous 125—215 mg%) but no ketonuria occurred. Healing of the fracture

was uneventful and a dense bony callus developed. After three months weight-bearing could be resumed, and good functional ability was regained. — The serum calcium level was lowered and urinary calcium excretion decreased to 30 mg per day, maintaining a low level throughout the period of hormonal treatment. Elevated serum phosphorus content was noted, with values between 4.3 and 4.6 mg%, while the urinary phosphorus excretion was mostly below 500 mg per day. At the same time the alkaline phosphatase activity showed increased values up to 3.8 Bodansky units.

Fractures of the Tibial Shaft

Altogether ten fractures of the tibia or fibula were present in eight patients. The cases with fractures of tibia and femur both have been referred to the femur fracture group and do not appear here. Five patients had a compound fracture and all but one of the others had comminuted fractures. All fractures were located in the middle and lower thirds of the lower part of the leg, except for one bilateral case with one fracture in the upper and another in the lower third.

Except for one case treated by open reduction and screw fixation, the treatment was conservative in all cases, consisting of closed reduction and plaster cast. These patients stayed only a relatively short time in the Clinic and the periods of hormonal treatment were shorter than in the group of femur injuries; average duration of hormone administration was 22 days.

The results reveal that bony consolidation of the fracture took place in nine out of ten cases, equivalent to 90 % successful recovery; average consolidation time was 4.0 months. Roentgenographic and clinical consolidation was achieved within 3 months in two cases (No. 34 and 35), in 4 months in four cases (No. 37 and 38, the bilateral fracture case No. 33 and the fracture of the right tibia in Case No. 36), in 5 months in one case (left lower leg of Case No. 36), and in 6 months in one case with compound fracture (Case No. 32). In one case osseous consolidation failed to occur, namely, in Case No. 39, involving compound fracture of the lower third of the lower part of the leg in a man aged 66. Subsequent operation with bone graft resulted in consolidation in this case.

Non-Union or Delayed Union of Tibia

The material contains four cases of non-union or delayed union in the lower part of the leg. In two of them (Cases No. 40 and 41) osteitis of the fragment ends and cutaneous fistula were present as a consequence of compound fracture when the treatment was commenced. The third case (No.42) was one of non-union after compound fracture that had occurred five years

Fig. 7. *Case No. 40.* — Roentgenograms of a case with serious compound fracture of tibia and fibula with bone defect of the tibia (*A*). The case was complicated by osteitis and non-union (*B, C*). Surgical treatment was osteotomy of fibula and compression-osteosynthesis of tibia. Combined growth hormone and thyrotropin treatment was applied during eight weeks, plus antibiotics. — The symptoms of inflammation were allayed and solid osseous union was achieved in 8 months (*D*). — Cf. Fig. 8.

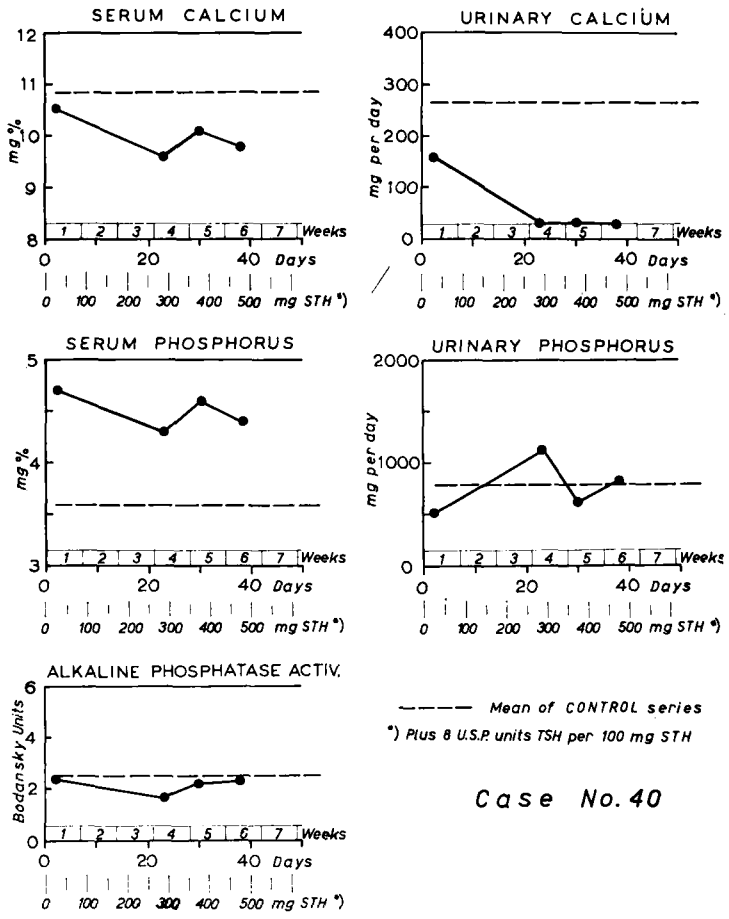

Fig. 8. *Case No. 40.* — Graphs showing the metabolic response to hormonal treatment of the case concerned in Fig. 7. Zero time corresponds to start of hormonal treatment. — Reduced urinary calcium excretion, as referred to the control level, down to values of 28 mg per day. — Elevated serum phosphorus content throughout the period of hormonal treatment. Urinary phosphorus excretion indicates retention of phosphorus in the initial stage but displays higher values at a later time. — No changes observable in alkaline phosphatase activity.

ago, while in the fourth (Case No. 43) inveterate non-union of the middle third of the lower leg was concerned, with failure of a previous bone graft operation to produce consolidation.

The method of surgical treatment in the aseptic cases was iliac bone graft operation; in the cases with concomitant infection, osteotomy of the fibula and compression of the ends of the tibia with the aid of Steinmann pins.

In both cases with combined non-union and osteitis routine antibiotic treatment was moreover applied. In all cases firm osseous union was obtained. This was achieved within 4 and 5 months, respectively, in the cases with uncomplicated non-union (Cases No. 42 and 43) and in 7 and 8 months, respectively, in cases No. 40 and 41, which presented non-union with osteitis as further complication; all times counted from the surgical intervention.

One of the two last-mentioned cases is concerned in the following case report (Figs. 7 and 8).

Case No. 40. — In this case of a student aged 22, osteitis of the tibia and non-union, consequent upon serious compound fracture of the lower part of the leg, was concerned. After three previous, unsuccessful operations, fibular osteotomy and compression-osteosynthesis of the tibia were performed 27. VI. 1960, without exposure of the pseudarthrosis on account of suppurating osteitis. Routine antibiotic treatment was given; 3. VIII. 1960 combined hormonal and antibiotic treatment, 8 weeks in duration, was started. Gradual consolidation followed: the sclerosis between the fragments lessened and the inflammatory symptoms disappeared. Considerable clinical stability had ensued in 6 months; after 8 months (21. II. 1961) there was roentgenologically patent consolidation.

Except for a shortening of the leg by 2,5 cm, good function was achieved. — The values describing the calcium and phosphorus metabolism reveal lowered urinary calcium excretion as referred to the control level, down to values of 28 mg per day. The serum phosphorus content was elevated throughout the time of hormonal treatment, increasing from 3.3 mg % to a level of 4.3—4.7 mg%. The urinary phosphorus excretion indicated retention of phosphorus in the initial stage, but at a later time the excretion increased. No changes were observable in alkaline phosphatase activity.

Fractures or Non-Union of Humerus

The material includes two cases with fracture of the humerus (Cases No. 44 and 45) and likewise two in which there was non-union after fracture of the same bone (Cases No. 46 and 47). Conservative treatment was applied in the first two, consisting of reduction and plaster cast. Both non-unions were treated by the same, surgical method: excision of the pseudarthrosis, and iliac bone graft operation with fixation by screws. Hormonal treatment was given during periods of 16 and 20 days in the fracture cases, and during 21 and 34 days, respectively, in the cases with non-union. In all cases hormone administration was commenced at an early stage after the trauma or surgical intervention.

Osseous union took place in all cases, in both fractures within 2 months of the trauma, and within 3 months of the operation in the cases with non-union of the fracture.

Fractures, Delayed Union or Non-Union of Cancellous Bone

13 cases in the material concern injuries of cancellous bone. Five of them were injuries of the femoral neck, namely, two recent fractures (Cases No. 48 and 49) and three cases of delayed union or non-union (Cases No. 53, 54 and 55). Three others (Cases No. 50, 51 and 52) were trochanteric fractures, in one case (No. 56) there was non-union after a pertrochanteric fracture, and one case (No. 57) concerned comminuted fracture of the neck and head of the femur. Finally, three patients referred to this series suffered of malunion after intraarticular fracture, with secondary arthrosis (Cases No. 58, 59 and 60).

Conservative methods of therapy were followed in one case with injury of the femoral neck (Case No. 48) and in the four recent trochanteric fracture cases (No. 50, 51, 52 and 53). In the other cases operative treatment was applied, namely, clavifixation (in Cases No. 49 and 54), intertrochanteric osteotomy (Cases No. 55 and 56) or arthrodesis (Cases No. 57, 58, 59 and 60).

The duration of hormonal treatment in this group of cancellous bone injuries varied between 20 and 62 days, on an average 35 days. Except for two cases with delayed union subsequent to fracture of femoral neck (Cases No. 53 and 54), this treatment was commenced not later than 48 days after the trauma or surgical intervention.

In all thirteen cases, osseous consolidation was achieved. This took place within 2—6 months (average 3.2 months); namely, 3 and 4 months, respectively, in the two cases with recent fracture of the femoral neck (Cases No. 49 and 48), within 4 months in one case with non union after fracture of the femoral neck (Case No. 55) and in one case with non-union after trochanteric fracture (Case No. 56). In the cases involving fresh trochanteric fractures consolidation was recorded after 2 months in one case (No. 52) and after 3 months in two others (Cases No. 50 and 51). After arthrodesis of the hip joint in comminuted fracture of the neck and head of the femur consolidation took place within 5 months (Case No. 57), and after arthrodesis of the knee joint firm union could be established after 2 months (Cases No. 58, 59 and 60). It is worth mentioning that in two cases of injury of the femoral neck with delayed union (Cases No. 53 and 54), in which hormonal treatment was instituted more than 100 days had passed since the fracture, osseous union was produced.

The obvious beneficial effect of hormonal treatment at a late time is illustrated by the report of a case (No. 54) involving delayed union after transcervical fracture of the femoral neck (Figs. 9 and 10).

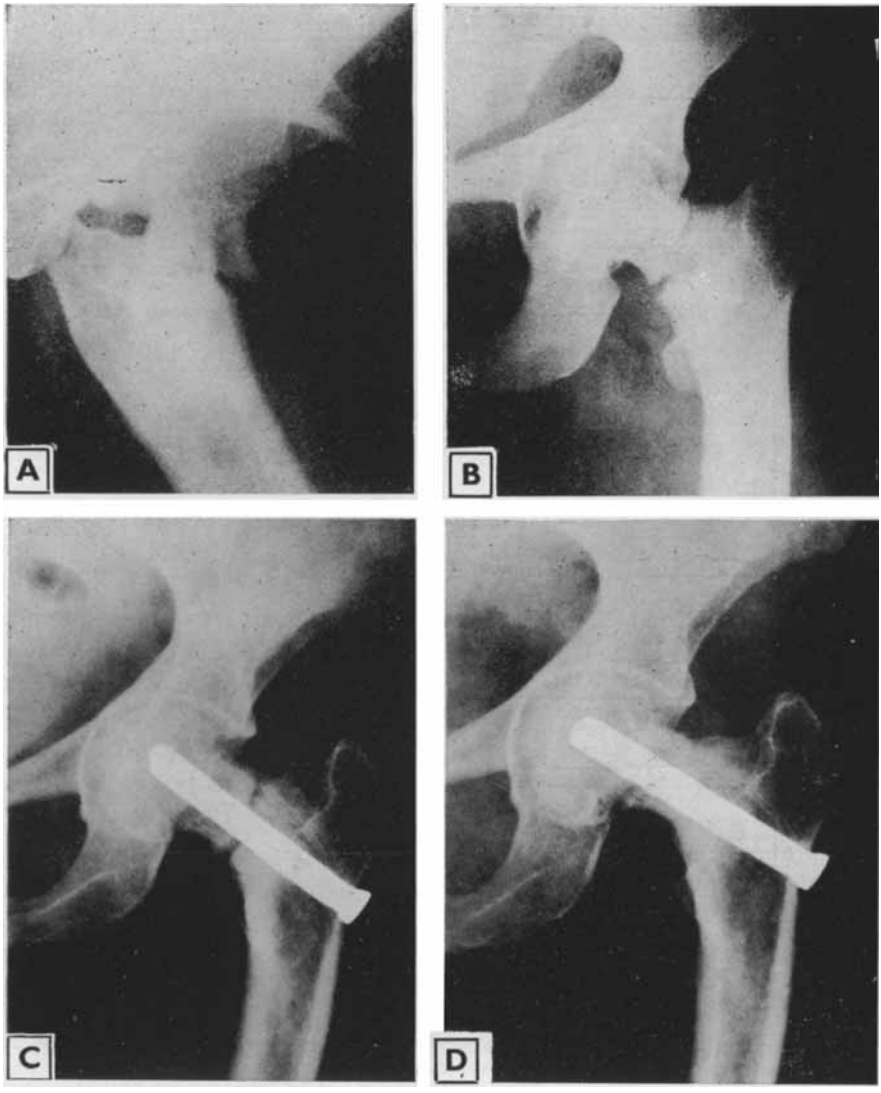

Fig. 9. *Case No. 54.* — Roentgenograms illustrating a case of transcervical fracture of the femoral neck (*A*, *B*) with delayed union after previous nailing. Gap between the fragments and incipient sclerosis observable 3 months after the nailing (*C*). Combined growth hormone and thyrotropin treatment applied during two months. The result, 3 months after the start of hormonal treatment is seen in Fig. *D*, which shows osseous union. — Cf. Fig. 10.

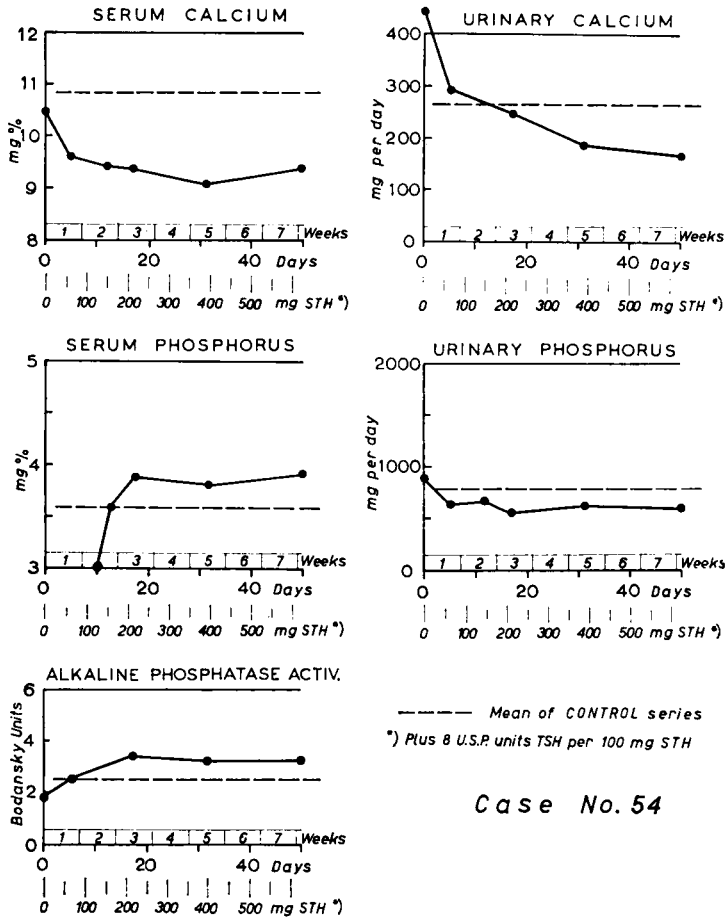

Fig. 10. *Case No. 54.* — Graphs showing the metabolic response to hormonal treatment of the case concerned in Fig. 9. Zero time corresponds to start of hormonal treatment. — Serum calcium content decreased during the time of hormonal treatment, being lowest at about 5 weeks and remaining below the control level also in its subsequent rise. Urinary calcium excretion reveals calcium retention, which increased in the course of treatment. — Serum phosphorus content and alkaline phosphatase activity were slightly elevated from control level.

Case No. 54. — A widow, aged 58, female, sustained a transcervical fracture of the neck of the femur, which was treated by nailing on the day after the fracture, 20. X. 1961. Repair of the fracture was delayed; after 3 months (26. I. 1962) roentgenography revealed a distinct gap between the fragments. Combined STH and TSH treatment was commenced, which was continued through two months at a dosage of 25 mg STH and 2 U.S.P. units TSH every second day, totalling 775 mg and 62 units, respectively. On 12. III. 1962 the gap between the fragments was found to be reduced,

and roentgenographic examination on 21. IV. 1962 established osseous consolidation. — The metabolic characteristics recorded in th s case show that the serum calcium content decreased during the hormonal treatment, being lowest at about 5 weeks and remaining below the control level also in its subsequent rise. The urinary calcium excretion revealed calcium retention, which increased in the course of treatment. Serum phosphorus content and alkaline phosphatase activity were slightly elevated from the control level.

Control Series

Among the cases constituting the controls of the present investigation, presented in Tables 1 and 2, there were 20 fractures of the femur, in 17 of which osseous consolidation took place within 4—8 months (average 5.3 months), namely, within 4 months in three, within 5 months in eight, within 6 months in four, within 7 months in one and within 8 months in one case. Three cases presented no roentgenological evidence of union.

The number of tibial fractures was six, in five of which consolidation occurred within 4—7 months (average 5.5 months); one compound tibial fracture did not progress to consolidation. A case of non-union of the tibia, in which bone graft operation had been performed, united in 6 months.

Of the three fractures of cancellous bone in this series, one fracture of the femoral neck showed osseous consolidation in 7 months, and two trochanteric fractures had consolidated within 4 and 5 months, respectively.

It has to be noted that the control series contains no cases in which osteitis would have been present, while in the hormonal treatment series this complication existed initially in four cases. It is therefore appropriate in the subsequent comparison of both series to disregard one of the last-mentioned injuries, which failed to unite.

Comments

Summarizing the main results reported in this chapter, the following observations can be stated:

Osseous consolidation took place in 62 out of the 64 bone injuries in the material with combined growth hormone and thyrotropine administration in addition to appropriate orthopaedic treatment. Excluding one case of non-union in which osteitis was present as complication, union failed to occur in one case (1.5 %). In the control series of 30 cases osseous union ensued in 26 and failed to take place in four (13.5 %). — Cf. Table 2.

TABLE 2. CLINICAL RESULTS IN THE HORMONAL TREATMENT SERIES AND CONTROL SERIES, PROVED BY RADIOGRAPHY

Type of Injury	Hormonal Treatment Series									Control Series						Average Consolidation Time in succesfully consolidated cases, months[4])		
	Injuries, Total	Number of Injuries showing consolidation after months							Failures of Union	Injuries, Total	Number of Injuries showing consolidation after months				Failures of Union	Horm. Treatm. Series	Control Series	Diff.
		2	3	4	5	6	7	8			4	5	6	7	8				
Fracture of femur	22	2	9	7	3	1			—	20	3	8	4	1	1	3	3.5	5.3	1.8***
Non-union or delayed union of femur	11		2	3	2	2		1[2])	1[2])								4.3		
Fracture of tibia	10		2	5	1	1			1	6	1	1	2	1		1	4.0	5.5	1.5
Non-union or delayed union of tibia	4			1	1		1[2])	1[2])	—	1			1			—	4.5	(6)	
Fracture of humerus	2	2							—								2.0		
Non-union or delayed union of humerus	2		2						—								3.0		
Fracture of femoral neck	3		1	1	1[3])				—	1				1		—	3.9	(7)	
Non-union or delayed union of femoral neck	3			1	1	1			—								4.9		
Trochanteric fracture	3	1	2						—	2	1	1				—	2.6	4.5	1.9
Non-union of trochanteric fracture	1			1					—								(4)		
Malunited condylar fracture	3	3							—								2.0		
All injuries	64	8	18	19	9	5	1	2	2	30	5	10	7	3	1	4	3.7	5.3	1.6***
All injuries[1])	63								1	30						4			
	100 %								1.5 %	100 %						13.5 %			

[1]) 1 osteitis-complicated non-union of femur omitted
[2]) Non-union and osteitis (not included in average consolidation time values)
[3]) Comminuted fracture of femoral head and neck
[4]) Logarithmic mean

***: Highly significant difference ($P < 0.001$)

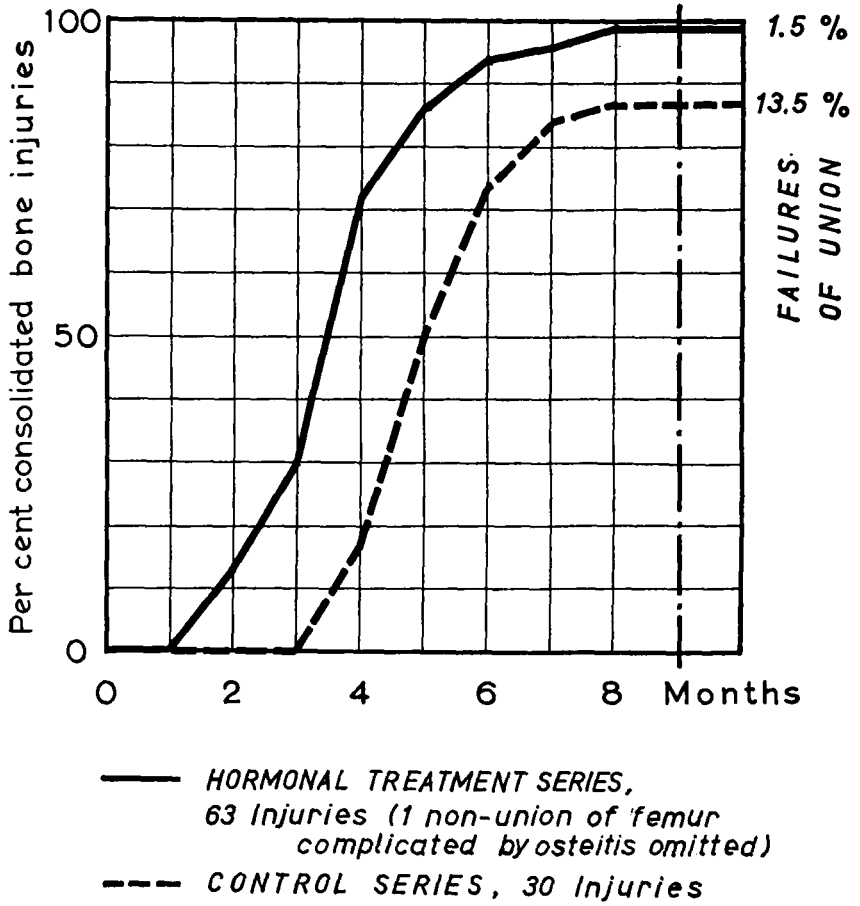

Fig. 11. Radiographically established clinical results in the hormonal treatment series and control series. Percentages of injuries (fractures, delayed unions or non-unions) observed to have consolidated within number of months marked on x-axis, and percentage of ultimate failures of union.

In Fig. 11 the average progress of consolidation in the hormonal treatment series is made evident by a line representing the percentage of all cases in the series that have been recorded as consolidated within 2, 3,4 months etc. The corresponding (dotted) line derived from the results of the control series shows a nearly constant delay of 1.5—2 months (horizontal distance) in comparison. — The figure also shows the percentage of ultimate failures, *i. e.*, of fractures that have not united in 8 months. This percentage is nine times as high in the control series (13.5 %) as that in the hormonal treatment series (1.5 %).

All 20 femur fractures comprised in the material consolidated, as did ten of its 11 non-unions or delayed unions, while one non-union case complicated by osteitis did not respond to the treatment. The time for osseous consolidation to occur was between 2 and 6 months with the femur fractures, on an average 3.5 months. In the group of non-unions or delayed unions this time was 3—8 months: average 4.3 months. — The control series contained 20 femur fractures, of which 17 united, and this took place within 3—8 months, on an average 5.3 months. In the other three the outcome was delayed union or non-union.

Ten tibial fractures belong to the hormonal treatment series; five of them were closed fractures and five were compound fractures. Nine of them terminated in osseous consolidation within 3—6 months, with an average of 4.0 months, but delayed union resulted in one compound fracture. In four tibial non-unions, two of them complicated by osteitis, the treatment was successful in producing osseous union; this took place within 4—8 months, average (excluding the cases with osteitis) 4.5 months. — The control series has six tibial fractures, of which five were united within 4—7 months, average 5.5 months. In one case union was not achieved.
Two fractures and two non-union cases of the humerus all united, the first-mentioned in 2 months both and the latter, also both, in 3 months.

The series concerning injury to cancellous bone comprised thirteen cases, in three of them fracture of the femoral neck, in three delayed union of the femoral neck, in three trochanteric fracture, in one non-union after trochanteric fracture, and in three malunited condylar fracture being involved. All produced osseous consolidation within 2—6 months, average 3.2 months. — Also the three fractures of cancellous bone in the control series terminated in osseous union; the time required to achieve this being 4—7 months.

Quantitative Callus Study

A particular study was carried out with regard to the quantity of callus formed in the course of the repair process and its rate of development under hormonal treatment and in the controls. Roentgenograms taken 2 months and 4 months after the trauma or surgical intervention of 20 patients

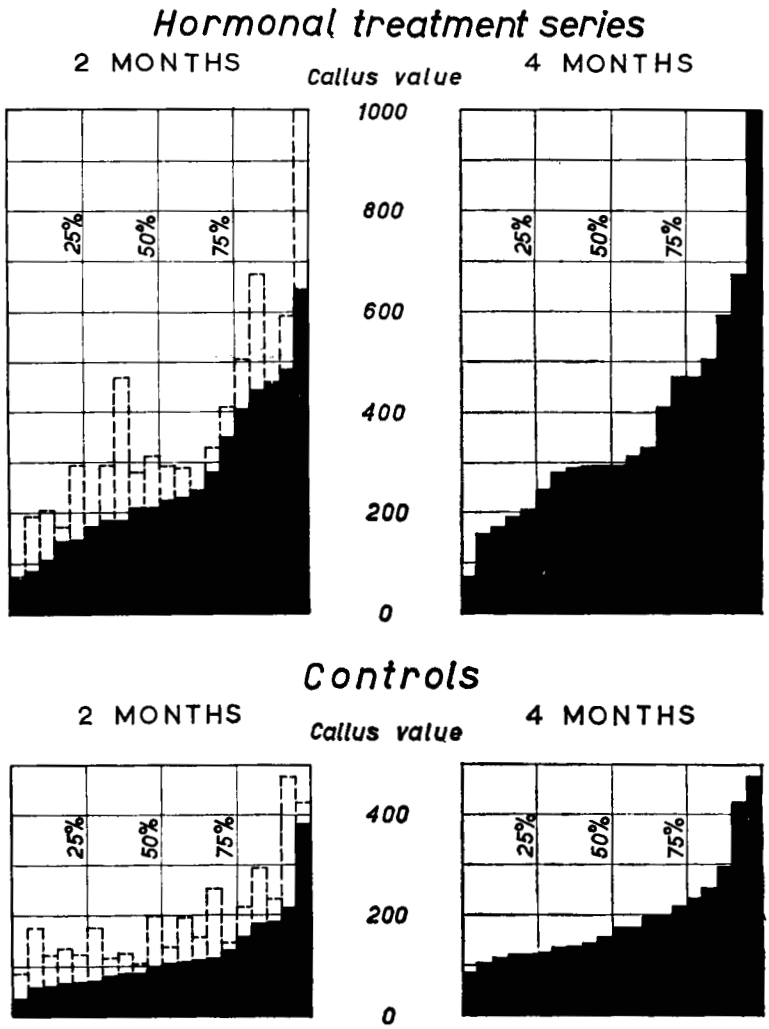

Fig. 12. Callus values found by planimetry of roentgenograms in hormonal treatment series and control series (20 femur fractures each) after 2 months and 4 months, shown by columns arranged according to their height. — Dotted columns in graphs referring to 2 months indicate values reached at 4 months in each individual case. Unit of callus value = 4 mm² area in roentgenogram.

in the hormonal treatment series and 20 controls were evaluated by planimetration as described in Chapter III. All 40 patients concerned here had a fracture of the femur; ten cases of each series were treated conservatively and ten cases by intramedullary nailing.

The readings of the planimeter (in units equivalent to 4 mm^2 of callus x-ray projection area) are called callus values in the following. They have been presented in Fig. 12 by columns, each column representing by its height the callus value of one patient, and the columns have been arranged in the order of their height. The four sets of columns, separate for the controls and for the hormonal treatment series and for the time of 2 months and 4 months in either case, reveal stronger formation of callus in the hormonal treatment group. They also show the development of callus that has taken place between the times of 2 and 4 months; the callus values of the latter time have furthermore been shown in the two-month diagrams as dotted columns, collated to the earlier value of the same individual case.

For closer statistical analysis, the cumulative frequency curve of the callus values was plotted on normal distribution paper in each instance, with logaritmic callus value abscissae (Fig. 13). It is seen that the logarithmic values have normal distribution. On the strength of this fact the calculation of mean values and the standard deviation considerations were performed on a logarithmic basis. The results are presented in Table 3 and Fig. 14.

The average quantity of callus at 2 months as well as at 4 months was thus about twice as high in the hormonal treatment series as in the control series and the difference is highly significant in both instances. The relative

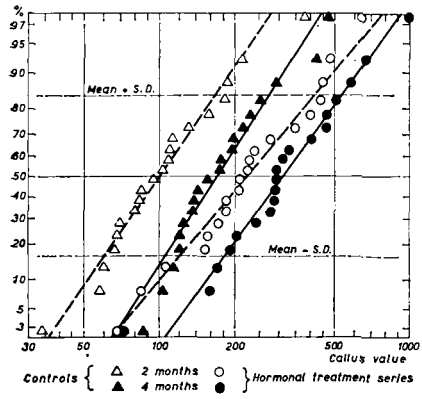

Fig. 13.

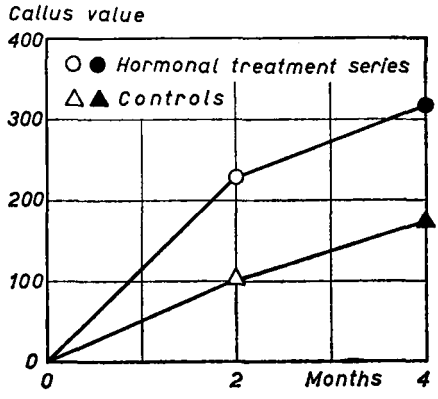

Fig. 14.

Fig. 13. Cumulative frequency distribution plots of callus values found by planimetry of roentgenograms in hormonal treatment series and control series (20 femur fractures each) after 2 months and after 4 months, revealing normal distribution of callus value logarithms and consequent appropriateness of treating the values statistically on a logarithmic basis.

Fig. 14. Average callus values (logarithmic means) in hormonal treatment series and control series (20 femur fractures each) in terms of time since trauma or operation.

TABLE 3. FORMATION OF CALLUS IN FEMUR FRACTURES, ACCORDING TO PLANIMETRY OF RADIOGRAMS

Time since fracture or surgical intervention	Callus value [1]	
	Control series (20 cases)	Hormonal treatm. series (20 cases)
2 months	101	228
4 months	172	316

*** between 2 months and 4 months (Control series)
*** between 2 months and 4 months (Hormonal treatm. series)
*** between 2 months (Control series) and 2 months (Hormonal treatm. series)
* between 4 months (Control series) and 4 months (Hormonal treatm. series)

[1]) Logarithmic means; 1 Unit = 4 mm² area in x-ray.

*** Highly significant difference
* Nearly significant difference.

excess of the callus size in the hormonal treatment group over that of the controls is less at 4 months than at 2 months; this indicates in another way the fact also clearly evident from Fig. 14 that the two-month callus average of the controls is only about half of their four month average (highly significant difference), whereas in the hormonal treatment series the average at 2 months is nearly 3/4 of that found for 4 months (only nearly significant difference). The important deduction from this is that the callus of the hormonally treated patients is not only greater in absolute quantity but especially is formed and obtains its maximum size at an earlier time than in the control series.

Metabolic Aspects

Of the metabolic characteristics (serum calcium and phosphorus contents, urinary calcium and phosphorus excretions and alkaline phosphatase activity) altogether 574 test values determined in the laboratory and derived from 50 patients of the present hormonal treatment series were available. A total of 105 corresponding values from the 13 patients of the respective control series served as a reference basis. For each of the five above-mentioned characteristics the values concerning observations made on the 1st to 50th day of hormone administration have been plotted in Figs. 15 and 16, identified by different symbols according to site of injury and surgical aspect. Dotted lines in the figures indicate the control level found as a mean of the control observation, and the deviation upward and downward of this level by the amount of the standard deviation in the control series has

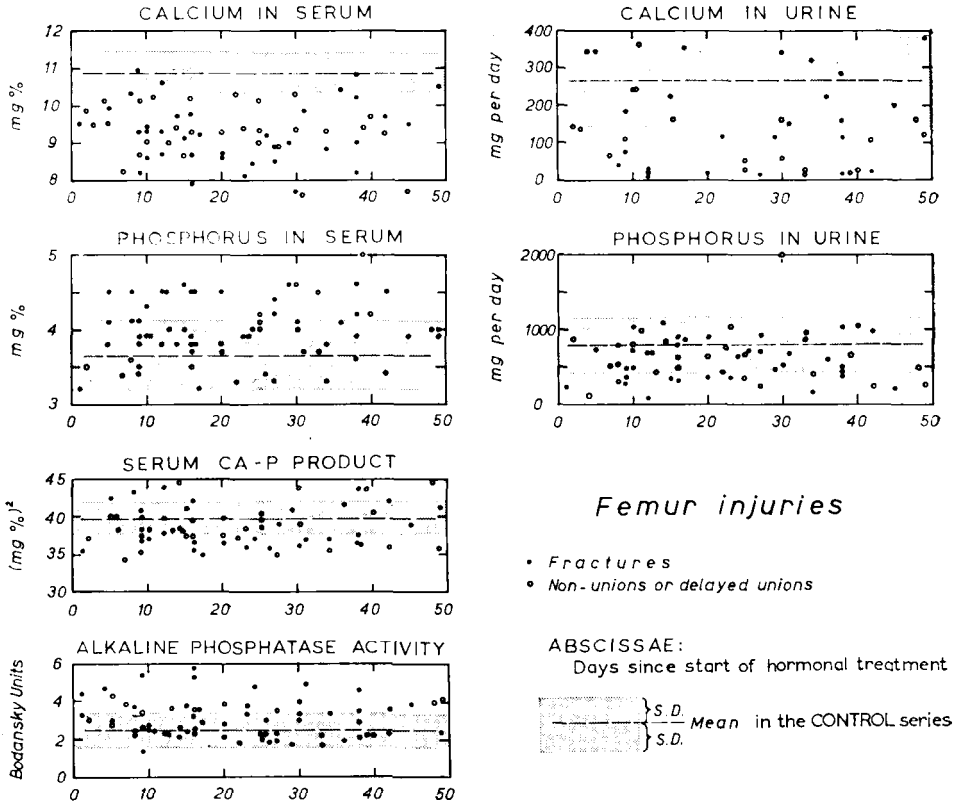

Fig. 15. Plots of metabolic values recorded in hormonal treatment series (fractures, delayed unions and non-unions of femur) and of serum calcium-phosphorus products computed from them, up to 50th day since start of hormonal treatment. — Dotted lines indicate mean level recorded in control series and shaded belts indicate spread equivalent to single standard deviation of the control series in either direction of its mean.

been shown as a shaded belt in each diagram. The plots display a grouping indicating departures in certain directions from the control level of the various metabolic values and this will be substantiated by the following more detailed analysis.

Table 4 contains for each of the five characteristics the means of the control observations and of the observations in the hormonal treatment series, the latter having been calculated separately for different groups of patients (different sites of injury and different surgical aspects) as well as for the entire series of 50 patients. The last column in the table gives the corresponding value of the product obtained by multiplying the serum calcium content and the serum phosphorus content. The role played by this

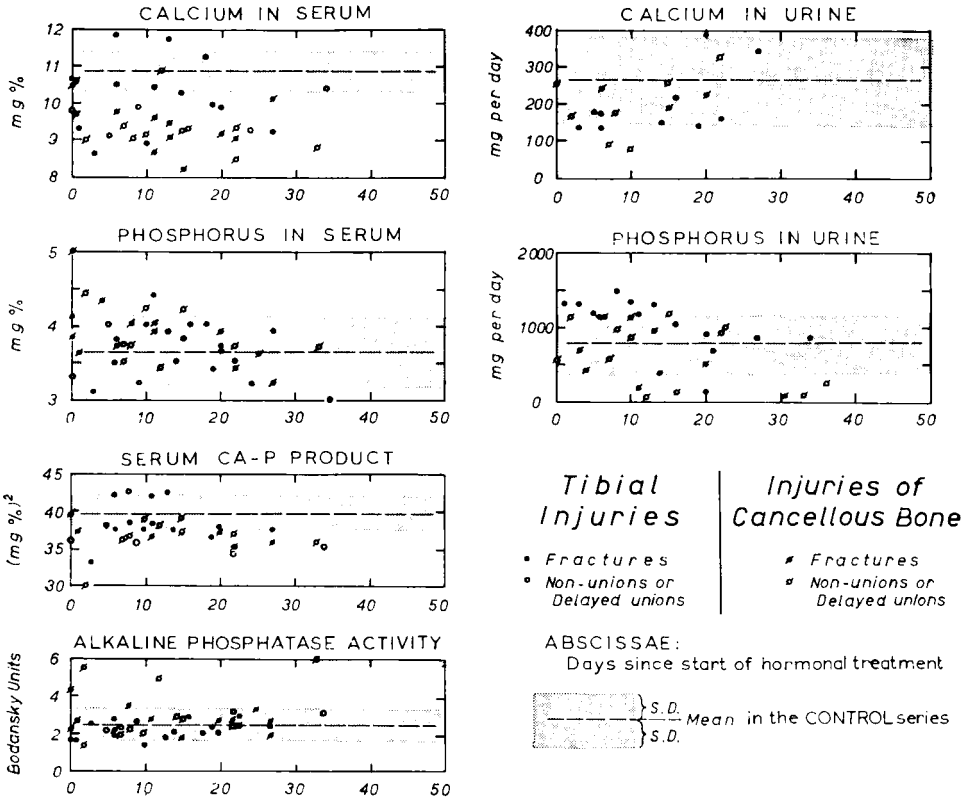

Fig. 16. Plots of metabolic values recorded in hormonal treatment series (fractures, delayed unions and non-unions of tibia and of cancellous bone) and of serum calcium-phosphorus products computed from them, up to 50th day since start of hormonal treatment. — Dotted lines indicate mean level recorded in control series and shaded belts indicate spread equivalent to single standard deviation of the control series in either direction of its mean.

quantity in blood chemistry, as described in the literature, will be discussed later.

On the whole, the table reveals that in the laboratory tests taken during hormonal treatment the serum calcium was lower than in the controls, the serum phosphorus was higher, while the urinary calcium and phosphorus excretion were both lower and the alkaline phosphatase activity was higher than the control level. The departures in the said directions from the control level, which shall be referred to as the hormonal effect in the following, constitute statistically highly significant differences[1] in respect of serum

[1] $P < 0.001$: Highly significant difference
$P < 0.01$: Significant difference
$P < 0.05$: Nearly significant difference

calcium content and urinary calcium excretion, while there is a nearly significant difference in serum phosphorus level. The absence of statistically significant differences in the other two metabolic characteristics (urinary phosphorus and alkaline phosphatase activity) is partly due to the fact that in some of the subgroups of the hormonal treatment series the deviation from control level was opposite in direction to the hormonal effect noted on the whole. This shall be discussed in detail below.

Site and Type of Bone Injury

Injuries of the femoral shaft. — In the group of the hormonal treatment series relating to injuries of the femur the values reflecting the calcium and phosphorus metabolism differ strikingly from the control level. The decrease of the serum calcium content from the control level of 10.85 mg% to 9.45 mg % is statistically highly significant, as is also that of the urinary calcium excretion from 265 to 140 mg per day. The same applies to the increase of serum phosphorus from 3.65 to 4.05 mg %. The decrease in urinary phosphorus excretion from the control level of 790 mg per day to 600 mg per day is statistically significant and the increase of alkaline phosphatase activity from 2.5 to 3.1 Bodansky units is nearly significant.

Injuries of the tibial shaft. — In this group the departure of serum calcium from the control level is only half of what it was in the group of femur injuries, but the difference is still statistically significant. The hormonal effect noted in the urinary calcium excretion is considerably less than in the femur group and there is no statistically significant difference in respect of this or any of the other three characteristics. The mean found for the serum phosphorus content is virtually the same as in the control series, and the urinary phosphorus excretion seems to indicate an opposite trend to the generally established hormonal effect.

Injuries of cancellous bone. — All means in this group display a hormonal effect similar in direction to that in the femur group, but the deviations from control level, except for the striking decrease of serum calcium, age much less and virtually nil for serum phosphorus and urinary calcium. There are no statistically significant differences except for that of serum calcium.

Comparison of the hormonal effect in the different groups reveals that the effect is strongest in the femur group, less in the group of cancellous bone injuries and least of all in the tibial injury group. Several of the differences in effect between the groups, consistent with this trend, are statistically significant, as can be seen in Table 4.

TABLE 4. MEANS OF METABOLIC VALUES IN HORMONAL TREATMENT SERIES (50 CASES) AND CONTROL SERIES

	Surgical Aspect	Number of Cases	Duration of Hormonal Treatment, Mean, Days	Serum: Calcium Content, mg %	Serum: Phosphorus Content, mg %	Urinary: Calcium Excretion, mg per day	Urinary: Phosphorus Excretion, mg per day	Alkaline Phosphatase Activity, Bodansky Units	Serum Ca-P Product, (mg %)[2]
Hormonal treatment series									
(a)	[1]	13	38	9.2***	4.1***	200	630	2.8	37.5
Femur	[2]	4	31	9.4*** → 9.8***	4.2*** → 4.1***	140* → 180*	540 → 610*	(4.6) → 3.3*	36.5 → 37.5
Injuries	[3]	11	49	9.7***	4.0***	100***	590*	2.9	38
	[1] [2] [3]	28	41	9.45***	4.05***	140***	600**	3.1*	37.5
(b)	[1]	7	23	10.2*	3.9	210*	1000	2.2	39
Tibial	[2]	—	—	— → 10.2*	— → 3.9	— → 210*	— → 1000	— → 2.2	— → 39
Injuries	[3]	4	27	10.1*	3.4	(170)	(900)	2.8	35***
	[1] [2] [3]	11	25	10.15**	3.75	200	990	2.4	37
(c)									
Cancellous	[1]	3	40	9.4***	3.5	(230)	(560)	2.4	34***
Bone	[2]	3	39	9.5*** → 9.4***	4.1 → 3.8	(370) → 300	(890) → 690	3.6 → 2.8	(35.5) → 34.5***
Injuries	[3]	5	31	9.2***	3.6	240	540	3.2	35.5***
	[1] [2] [3]	11	35	9.20***	3.70	260	650	3.0	35***
All Cases	[1] [2] [3]	50	36	9.55***	3.95*	165***	690	2.85	38
Controls									
	[1] [2] [3]	13	—	10.85	3.65	265	790	2.50	40
Differences between groups:									
(a)—(b)				—0.7**	+0.3**	—60	—390	+0.65	
(a)—(c)				+0.15	+0.35**	—120**	—50	+0.1	
(c)—(b)				—0.85**	—0.05	+60	—340	+0.55	

[1] Fractures, conservatively treated
[2] » operated
[3] Non-unions or delayed unions, operated

*** Highly significant difference ($P < 0.001$)
** Significant difference ($P < 0.01$)
* Nearly significant difference ($P < 0.05$)
In upper part of table: Referred to Controls

Non-Union or Delayed Union

Within each above-mentioned group, means of the metabolic characteristics have also been computed separately for cases with recent fractures and for those with non-union or delayed union, and presented in Table 4. On the whole, hormonal treatment seems to have elicited a stronger response in the cases with non-union or delayed union. Particularly the urimary calcium excretion found for the femoral non-unions differs by a statistically highly significant amount from the control level, whereas the complementary group of recent femur fractures only displays a nearly significant difference.

As far as a comparison is possible between cases which were not affected with non-union or delayed union and which were treated operatively and conservatively, the impression is that the hormonal effect seems to have been strong in operated than in conservatively treated cases.

Amount of Dosage

The differences in response to hormonal treatment reported in the foregoing may be partially due to the circumstance that the different groups are not mutually fully equivalent with respect to duration of the hormone administration, *i. e.*, that in some means metabolic test values referring to samples taken only after a short time of hormonal medication dominate, while in others the values referring to a long period of treatment may be in the majority. A detailed study of the effect of hormonal treatment time, that is, of the accumulated quantity of hormones given to the patient has therefore been made.

For this purpose an analysis was made of the 20 cases in which the duration of hormonal treatment was 30 days or more. The distribution of these cases by site and aspect of the injury (*e. g.* non-union) is satisfactorily consistent with that of the entire series and it can be considered a representative miniature sample of the whole material. The recorded metabolic values were arranged by the time of hormonal treatment in ten-day groups (1—10, 11—20, 21—30, 31—40 and 41—75 days) and the respective means together with their standard deviations can be seen in Table 5, which also contains the means of the control series and their standard deviations and a column stating the Ca-P product for each group (Fig. 17).

It can be seen that already within the first ten days of hormonal treatment the *serum calcium* decreases abruptly from 10.85 mg % control level to 9.5 mg %. The decreasing tendency continues until a minimum of 9.1 mg % is seen about 25 days. The subsequent increase carries to the mean

TABLE 5. MEANS OF METABOLIC VALUES IN SERIES OF 20 CASES WITH HORMONAL TREATMENT OF NOT LESS THAN 30 DAYS DURATION, AND IN THE CONTROL SERIES

Time Since Start of Hormonal Treatment, days	Serum Calcium Content, mg %		Serum Phosphorus Content, mg %		Urinary Calcium Excretion mg per day		Urinary Phosphorus Excretion, mg per day		Alkaline Phosphatase Activity, Bodansky Units		Serum Ca-P Product, $(mg\ \%)^2$	
	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.
1—10 (a)	9.5***	1.0	3.7	0.4	250	170	680	380	3.2*	1.1	36*	4.5
11—20 (b)	9.4***	1.0	3.8	0.4	180	130	660	480	3.0	1.0	36*	4
21—30 (c)	9.1***	0.7	3.9	0.4	150*	120	660	210	2.9	0.8	35**	3.5
31—40 (d)	9.6***	0.9	4.0	0.5	125**	110	560	320	3.3*	1.3	37.5	6
41—75 (e)	10.2*	1.0	4.2**	0.4	125**	100	550	300	2.9	0.9	42	5.5
Controls	10.85	0.5	3.65	0.4	265	120	790	380	2.50	0.8	39.5	4.5

*** Highly significant difference ($P < 0.001$)
** Significant difference ($P < 0.01$)
* Nearly significant difference ($P < 0.05$)
} In the table: Referred to Controls

Differences between groups: Serum Calcium (c—e) **
Serum Phosphorus (a—e) *, (b—e) *, (c—e) *
Serum Ca × P (a—e) *, (b—e) **, (c—e) **

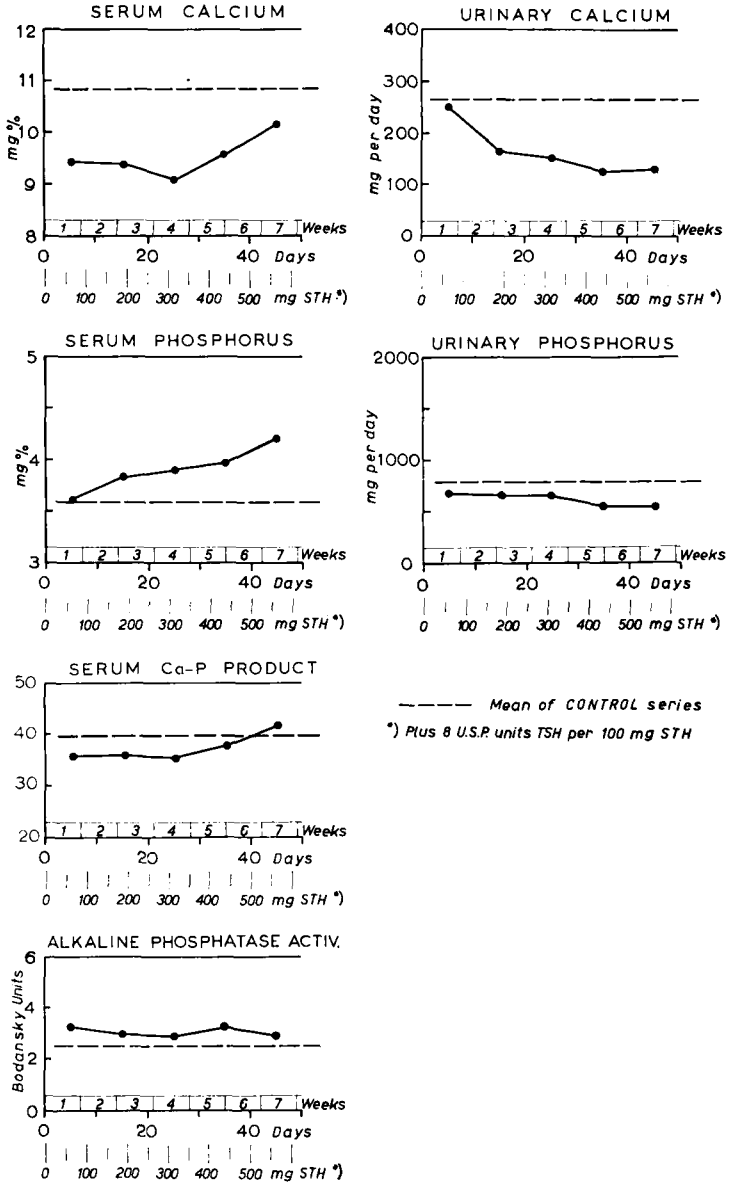

Fig. 17. Means of metabolic values recorded in hormonal treatment series (20 cases subjected to hormonal treatment during 30 days or longer) and of the serum-calcium products computed from them, for periods of 1—10, 11—20, 21—30, 31—40 and 41—75 days since start of hormonal treatment. — Dotted lines indicate mean level recorded in the control series.

of 10.2 mg % during continued treatment in excess of 40 days Distinct response to hormonal treatment would thus be concentrated in the first 3—4 weeks. The last-mentioned value indicating return to the control level differs in statistically significant degree from the lowest recorded serum calcium mean (9.1 mg %).

The ten-day means of *serum phosphorus* all deviate upwards of the control level and the deviation seems to be approximately proportional to the time of hormonal treatment (to the aggregate hormone dosage). The outcome of this continuous increase is a mean of 4.2 mg % for the group referring to 41—75 days of hormonal treatment, which differs significantly from the control level of 3.65 mg %. This latest value also differs significantly from the means for the treatment periods of 1—10, 11—20, and 21—30 days.

The *urinary calcium* excretion mean decreases more or less uniformly from control level (265 mg per day) during the first five weeks, after which it seems to remain stationary at about 125 mg per day. This level is represented by the means referring to 31—40 and 41—75 days, both of which differ significantly from the control level. Already at 21—30 days there was a statistically nearly significant difference from the controls.

The *urinary phosphorus* excretion lies below the control level in all periods considered here, but no statistically significant differences can be established. Immediately on commencement of hormonal treatment a decrease seems to take place from control level 790 mg per day to about 670 mg per day, with another decrease at the end of 4 weeks to the level of 550 mg per day, which is maintained from 6 weeks onward.

The mean in the control series, 2.5 Bodansky units, of the *alkaline phosphatase activity* value is exceeded by all means found for the different periods in the hormonal treatment series, which vary irregularly in the range of 2.9—3.3 Bodansky units (on an average 3.1 Bodansky units, which is 0.6 units higher than control level).

Product of Serum Calcium and Serum Phosphorus

It was considered worthwhile to compute from the above-mentioned immediately observed values the product of serum calcium content and serum phosphorus content (in mg % squared) for each pair of such observations. This quantity, which is associated with the phenomena of inorganic blood chemistry through the rules governing the solubility product, has been stated in the literature (*Watson-Jones* 1955) to have a normal value of about 40. An excellently conforming value, 39.5, was found in the present investigation as the mean for the control series.

If the solubility product in the blood serum of the Ca and P ions and CO_3 anions is supposed to be constant (cf. *Watson-Jones,* 1955), lowered Ca-P product would imply increased carbonic acid concentration, or higher acidity, which seems to parallel roughly the increased activity indicated by the elevated alkaline phosphatase values.

The values obtained for the Ca-P product in the different groups and subgroups of the hormonal treatment series and for the entire series appear in Tables 4 and 5 and in Fig. 17. The Ca-P product displays during the first 3—4 weeks of hormonal treatment a lowered level of about 35 and a subsequent, fairly linear return to normal level.

Closer study of Table 5 and Fig. 17 reveals that the immediately lowered value of the Ca-P product after commencement of hormonal treatment is due solely to the abrupt fall of serum calcium. As the hormone administration is kept up, the serum phosphorus content gradually begins to increase, but its effect on the product is compensated by the further decrease of serum calcium, maintaining the said level of about 35. At last, when the serum calcium content begins to increase once more, both factors act in the same direction and the Ca-P product returns fairly rapidly to normal.

Comments

Summarizing the principal results obtained in laboratory examinations of 50 patients, who received combined growth hormone and thyrotropin treatment in addition to appropriate orthopaedic therapy, the following observations can be made.

In the entire hormonal treatment series the average serum calcium content was lower and the serum phosphorus content higher than in the control series. Urinary calcium and phosphorus excretion were lowered from the control level, while the alkaline phosphatase activity was elevated. These deviations from the controls amounted to highly significant dfiferences with regard to serum calcium and urinary calcium excretion; in the case of serum phosphorus a statistically nearly significant difference was noted. — More detailed study aiming at elucidation of the influence on the hormonal effect exerted by various factors brought the following results.

In injuries of the shaft of the femur the changes elicited in the metabolic values were most clearly evident. The mean of the serum calcium content

was lowered from 10.85 mg % control level to 9.45 mg % and the urinary calcium excretion from 265 to 140 mg per day, while serum phosphorus had increased from 3.65 to 4.05 mg %. All three differences are statistically highly significant. The decrease of urinary phosphorus excretion from 790 to 600 mg per day was statistically significant and the increase of alkaline phosphatase activity from 2.5 to 3.1 Bodansky units was nearly significant.

In the cases with injury of cancellous bone nearly all metabolic values displayed changes in the same direction as in the femur group, but the effect was less marked and in fact virtually nil with regard to serum phosphorus and urinary calcium. Here too, the lowering of serum calcium from control level was statistically highly significant.

Hormonal treatment of patients with tibial injuries elicited only half the lowering of serum calcium compared to the femur series, but even this difference was statistically significant. The decrease in urinary calcium excretion was less than in the femur group and the serum phosphorus content was virtually the same, as well as the alkaline phosphatase activity. Urinary phosphorus excretion was higher than the control level.

On the whole, the response to hormone administration can be said to have been strongest when injury of the femur was concerned, less in the case of cancellous bone injury and least of all in tibial injuries, Statistical analysis of the differences between effects in the different groups as regards site of the injury is in support of this statement. Comparison between subgroups made up of recent fractures on one hand and of cases with non-union or delayed union on the other reveals that the response to hormonal treatment was stronger, as a rule, in the last-mentioned than in recent fractures. In particular, a strong decrease of urinary calcium excretion from the control level was noted in the subgroups of non-union or delayed union; this can be taken to indicate greater calcium retention and storage during progress of the repair process.

Investigation of the response to hormonal treatment in terms of time, and thus of the total hormone quantitity administered to the patient, in the series of patients treated with hormones at least 30 days revealed the following points of interest.

The serum calcium content shows an immediate strong decrease from control level within not more than ten days, continuing through the third or fourth week. The subsequent increase still left the serum calcium below control level after 41—75 days of hormonal treatment, but the maximum effect is seen to be concentrated on the first 3—4 weeks. The urinary calcium excretion fell correspondingly, though rather uniformly, starting at control level, during about five weeks and then remained stationary at only about half of the control level.

The serum phosphorus content was above control level throughout the period of prolonged hormonal treatment, increasing about linearly with the total hormone quantity. Its highest value, which was not recorded until at a late stage, differed significantly from the control level. The urinary phosphorus excretion was lower than the control level throughout the investigated period. Having gone down to about two thirds of the control level by the beginning of the sixth week, it seems to have maintained this value at all later times.

With regard to alkaline phosphatase activity, elevated values were noted throughout the period of observation, although the increase was fairly slight, on the average 0.6 Bodansky units above control level.

V DISCUSSION

It is well-known that a great number of local as well as general factors exert an influence on the healing of fractures, depending mainly on the kind and severity of the injury, the type of the fracture, its localisation, vascular conditions, age, etc. Accordingly, experience has shown that it is possible in common uncomplicated fractures to estimate in advance at least the approximate time required for healing.

Several attempts have been made to find some improvement of existing therapeutic expedients by which the bone repair might be stimulated. This effort is readily understandable, seeing that the repair process requires a prolonged time and there is still a risk that after the anticipated period delayed union or non-union may be the result.

The theoretical background of growth hormone and thyrotropin administration and of the effect of these hormones has been elucidated by earlier investigations, among which those of *Asling et al.* (1956) occupy a prominent position. Existing previous investigations are mainly experimental and even today only very scanty information is available concerning the effect of growth hormone in the repair of human fractures. Moreover, investigations of this kind unfortunately lack the necessary control series.

The present studies revealed that failure of the fracture to unite occurred, when no hormonal treatment was added to appropriate orthopaedic care, at a frequency nine times that observed under the effect of growth hormone and thyrotropin administration during periods of varying length.

Additional light was thrown on the question of the progress of bony consolidation on the clinical level under hormonal effect and without administration of hormones by quantitative study of the callus formation in the phase when the repair process is proceeding with its greatest vigour and activity. Except that in the hormonal treatment series the amount of callus at the times of two months and four months was markedly higher than in the control series, the particularly noteworthy observation was made that

under hormonal effect the greater part of the callus development took place in an early phase, within two months. In this time the callus had reached about 3/4 of its ultimate measured size, while in the controls nearly one half of the callus did not develop until during the second half of the observation period, that is during the third and fourth month. Since on the other hand callus formation is correlated with good blood supply (*Charnley* 1961) and with a favourable progress of bone repair, as has been shown by autoradiography with radiophosphorus and by histologic investigations, this has to be considered to constitute evidence of an accelerating effect on fracture healing.

Comparing both series from the viewpoint of rehabilitation, the observation was made that ultimate healing was earlier in the hormonal treatment series than in the controls, the gain in time being on an average nearly 2 months in fractures of the femur and 1 ½ months in tibial fractures. In cases with non-union or delayed union added hormonal treatment was applied in femur fractures in connection with nailing and bone graft operations. In all but one case firm osseous consolidation was achieved, also in two non-unions and in four cases of non-union of the tibia; of the latter, two were moreover complicated by osteitis.

The changes observable in the metabolic characteristics are useful criteria reflecting the effects of endocrine agents in their clinical application. Analysis of the calcium and phosphorus contents in the serum and of the urinary calcium and phosphorus excretion therefore provides a means of corroborating the effect of the hormonal treatment on fracture repair that may be seen on the clinical level. Better possibilities are also created by this means for an understanding of the mode of action of these hormones, of the dynamics of skeletal salt metabolism under their influence and of the optimum dosage levels.

In addition to growth hormone, the hormonal administration also contained thyrotropin, which has been found to exert a synergistic influence on the activity of growth hormone with respect to bone. It is conceivable that the daily dosage of growth hormone can be reduced with the aid of thyrotropin owing to the latter's capacity of exerting a beneficial effect on the maturation of bone (*Sissons* 1956, *Asling et al.* 1956). This has been experimentally proved in investigations establishing the boosting effect of thyrotropin on growth hormone activity in the form of increased formation of new bone in the callus with simultaneous reduction of the quantity of immature tissue components, fibrous tissue and fibrous cartilage, as established by the histological line sampling method (*Koskinen* 1959, 1962).

The decrease of urinary calcium excretion seems to be one of the most distinct changes in metabolic values during the progress of fracture repair under hormonal effect, together with a decrease of serum calcium content. In this respect reference can be made to *Henneman*'s *et al.* (1960) observations. They explain the increased urinary calcium excretion noted under growth hormone effect by the fact that the hormone promotes the absorption of calcium; if the calcium cannot be rapidly deposited in new bone, it will appear in the urine. Under the conditions existing in the present investigation the decrease of the calcium quantity found in the urine is thought, conversely, to indicate that calcium is stored in the organism. This relative hypocalciuria thus reflects stimulation of calcium deposition and osteogenesis

The relationship between the calcium content and phosphorus content of the serum is derived from the fact that calcium, phosphate and carbonate ions are present in crystalline compounds in bone and in soluble form in plasma and there is constant interchange between them (*Watson-Jones* 1955). In the present investigation the product of serum calcium and serum phosphorus (both in mg %) was found to be at a level of about 35 under hormonal effect, on an average 39.5 in the controls. According to the literature it should be constant in normal humans at a level of 40. The lowered value in the hormonal treatment serise during the first weeks of treatment is due to the lowered serum calcium, as long as there is no appreciable increase in serum phosphorus. — If the calcium, phosphate and carbonate ions together are assumed to obey a law of constant solubility product, the lowered Ca-P product can be interpreted as indicating increased acidity of the serum, and this is a condition characteristic of the bone repair process and consistent with previous reports (*Stirling* 1931). The inference is that the hormonal treatment acts toward maintaining, and perhaps increasing, this acidity and producing optimum conditions for fracture healing.

Comparison of the metabolic values found for the groups corresponding to different sites of the fracture (Table 4) reveals that the hormonal effect expressed by the changes in said values was strongest with injuries of the femoral shaft, in which group the serum calcium and urinary calcium excretion had decreased and the serum phosphorus increased in statistically highly significant degree from the control level. In injuries of cancellous bone the effect was considerably less, with a highly significant difference from the control level only in the serum calcium value, and an even inferior effect was seen in the injuries of the tibial shaft, for which still a serum calcium value differing significantly from the control level was obtained.

The question arises what may be the cause responsible for the difference in metabolic values observed between the groups of femur, cancellous bone and tibial injuries. On the clinical level the extent of the available material did not render any corresponding observations possible. A number of factors may have contributed to the different behaviour of the different fractures. It should be noted in particular that the duration of hormonal treatment was longest in the femur group, 41 days on an average, the cancellous bone injuries ranging next in this respect with 35 days, while the tibial injuries received hormonal treatment during an average of 25 days only. Another influential factor is thought to be the mode of healing of the femur, which is special in that no other long bones except the humerus have a periostal callus formation of the strength frequently seen in the femur. A third factor among the most prominent ones might be the great size of the femur; it is the largest long bone and the effects of its injury on the metabolism in themselves may cause changes of the described kind.

Hormonal treatment continued through a prolonged period was seen to exert a more profound effect on the anabolism of bone, as reflected by the metabolic values, than treatment of shorter duration. This was seen on analysis of the values in the series composed of patients who had been subjected to hormonal treatment during 30 days or longer.

The changes in metabolic values with varying length of the hormonal treatment period are deserved of attention, particularly as regards the urinary calcium and phosphorus excretion and the serum calcium content. They account for the direction of the trend displayed by the cases with non-union, which received the longest treatment, in comparison with other subgroups of the material (cf. Table 4). The urinary calcium excretion was lower in the group of non-unions of the femur than in the recent femur fractures, and Table 5 reveals that particularly low urinary calcium values are characteristic just of the observation periods corresponding to prolonged hormonal treatment. Similarly, the low urinary phosphorus excretion in the non-union groups is consistent with the fact that the lowest urinary phosphorus values in Table 5 are found in the observation periods of 31—40 and 41—75 days.

The strength of the hormonal effect varies with the duration of hormonal treatment, the maximum effect on serum calcium being concentrated on the first 3—4 weeks, while the decrease of urinary calcium excretion was approximately uniform during the first five weeks, with a subsequent stationary level. It is obvious that full effect of the hormonal treatment has been attained within about 5—6 weeks from its commencement; this is the

optimum period for bone repair under hormonal treatment if the treatment is started in an early phase of the reconstruction process. Also hormonal treatment instituted at a later time may exert a beneficial effect, but the results are not equally reliable.

On the strength of the present results the observation can be made that growth hormone and thyrotropin possess an osseous anabolic effect and their administration can be beneficially employed as an aid to appropriate, conservative or operative, orthopaedic treatment to promote bone repair in human patients and to shorten their time of recovery. Especially in cases in which delayed union is anticipated or non-union has already ensued and operative treatment is undertaken, it seems to be possible to aid the healing of the bone by means of these consolidation-promoting substances.

VI SUMMARY

In the present investigation concerning the effect of hormone administration on the healing of fractures, roentgenological and clinical examination revealed that in the material in which appropriate conservative or operative treatment was augmented by growth hormone (STH) and thyrotropin (TSH) given during periods of 3—10 weeks osseous consolidation took place in 62 out of 64 bone injuries. The failure percentage was 1.5% (one osteitis-complicated non-union omitted). In the control series consisting of 30 patients under corresponding care but without hormonal treatment, osseous union ensued in 26, while four (13.5%) failed to unite.

All 22 femur fractures in the hormonal treatment series resulted in osseous union and so did ten of the 11 delayed unions or non-unions of the femur, while one of them failed to unite. The average time required for osseous union to occur was 3.5 months in the femur fractures and 4.3 months in the cases with delayed union or non-union. The control series contained 20 femur fractures, of which 17 achieved osseous union in 5.3 months on an average. Three fractures failed to unite.

Of five compound and five closed tibial fractures in the hormonal treatment series nine united; delayed union resulted in one compound fracture. Osseous union was achieved in all four non-unions of the tibia in the series, of which two were complicated by osteitis. The time in which consolidation took place was 4.0 months on an average in the tibial fractures and 4.5 months in the cases with non-union. In the control series five of six tibial fractures consolidated in 5.5. months, and one failed to unite.

All 13 injuries of cancellous bone in the hormonal treatment series, consisting of three fractures and three delayed unions of the femoral neck, three trochanteric fractures, one non-union after trochanteric fracture and three malunited condylar fractures, united in 2—6 months. The three fractures of cancellous bone in the control series also united, which took place in 4—7 months.

Quantitative radiographic study of the callus in femur fractures revealed that in the hormonal treatment series the callus 2 months and 4 months after the trauma or surgical intervention was about twice the size of the callus at corresponding times in the control series. It was seen that the callus of the hormonally treated patients was not only greater in absolute quantity but especially was formed and obtained its maximum size at an earlier time than in the controls.

The following main results were recorded in the study of the metabolic values found in 50 cases of the hormonal treatment series and in 13 controls. Several of the effects observed under hormonal treatment were found to be statistically significant.

The mean serum calcium content of the entire hormonal treatment series decreased from control level 10.85 mg % to 9.55 mg % and the serum phosphorus content increased from 3.65 mg % control level to 3.95 mg %. The urinary calcium and phosphorus excretion values decreased (from 265 to 165 mg per day and from 790 to 690 mg per day, respectively), indicating retention of calcium and phosphorus.

The metabolic effect was strongest in the group of injuries of the femoral shaft, less marked in injuries of cancellous bone and least in injuries of the tibial shaft. Regardless of the site of injury, the metabolic response to hormonal treatment was stronger in cases of non-union or delayed union than in those involving recent fractures, indicating calcium retention at a higher rate in the first-mentioned.

The following particulars were noted in an analysis of the response to hormonal treatment with different durations of hormone administration. The serum calcium content fell abruptly within the first ten days and maximum response was concentrated on the first 3—4 weeks. In spite of its subsequent rise, the serum calcium level remained below that of the controls even after 40—75 days of hormone administration. The urinary calcium excretion decreased uniformly during about five weeks, after which it remained at a level about one half of that in the control series. The serum phosphorus content was elevated from control level at all times, its increase appearing to be proportional to the total quantity of administered hormones, with its highest value after hormonal treatment during 40—75 days. The urinary phosphorus excretion displayed a level below the controls in all periods of observation; from about five weeks onward it seemed to be stationary at about one third of the control level. Alkaline phosphatase activity was elevated, though only in slight degree, from the control level at all observed times.

Growth hormone and thyrotropin have been concluded to possess an osseous anabolic effect. Their administration is thought to be beneficial as an aid to appropriate orthopaedic treatment, promoting the healing of fractures and shortening the time required to achieve osseous consolidation, especially in cases in which delayed union is anticipated or non-union is an established fact.

VII ZUSAMMENFASSUNG

In der vorliegenden, die Wirkung von Hormonverabreichung auf das Heilen von Knochenfrakturen betreffenden Untersuchung ergab die röntgenologische und klinische Untersuchung, dass in dem Material, dessen Patienten zuzüglich sachgemässer konservativer oder operativer Pflege Wachstumshormon und Thyrotropin während Perioden von 3—10 Wochen Dauer erhielten, knöcherne Konsolidierung in 62 von 64 Knochenverletzungen stattfand. Die Behandlung versagte in 1,5% (unter Auslassung eines Falls von Pseudarthrose, durch Knochenentzündung kompliziert). In der Kontrollreihe, bestehend aus 30 Patienten in entsprechender Pflege, jedoch ohne Hormonbehandlung, wurde knöcherne Vereinigung in 26 Fällen verzeichnet, während sie in 4 Fällen (13,5%) ausblieb.

Sämtliche 22 Oberschenkelfrakturen in der Hormonbehandlungsreihe endigten in knöcherner Vereinigung, und gleichfalls 10 der 11 Fälle mit verzögerter Vereinigung bzw. Pseudarthrose. Die im Durchschnitt zur knöhernen Vereinigung benötigte Zeit belief sich bei den Oberschenkelfrakturen auf 3,5 Monate und bei den Fällen mit verzögerter Vereinigung oder Pseudarthrose auf 4,3 Monate. Die Kontrollreihe enthielt 20 Oberschenkelschäden, von denen 17 im Verlauf von im Durchschnitt 5,3 Monaten knöcherne Konsolidierung zeigten. Bei drei Frakturen blieb die Vereinigung aus.

Von 5 offenen und 5 geschlossenen Tibiabrüchen in der Hormonbehandlungsreihe entstand knöcherne Vereinigung in 9; bei einer offenen Fraktur was das Ergebnis verzögerte Konsolidierung. Knöcherne Vereinigung wurde bei allen 4 Pseudarthrosen in der Tibiareihe erzielt, von denen zwei durch Knochenentzündung kompliziert waren. Die zur Konsolidierung notwendige Zeitspanne war bei den Tibiafrakturen 3—6 Monate, im Durchschnitt 4,0 Monate, und bei den Fällen mit Pseudarthrose war sie 4—8 Monate, im Durchschnitt 4.5 Monate. In der Kontrollreihe ergab sich bei 5 der 6 Tibiafrakturen Konsolidierung in 4—7 Monaten, im Durchschnitt 5,5 Monate, während Vereinigung in einem Fall ausblieb.

Bei sämtlichen 13 Verletzungen von kanzellösen Knochen in der Hormonbehandlungsreihe, bestehend aus 3 Frakturen und 3 Fällen verzögerter Vereinigung des Schenkelhalses, 3 trochanteren Frakturen, 1 Fall ausgebliebener Vereinigung nach trochanterer Fraktur und 3 Malunionen von kondylären Frakturen, trat Vereinigung in 2—6 Monaten ein. Die 3 Frakturen von kanzellösem Knochen in der Kontrollreihe endigten ebenfalls in Vereinigung, und zwar geschah dies in 4—7 Monaten.

Quantitative planimetrische Untersuchung des Callus bei Oberschenkelfrakturen ergab, dass in der Hormonbehandlungsreihe der Callus 2 und 4 Monate nach dem Trauma bzw. dem chirurgischen Eingriff etwa die doppelte Grösse des Callus zu entsprechenden Zeitpunkten in der Kontrollreihe hatte. Es war festzustellen, dass der Callus unter Hormonbehandlung nicht nur in seiner absoluten Menge grösser war, sondern insbesondere zeitiger als in der Kontrollreihe entstand und seine maximale Grösse erreichte.

Die folgenden Hauptergebnisse wurden beim Studium der metabolischen Werte verzeichnet, die in 50 Fällen der Hormonbehandlungsreihe und in 13 Fällen der Kontrollreihe gefunden wurden. Mehrere der bei Hormonverabreichung notierten Effekte stellten statistisch gesicherte Differenzen dar.

Der durchschnittliche Calciumgehalt des Serums der gesamten Hormonbehandlungsreihe ging vom Kontrollspiegel 10,85 mg auf 9,55 mg % herab und der Phosphorgehalt des Serums stieg von 3,65 mg Kontrollspiegel auf 3,95 mg%. Die Werte der urinären Calcium- und Phosphorexkretion gingen herab (von 265 auf 165 mg je Tag bzw. von 790 auf 690 mg je Tag), Retention von Calcium und Phosphor anzeigend.

Der metabolische Effekt, der sich als Änderungen in den obengenannten Richtungen äusserte, war am stärksten in der Gruppe der Verletzungen des Oberschenkelschafts, weniger hervorstehend in solchen von kanzellösen Knochen und am geringsten bei Verletzungen der Tibiaschafts. Unabhängig vom Ort der Verletzung schien das metabolische Ansprechen auf die Hormonbehandlung in der Regel bei den Fällen mit Pseudarthrose oder verzögerter Vereinigung stärker als bei frischen Frakturen zu sein, kräftigere Calciumretention in den erstgenannten andeutend.

Eine Analyse der bei verschiedener Dauer der Hormonverabfolgung zu beobachtenden Wirkungen zeitigte folgendes. Der Serum-Calciumgehalt fiel steil innerhalb der zehn ersten Tage ab, und die maximale Wirkung bezog sich auf die ersten 3—4 Wochen. Trotz seines anschliessenden Anstiegs blieb der Serum-Calciumspiegel selbst nach Hormonverabreichung während 40—75 Tagen unter dem Spiegel der Kontrollreihe. Die urinäre Calciumexkretion ging ungefähr gleichmässig während 5 Wochen herab und hielt sich danach

auf etwa halber Höhe des Kontrollspiegels. Der Serum-Phosphorgehalt lag zu allen Zeiten etwas über dem Kontrollspiegel, und zwar schien seine Zunahme der Gesamtmenge von verabreichtem Hormon proportional zu sein, mit einem höchsten Wert nach 40—75tägiger Hormonbehandlung. Die urinäre Phosphorexkretion zeigte zu allen Zeiten einen unter dem der Kontrollreihe liegenden Spiegel; von etwa 5 Wochen an schien er bei etwa einem Drittel des letztgenannten Werts stehenzubleiben. Die alkalische Phosphataseaktivität war zu allen Zeiten dem Kontrollspiegel gegenüber erhöht, wenngleich nur in geringem Mass.

Es wird gefolgert, dass Wachstumshormon und Thyrotropin einen ossealen anabolischen Effekt entfalten. Ihre Verabreichung dürfte als Zusatz zu sachgemässer orthopädischer Pflege zu empfehlen sein, indem sie die Heilung von Frakturen fördert und die zur Erreichung knöcherner Konsolidierung erforderliche Zeit verkürzt, dies insbesondere in Fällen, in denen verzögerte Vereinigung zu erwarten ist oder tatsächliche Pseudarthrose vorliegt.

VIII ACKNOWLEDGEMENTS

This investigation was carried out in the Clinic for Orthopaedics and Traumatology, University of Helsinki, whose Chief, Professor K. E. Kallio, M.D., has kindly permitted the author to use the present material. For this I feel deeply obliged to him, and equally for his valued support during progress of the work.

My sincere thanks are due to Professor Unto Uotila, M.D., Chief of the Department of Forensic Medicine, University of Helsinki, to whom I owe the instigation to embark on research concerning hormones in bone repair.

The Physician of the Clinic's Laboratory Department, University Lecturer R. Gordin, M.D., is deserved of my gratitude for assistance given in the laboratory work. I also wish to give expression to my appreciation of all that has been done in aid of this work by my other colleagues and by the nurses of the Clinic.

Mr. U. Attila, M.Sc., has given his help in the statistical treatment and tabular and graphical presentation of the results, and he has translated the manuscript.

This work has been aided by a grant from the Sigrid Juselius Foundation. My understanding of its subject was essentially deepened by my attendance of the Gordon Research Conference on the Chemistry, Physiology and Structure of Bones and Teeth in Meriden, N.H., U.S.A. on July 9—13, 1962, which was made possible by a grant received form the Trustees of the Conference.

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