

Acta Medica Okayama

Volume 13, Issue 2

1959

Article 6

JUNE 1959

Some clinical aspects of rheumatoid arthritis

Toshio Kodama*

*Okayama University,

Copyright ©1999 OKAYAMA UNIVERSITY MEDICAL SCHOOL. All rights reserved.

Some clinical aspects of rheumatoid arthritis*

Toshio Kodama

Abstract

In our department we have been placing a special emphasis on the treatment and study of rheumatoid arthritis, and during the last four years we have handled about 1,600 cases visiting our outpatient clinic and approximately 100 hospitalized cases. Our experiences with these patients are only what might be called an introductory phase in the study and treatment of rheumatoid arthritis when compared with those in Europe and America. In estimating the incidence of rheumatoid arthritis in Japan from various available data, although it would not reach the level of England and U.S.A., it will be about 100 cases per 100,000 population, matching more or less the incidence in the northern Europe. As regards sex and the predisposing age we find no great difference from those in Europe and America. One striking difference that we find is the fact that patients in our country have very little resistance against salicylic acid drug used in treatment. Therefore, it is unreasonable to expect a good anti-inflammatory action by administering a large dosage of 5-10g of such a drug as aspirin per day. It must be limited within a comparatively small dosage of 1.0 to 2.0 g or with concomitant administration of prednisolone and aspirin in the hope of utilizing its analgesic effect. Furthermore, it is not feasible to introduce the results of studies made in Europe and America on the salicylic drug and its prescription all of them showing the concentration in blood 35 mg%, which is on the borderline of intoxicating dosage. This is only one example, and with some more experiences we shall undoubtedly encounter many dissimilar points. Therefore, it is essential that rheumatology specific to Japan needs to be established.

Acta Med. Okayama 13, 137—168 (1959)

SOME CLINICAL ASPECTS OF RHEUMATOID ARTHRITIS*

Toshio KODAMA

Department of Orthopedic Surgery, Okayama University Medical School, Okayama, Japan (Director : Prof. T. Kodama)

Received for publication, November 18, 1958

With the remarkable advance in the studies of steroid hormones the treatment of rheumatoid arthritis is now entering into a new phase. However, this disease, rheumatoid arthritis, is as yet adamant to all practitioners and scientists alike, keeping as it does its time-immemorial veil of mystery.

Even in Japan the incidence of rheumatic diseases is not at all rare, and the patients in Japan will naturally present in various ways many characteristics different from those in Europe and America. In the past ten years while engaged in the research of rheumatoid arthritis the author has endeavored to uncover the specific characteristics of this disease in our country and also tried to learn the differences between the patients in Japan and those in Europe and America. In this paper are presented mainly clinical aspects of this disease from author's own experiences.

Incidentally, the author's investigations were carried out at the Department of Orthopedic Surgery (Director Prof. I. Miki), Tokyo University from 1948 to 1952, and then in the Orthopedic Department of Okayama University Medical School since 1953.

The essential part of this work was prepared for the reading at the 66th General Meeting of Okayama Medical Society, held in February 1957 with a few of more recent findings.

THE CLASSIFICATION OF ARTHRITIS

There are many classifications of arthritis, and in any one of these classifications it would be a simple matter, were it to classify just by selecting those classical syndromes only. However, it is not so simple, as there are actually many cases with a migratory or transient type or type presenting symptoms overlapping with one another ; and different investi-

* This research reported here was aided in part by a grant for the Scientific Research from the Ministry of Education (1954—1958)

gaters have different opinions according to which group these syndrome are to be included, thus bringing about confusion and ambiguity in understanding the classification.

The first problem that the author encountered at Tokyo University was what would be the best and most concrete way to explain to a third person the joint disesae or the deformative joint ailments that we had been caring for. Finally we made an entirely new and logical classification, by discarding so-far known processes and by analyzing symptoms and findings of rheumatoid arthritis, and by grouping those having similar pathological picture and those taking a similar course (Table 1)¹.

Table 1. Classification of Arthritis (T. Kodama)

Nos. of affect. joints	Inflam. of joints	system. sympt.	course	age	causes	x-ray findings	histolog. findings
1. Mono-	1 -arthrosis	1 non-systemica (no system. sympt.)	acuta	infantilis	traumatogena	r. deformans	h. rheumatica
			chronica	juvenilis	deformatogena	etc	h. tuberculosa
2. Poly-	2 -arthritis	2 systemica (system. sympt.)	tansitoria	presenilis			h. synoviditica
			recidiva etc	senilis etc	etc		etc

Note: r. deformans means roentogeno-deformans; h. rheumatica means histo-rheumatica.

For example;

monoarthrosis non-systmica chronica senilis r. deformans stands for osteoarthritis or arthrosis deformans and diagnosis is abbreviated as "111 chr. senilis r-def".

Polyarthritis systemica chronica h. rheumatica stands for rheumatoid arthritis and is abbreviated as "222 chr. h-rh".

First of all, we divided clinical pictures, roentgenographic findings, synovial fluid picture, arthroscopic picture, and pathological findings into four grades according to their degree and classes. In analyzing each category of symptoms so divided according to individual cases, it became obvious that the most important items for the classification of these joint diseases are whether diseased joint is "mono-arthritis", "poly-arthritis", or whether it has arthrosis, whether it shows arthritis, and in addition, to see whether it shows non-systemic symptoms or systemic symptoms comprising of fever, fatiguability, wasting, acceleration of red cell sedimentation, and anemia. Therefore, we devised some symbols of diagnosis such as mono- (1), poly- (2); arthrosis (1), arthritis (2); non-systemica (1), systemica (2); mono-arthrosis non-systemica as (111), and poly-

arthritis systemica as (222), and mono-arthritis systemica as (122), as shown in Table 1. Then additional findings such as the course of disease, age, etiology or cause, inducing factor, roentgen findings, pathological, bacteriological findings, etc., are to be added to each item of the above-mentioned nonmenclatures for diagnosis as illustrated in Table 1. The point that needs to be emphasized especially here is to specify the evidence of the finding clearly as roentgeno-deformans (r-def.) when deformative change is recognized in roentgen finding; histo-rheumatica (h-rh) when diagnosed as rheumatism from pathological findings; clinical tuberculosis (c-tbc) when diagnosed as tuberculosis from clinical findings; and bacterial tuberculosis (bac-tbc) when tubercle bacilli are detected. Thus, when these findings are arranged, it will be found that mono-arthritis non-systemica chronica senilis roentgeno-deformans (111 chr. senilis r-def) corresponds to a fairly genuine form of what used to be called as osteo-arthritis and poly-arthritis systemica chronica histo-rheumatica (222 chr. h-rh.) corresponds to chronic rheumatoid polyarthritis.

We have recently combined the logical classification so far mentioned with the conventional classification, and have divided the cases roughly into rheumatoid arthritis, ostco-arthritis and fibrosis, and any other finding is to be appended in brackets.

By this classification or the method of designation it seems possible to eliminate the major portion of confusion and trouble that we have to deal with. In the case of arthritis of knee joint suggesting clinically tuberculosis but histologically diagnosed as rheumatism, it is to be diagnosed as *gonitis systemica chr. cl-tbc. h-rh* (122 chr. cl-tbc. h-rh); in the case being clinically rheumatism but later verified to be patho-anatomically tuberculosis, it can be changed from rheumatoid arthritis (122 chr. cl-rh) to (122 chr. cl-rh, h-tbc). Consequently, the rather umbiguous term, tuberculous rheumatism (Poncét), may possibly be discarded. Likewise, supposing we call Still's disease as "(222 subacuta infantilis clinico-subseptidica), its pathological picture will become much more accurate. (In this instance, this nonmenclature was given on the suggestion of Prof. Tomio OGATA).

HISTO-PATHOLOGICAL STUDIES OF THE SYNOVIAL MEMBRANE

We tried arthroscopic examinations² on as many cases as possible and pinched out the synovial membrane under the arthroscope at each examination (Fig. 1). And in the case where such an arthroscopic examination proved to be not feasible, histo-pathological examination was car-

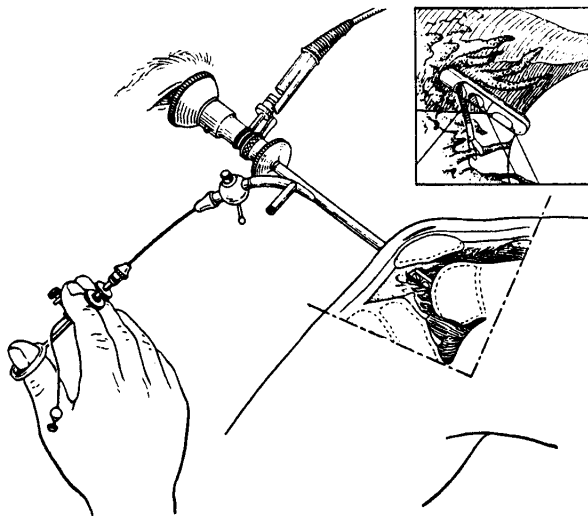


Fig. 1 Arthroscope
Extracting the specimen with a forceps under the arthroscope (Takagi)

ried on the specimen of the synovial membrane punched out by the method devised by *Polley*³ of the Mayo Clinic. Moreover, in the observation of the tissue picture of *Poly-arthritis systemica* (222) as mentioned above, taking the classical case of what is known clinically as chronic rheumatoid polyarthritis, we could also observe such findings as the fibrinoid degeneration, the basophylic reaction, fibrinin exudate, changes in small arteries, scar-formation, and the exudation of round cells as have been stated by predecessors. We found the first three findings to be particularly

Table 2. Histological picture and diagnosis of chronic arthritis

	rheuma.	tubercl.	synovitis simplex	fibrosis
fibrinoid degeneration	●			
basophilic cell reaction	●			
fibrin exudation	●	○	○	
arteriolus change	○	○	●	○
scar formation	○	○	●	●
infiltration of round cell	○	○	●	
serous exudation		○	●	
necrosis		●		
epitheloid cell reaction		●		
tubercle		●		
appearance of Langhans' giant cell		●		

marked in the case of rheumatism. When the histopathological pictures such as tuberculosis and simple synovitis are arranged in this manner, they will be like as shown in Table 2.

Now, scanning over the histological pictures of actual cases, here again we will find many cases that are difficult of defining decisively as rheumatism or tuberculosis. Therefore, we have improvised the terms, rheumatism (R), tuberculosis (T), simple inflammation (S), fibrosis (F), and their intermediaries as Rs, Sr, Rt, Rf, and Fr. (Fig. 2) Then the serial

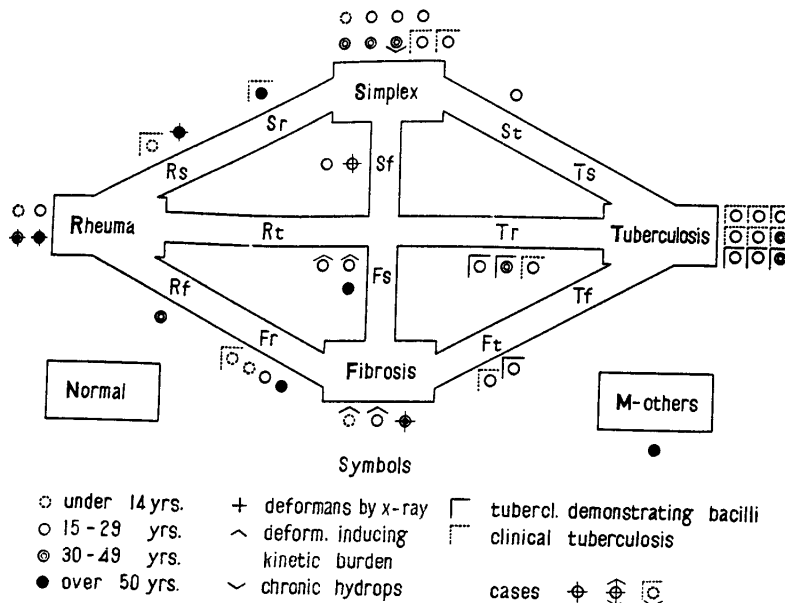


Fig. 2. Histological picture of Monoarthritis Systemica~122

combination of the classification of types with the histological pictures shown in Table 1 will become as the ones shown in Table 3; in other words, the majority of *poly-arthritis systemica* (222) from the histological picture may safely be considered as rheumatic.

On the contrary, in the case of mono-arthritis which presents complex findings, especially in *gonitis systemica* (122), there are quite many cases whose clinical diagnosis does not agree with the pathological diagnosis. Those shown in Table 2 as clinical tuberculosis (cl-tbc), differing from classical tuberculous arthritis, are the ones that show the swelling of articular capsule, a high density of synovial fluid or no destruction of bone even during a protracted observation on its course, and those that do not include syndrome, so-called knee arthritis of unknown origin (Go-

Table 3. Clinical and Histological Picture of Joints

clinical	histological	rheumat.		tuberculosis		simplex		fibrosis		others		total
		(rheumat.)	(rheumat.)	(t. b.)	(t. b.)	(simplex)	(simplex)	(fibrosis)	(fibrosis)	normal		
1 1 1		1	3	1		6	2	5	15		3	36
1 1 2												
1 2 1		4	8		1	8	6	7	9	2	5	50
1 2 2		8	6	17	7	12	8	3	11	2	1	75
2' 1 1			1	1		2		1	2		2	9
2' 1 2												
2' 2 1		4										6
2' 2 2		2	1			1	2	1	2		1	8
2 1 1		3				1		2	3			9
2 1 2						1						1
2 2 1		1							3	1		5
2 2 2		29	5			11	6		9			60
total		56	20	19	8	42	24	19	54	5	12	259

Note: R stands for rheumatism; (rheumatism) for the total of Rf, Rs, and Rf.
Others are equivalent to this symbol (see Fig. 2).



Case 1. G.H. male, 52 years old.

Diagnosis: Gonitis chronica sin. clinico-deformans histologico-rheumatica (111 chr. cl-def, h-rh)

Clinical findings: Began to have pain in the left knee joint for the previous 5 months, but no inducing factor is discernible. At the examination a slight swelling of the left knee joint and by roentgen finding osteoarthritis can be observed. E.S.R. equals 15 mm/hr.

The pathological diagnosis by biopsy is a marked diffuse fibrinoid degeneration of the subsynovial region. In this lump cell reaction can be observed, and these cells contain small round cells.

ritis chronica uncertae cause). Among them even out of the six cases confirmed to be bacterial tuberculosis (bac-tbc) because of tuberculous bacilli in culture, some presented the fibrinoid degeneration suggesting rheumatic findng in combination with the tuberculous picture (Tr); and out of the 13 cases demonstrating tuberculous bacilli in their culture, five cases had what might be considered to be rheumatism as well.

STATISTICS⁴

1. *The 1952-Survey of the Ministry of Welfare.* In Japan we had no general statistics on rheumatic diseases, and only after the survey made on the crippled children throughout Japan in March 1952 under the co-sponsorship of the Ministry of Welfare and the Japan Society of Orthopedic Surgery, had we been able to get a glimpse of rheumatic diseases. According to this survey, those with severe rheumatoid poly-arthritis receiving the aid under the Rehabilitation Law for the Disabled are estimated to be about 15,000 throughout Japan (17 persons per 100,000 population), and this disease occupies the sixth place after the fracture of bones, polio., cerebral palsy, purulent inflammation, and congenital dislocation of hip joints in point of number.

According to the distribution picture of rheumatoid arthritis in Japan as shown in Table 4, in Hokkaido District and in northeastern districts rheumatoid poly-arthritis is rare, and osteo-arthritis is numerous. In the

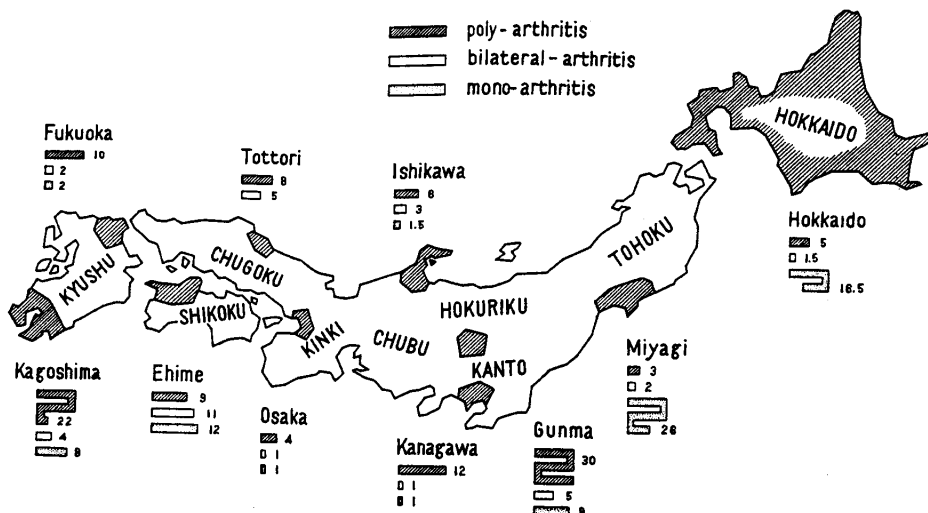


Table 4. The Random-selective Survey (1952) by the Ministry of Welfare (patients per 100,000 population)

opinion of *Hench*,⁵ both rheumatic fever and rheumatoid arthritis do not occur in the tropic, but they occur frequently in the temperate zones where there is heavy rain-fall. Looking at the atmospheric conditions in Japan, the Hokkaido District and the northeastern parts are cold but these regions have conspicuously small rain-fall throughout the year as can be understood from Table 5. It seems that there is no appreciable relation-

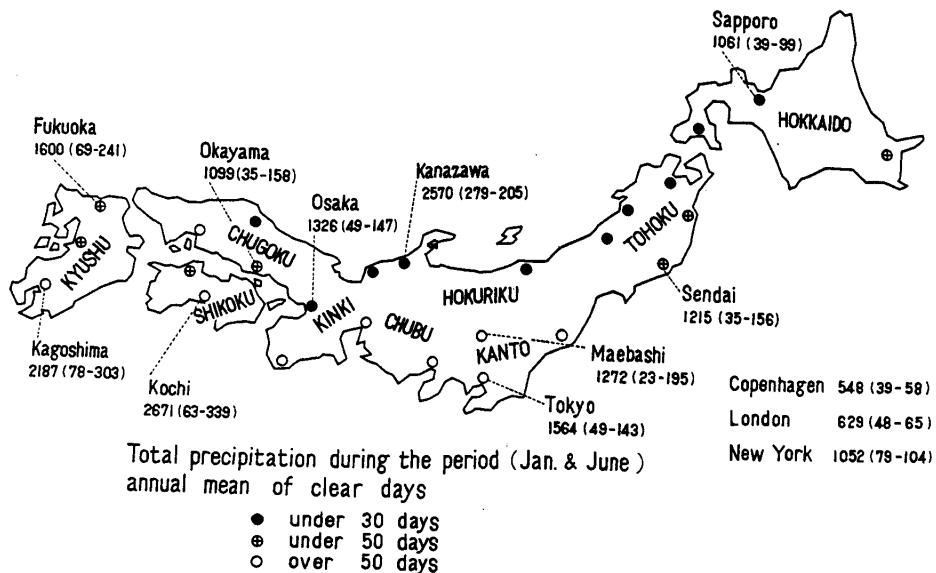


Table 5. The Amount of Precipitation

ship between humidity and the amount of sunshine from the statistical point of view. However, it goes without saying that this point requires further investigations.

2. *The statistics of the clinics in Okayama University Medical School.* The number of patients with rheumatic joint diseases visiting our Out-patient Clinic for Rheumatoid Arthritis in Okayama University during the period of four years from June 1954 to May 1958 amount to about 1,600 cases. The types of these patients and the age at the onset of disease are as shown in Table 6.

As can be observed in Table 1, (222) is rheumatoid polyarthritis; (2'22) is the case in which lesion appears localized on both sides of the knee joint only; and (111) is osteoarthritis. All these three types are found more in female, while (211), *polyarthrosis non-systemica*, presents pain in various joints of the whole body but shows no inflammation at the

Table 6. Types of Disease and Age of Onset
(female)

age of the onset types of disease	I 0—14 yrs.	II 15—29 yrs.	III 30—49 yrs.	IV 50— yrs.	total
2 2 2	15	98	93	48	254
2 2' 2	0	7	22	21	50
2 1 1	2	6	6	1	15
1 1 1	6	44	34	40	124
total	23	155	155	110	443

(male)

age of the onset types of disease	I 0—14 yrs.	II 15—29 yrs.	III 30—49 yrs.	IV 50— yrs.	total
2 2 2	9	33	40	22	104
2 2' 2	2	16	10	22	50
2 1 1	2	20	8	2	32
1 1 1	16	32	16	24	88
total	29	101	74	70	274

types of disease: 2 2 2 polyarthritis systemica
 2 2' 2 diarthritis systemica
 2 1 1 polyarthritis non-systemica
 1 1 1 monoarthrosis non-systemica

joint nor is it accompanied by any acceleration of erythrocyte sedimentation rate or any other somatic symptoms. This latter is generally known as psychogenic rheumatism or primary fibrositis. This type (211) is found more frequently in male, and it has a prominent peak at the adolescent age of 15 to 29 years.

Now, turning to the classical type of rheumatoid arthritis (222), its incidence in female is 2.5 times that in male, reaching its peak somewhere between 15 to 49 years old, and especially in the age range of 15 to 29 years the incidence in female reaches three-fold of that in male. No such phenomenon is encountered in other types such as (2'22), (111), and (211). In other words, rheumatoid poly-arthritis accompanied by somatic reactions is more frequent in the age range where the female sex metabolism is at its height.

As for the stage and the class of diseases, we followed those of Steinbrocker⁶ of U. S. A., which are being widely used the world over. As shown in Table 5. in our out-patients Stage I and Stage II are most numerous, and as for the class, Class 2 and Class 3 are more frequent. Undoubtedly there are actually many more other moderate cases, but the figure

may be said to be suggestive of that the patients finally reached the stage where they at long last decided to receive professional treatment.

Next, out of these cases listed above taking up the patients residing in Okayama City, there are 63 males and 185 females, to the total of 248 cases with rheumatoid arthritis. In comparing this with the statics of Copenhagen⁷, it is interesting to note that there are two peaks in the age at which the disease attacks female, and that the onset of disease in male reaches its peak around 50 years of age, showing a relatively higher peak in proportion to the population and making almost identical curves Tables 7—10. Moreover, the frequency of the disease is 105 persons per 100,000

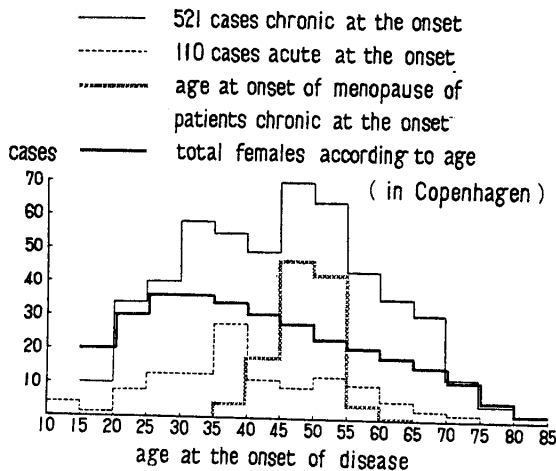


Table 7. The Age Range of the Onset of Rheumatoid Arthritis in Female

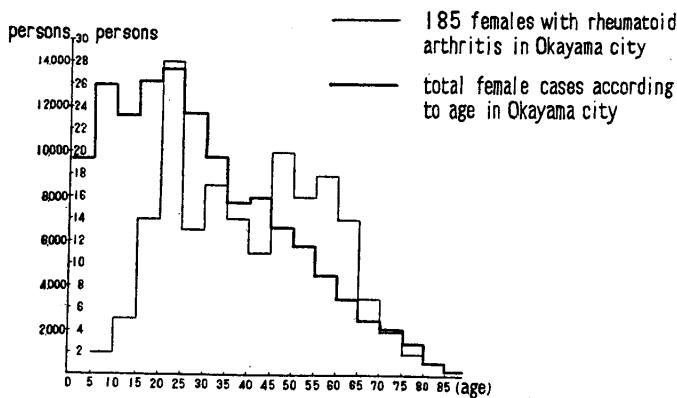


Table 8. The Age Range of the Onset of Rheumatoid Arthritis (chronic at the onset) in Females (Okayama City)

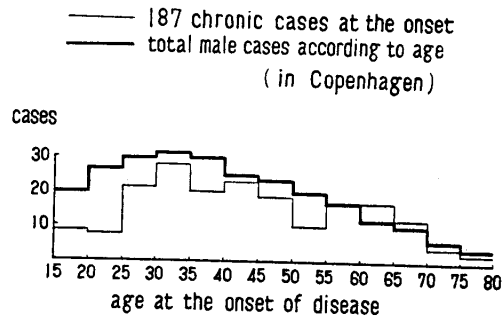


Table 9. The Age Range of the Onset of Rheumatoid Arthritis

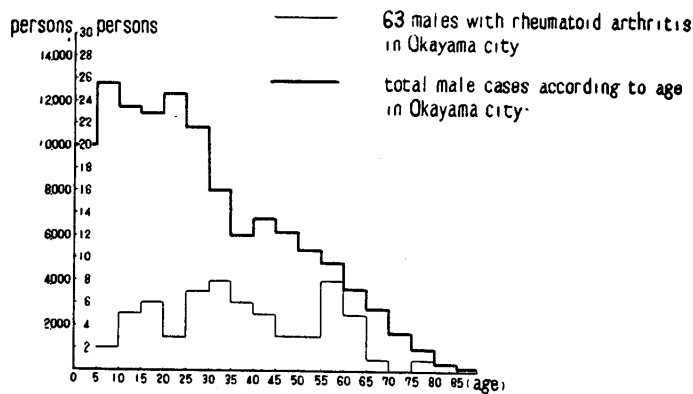


Table 10. The Age Range at the Onset of Rheumatoid Arthritis (chronic at the Onset) in Male (Okayama City)

population in Okayama City, about 2/3 of 163 cases in the case of Copenhagen, but this statistics being based solely on those patients registered in our clinics, in all likelihood the actual number of cases in Okayama City will match the figure in the latter city. In addition, of these registered cases, those to whom the Rehabilitation Law for the Disabled is applicable or coming close to be eligible for the law are about one eighth of the total; and when compared with the survey of the entire Japan made by the Ministry of Welfare in 1952 in which it was found the persons disabled by rheumatoid arthritis amounted to 17 persons per 100,000, seems to coincide roughly with the statistical figure of the Ministry.

Deducing from these general figures, it may be said that cases of chronic rheumatoid arthritis in Japan approach closely to the figure in the northern Europe including Copenhagen, and that the sex-differences in frequency of the disease and the age range of its onset are almost the same.

TREATMENT

1. *Oral administration of prednisolone.* The core of the anti-inflammatory therapy for rheumatoid arthritis lies in the use of drugs such as adrenocortical hormones and salicylates belonging to the cortisone group, and those of the Pyrazol group. We prefer to use mainly prednisolone of the former, and of the latter we use aspirin or Phenylbutazon in combination of prednisolone

In the prednisolone administration we follow the paraphysiologic method of Hench's⁸, given smaller amounts for a long period; namely, at first the dosage of 5 mg is divided into 1.25 mg to be given in the morning and 3.75 mg at night observing the results for 3 to 4 days. According to the symptoms thus observed the dosage is either increased or decreased by 1.25 mg to meet the individual condition.

Table 11. Maintenance Dose of Prednisolone and its Relationship with various Symptoms

maintenance dose of prednisolone	nos. of patients	stage	age	av. duration of disease	nos. of joints (max. min.)	activity of joints	systemic reaction
over 5 mg	5	3.6 (2-4)	34 (22-47)	1 5/12	9 (6-over 10)	305 (210-395)	72 (60-80)
5-2.5 mg	17	2.3 (2-3)	39 (21-59)	4 4/12	6.8 (3-over 10)	261 (180-350)	51 (25-70)
under 2.5 mg	7	2.4 (2-4)	37 (9-57)	5 6/12	4 (3-6)	195 (160-230)	27 (15-45)

Note 1: Factors used evaluating exacerbation of rheumatoid arthritis and maximum number of points assigned to each factor (Short)

Factors	Maximum no. of points
Functional activity	100
Pain and tenderness	100
Stiffness	75
Swelling of joints	75
Joint effusion	50
Heat and/or redness of joints	50
Limitation of joint motion	50
Maximum degree of exacerbation	500

Note 2: Estimation of the systemic reaction (Kodama, Kobayashi)

	Maximum No. of points
E. S. R.	30
Anemia	30
Wasting	20
Appetite	20
Total	100

The results obtained by the prednisolone administered in the manner mentioned above are shown in Table 11. The estimation of the activity of the joints is indicated by SHORT⁹ in the note 1, and estimation of the systemic reaction is indicated by the note 2, our own design. As can be seen from the table, five cases that required the maintenance dosage of over 5 mg prednisolone all showed a strong activity of the joints, and their mean value was 305 and even the systemic reaction gave the value well over 70. The number of diseased joints were likewise many, and four cases proved to be beyond Stage 3. Moreover, it is noteworthy in that the duration of disease is comparatively short period of 1 to 2 years. In other words, those requiring the maintenance dosage of over 5 mg prednisolone can generally be said to show relatively severer systemic and local inflammation and their symptoms seem to progress quite rapidly within a short period of time.

Those requiring the maintenance dosage of 2.5 to 5 mg prednisolone were 17 in number; and their average value for the estimation of joint activity was 261, and that for the systemic reaction 51, showing lower values as compared with those requiring the dosage of over 5 mg. The majority of them had a comparatively longer history of disease.

In the cases requiring the maintenance dosage of less than 2.5 mg prednisolone, the estimated value for the joint activity was 195, and that for the systemic reaction was 26, both showing lower values. With a single exception, all of them had a long history of disease.

In other words, those showing severer systemic symptoms of joints and more rapid progress in symptoms require a greater maintenance dosage of prednisolone, but the age and the duration of illness seem to be not involved in this.

2. *Curettage of the synovial membrane and synovectomy*¹⁰ Those requiring the maintenance dosage of over 10 mg prednisolone per day are hospitalized and given a thorough examination. In this instance the majority of these cases will present (1) the complication of such other collagen diseases as *Periarteritis nodosa* and *erythematosis*; (2) toxic symptoms due to the faulty administration of prednisolone; and (3) the inflammation of joints and lymph nodes presenting sub-septicemia or sub-purulent reaction.

Excepting the cases as (1) and (2), in the case of (3) the tissue picture is examined with biopsy specimen obtained by punch method. When the histological examination proves to be non-tuberculous, at first prednisolone injection into joint is attempted. When the local and systemic

symptoms do not turn for better after two prednisolone injections a week, we make it a rule to perform the curettage of the synovial membrane.

The curettage of the synovial membrane can be performed quite simply. Taking an example of the knee joint, we make about 5 mm incision of the skin at the median upper part of the patella, and then insert

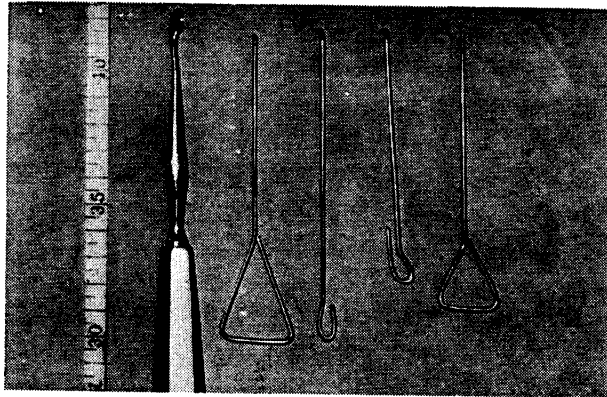


Fig. 4. Various curettes used for the curettage of the synovial membrane. Smaller ones are for finger joints.



Fig. 5. Curettage of the synovial membrane of knee joint

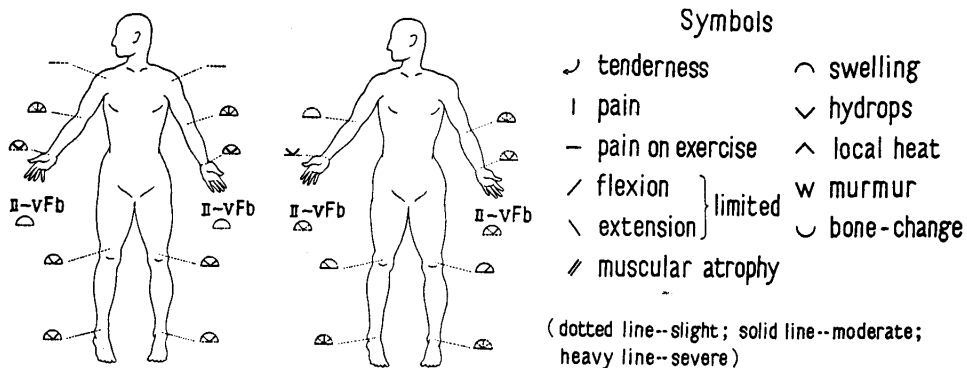
When there are granules in the joint cavity and the synovial membrane is covered with sub-purulent mossy-growth, the curettage with a curette, will make subsequent injections of such hydrocortisone more effective.

This shows a case at an early stage and the incision of the skin is a little too big. The skin is incised 6 mm upward into the knee joint, and by inserting small curette, and the curettage is done through that hole. As there is no severe pain during the curettage, local anesthesia is sufficient. After rinsing the cavity through physiological saline solution, it is sutured one stitch.

a curette and the interior wall of the joint space is curettaged. Next, after washing thoroughly well the space with physiological saline solution and injecting 25 mg of prednisolone, the skin is sutured one stitch and the operation is over. Local anesthetic is sufficient as there is no severe pain accompanying the curettage of the inner wall of the joint space by the curette (Figs. 4, 5).

After such a curettage the effect of prednisolone injection into the joint becomes remarkably good, and the systemic condition also improves with it. Moreover, the articulation of the joint is in no way impaired by this curettage.

As for the mechanism of this improvement, in the sub-purulent case the edematous proliferation can be seen on the outermost surface of the articular capsule, and the infiltration of various cells including multi-nuc-



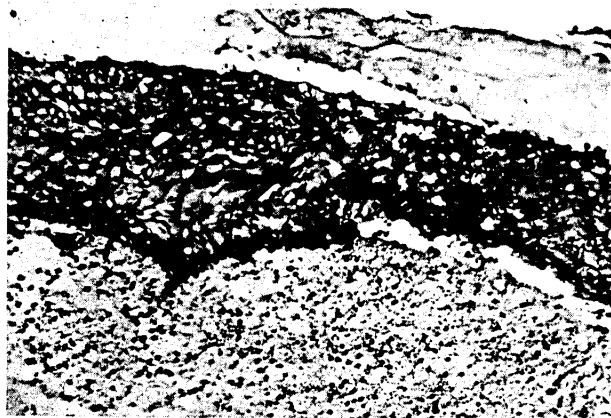


Fig. 6 Case 2

Case 3. S. K. male, 28 years old.

Onset of disease in April 1954. Received 50—25 mg/day cortisone, but symptoms progressed just the same.

Admitted to our clinic on Sept. 13, 1955. E. S. R. =44 mm/hr., no anemia.

On the twentieth of December, the fenestration of the right knee joint was performed with polyethylene tube.

Histopathological findings: A portion of the surface layer is necrotic with the exudate of fibrin. On the whole hyperplasy of connective tissues can be recognized. Fibrinoid degeneration can be observed here and there. Cell infiltration is marked, and in places multi-nucleated leucocytes can be seen, but the majority of them are plasma cells. Changes in the blood vessel wall are striking (Fig. 7).

On June 26, 1956 the polyethylene tube was removed.

Histopathological findings at the time of the removal: Inflammatory cell reaction has almost completely subsided; while the connective tissues are found rather loose. In places fibrinoid degeneration is quite marked (Fig. 8)

On July 5, 1957 the fenestration with polyethylene tube of the left knee joint was performed. By November 1957 almost all symptoms disappeared.

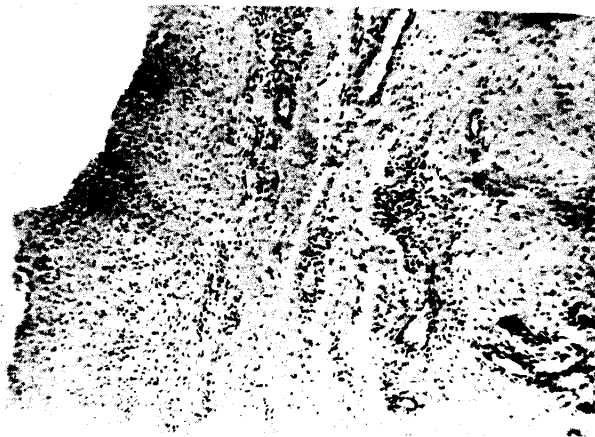
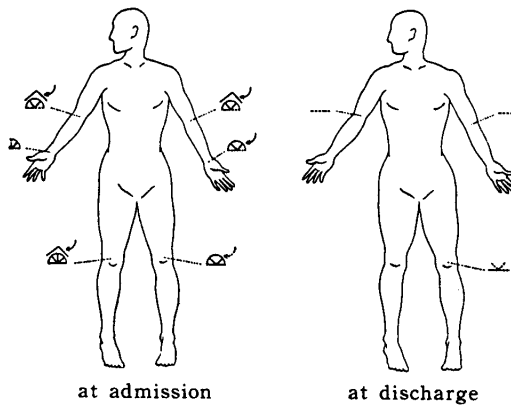


Fig. 7 Case 3. Before fenestration



Fig. 8 Case 3. 1 year after fenestration



Case 4. K.M. female, 65 years old, Stage II, Class II.
Onset of disease in Nov. 1945. At first she had swellings in many joints, and the onset of disease was gradual. Soon afterwards all other joints with exception of both knees improved almost completely.

Admitted to our clinic on August 8, 1958. At the admittance, she was slightly obese; nutrition good; no anemia; E.S.R. 18 mm/30 min.; 48 mm/hr. Blood pressure, 148/82.

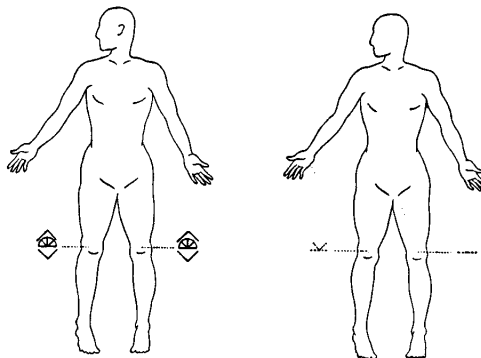
Histopathological findings of biopsy (Fig. 9): The connective tissue near surface layer is loose, but the tissues of the deeper layer are hyperplastic. Cell infiltration can be seen running from the surface layer to the deeper layers along blood vessels. There are many plasma cells, but some present a construction similar to giant cell. Hardly any change can be recognized in the blood vessel wall.

On August 12th the curettage of both knees was performed. By the injection of 10 mg predonisolone (TBA) the effect began to appear around 10 days after the operation, which equals twice the preoperative duration.

On Sept. 9th synovectomy of the right knee joint was performed. Discharged on Nov. 5, 1958. Clinical symptoms improved to 20 per cent of that at the admission.



Fig. 9 Case 4



Case 4 at admission

at discharge

Case 5. H. K. male, 45 years old.

In May 1952 the left knee joint showed swelling, followed by sharp pain in the right knee joint and elbow. In Jan. 1954 the fenestrations (without plastic tube) were performed in both knee joints, but failed to obtain any good result. During the period from April to August 1955 the patient received 23 injections of hydrocortisone into knee joints, but the effect of the injection lasted for about one week each time.

Admitted to our clinic on Oct. 8, 1955. E. S. R. equals 15 mm/hr. at the admission. Synovectomy of the left knee joint was performed on Oct. 18, 1955. Histopathological findings at the time of the operation (Fig. 10): Hardly any lining cells can be found, and cell infiltration is marked in the surface layer of the synovia. Likewise in the deeper layer the cell infiltration is marked centering around large blood vessels. These cells are blood



Fig. 10 Case 5 Before synovectomy

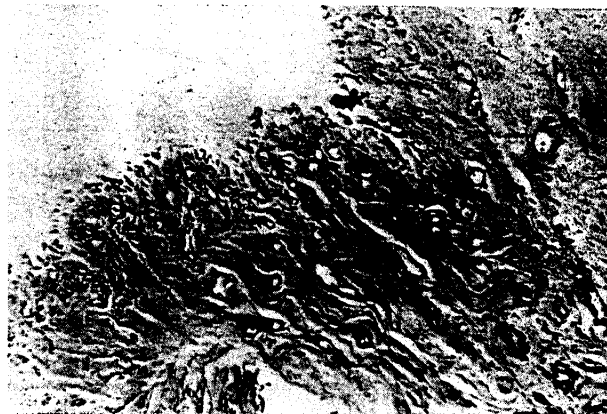
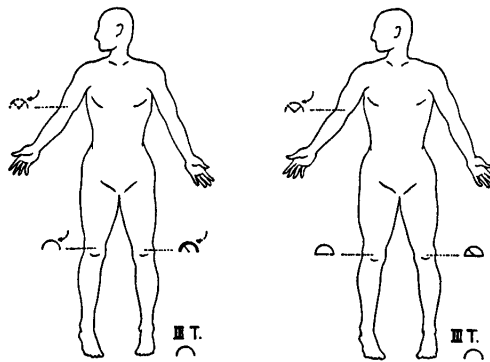


Fig. 11 Case 5 2 years after synovectomy



Case 5 at admission

at discharge

vessel wall is not so marked. On the whole the proliferation of connective tissues is striking, and some reveal fibrinoid degeneration.

The swelling of the left knee was alleviated by August 1957. E. S. R. = 37 mm/hr.; histopathological findings by biopsy (Fig. 11): Fibrosis is marked, and fibrinoid degeneration can be observed here and there. Infiltration of inflammatory cells can hardly be recognized.

leated leucocytes and fibrinoidal mass can be found there. Likewise in the case of fibrinoid degeneration fibrinoidal mass may be found occasionally on the surface of the synovial membrane, but in the presence of such a layer the effect of prednisolone injection into the joint is poor, and also this layer seems to give adverse influences on the whole body. Curettaging with a curette, this surface layer is removed and the effect of subsequent prednisolone injection becomes marked thereby.

This synovial curettage is mainly performed on the knee joint, but it is sometimes performed on the ankle and the arm and phalangeal joints as well with smaller curette specially prepared for such an operation (Fig. 4).

In the cases that show severe rheumatic pathological changes in the connective tissue of the joint capsule and marked lymphatic foci around small arteries, and those that show no improvement by prednisolone injection and in case even the curettage of the synovial membrane as mentioned above, we perform synovectomy. In this instance we found many whose systemic conditions improved after the operation.

3. *Arthroplasty*¹⁰. AKIYAMA who is studying synthetic resin for the use in the medical field made a covering with dimethylpolythroxine (containing silicon compound) in the shape of socket to be placed over the resected bone in place of artificial fat and FUKUSHIMA and his co-workers applied mainly for arthroplasty of rheumatoid arthritis, chiefly on the ankylosed side of elbow. This silicon resin is elastic, and it can be easily molded in any desired thickness and shape to suit the individual requirements. Its heat-resistance is safe up to 200°C, and as for its absorption and irritation in the body it is safe, and moreover, it is said to be an excellent material possessing X-ray permeability and the resistance against rubbing almost as strong as nylon. In the case on whom arthroplasty was performed by FUKUSHIMA, with this material, it is said that at present the result is quite satisfactory about two years after the operation.

Through the courtesy of AKIYAMA the author is following his method of arthroplasty. In two cases, one for the elbow joint and the other for the knee, although only a few months have elapsed since the operation, both are taking the course not observable in any other interpositions of

articular membrane. That is to say, it has been possible to obtain, by this operation for moveable joint, the results made it possible to start exercise with no pain whatever only after two weeks' cast period and to be able to move the joint nearly in the same range as obtained at the time of operation (Figs. 12~16).



Fig. 12 Arthroplasty of the elbow joint (1)
23 yrs. old female, the onset of disease, 6 yrs. ago, ankylosis of the left elbow at 140°, E. S. R. 5mm (1hr.)



Fig. 13 Arthroplasty of the elbow joint (2)
During the operation, a silicon resin cap (by Prof. Akiyama) is being placed on the bone.

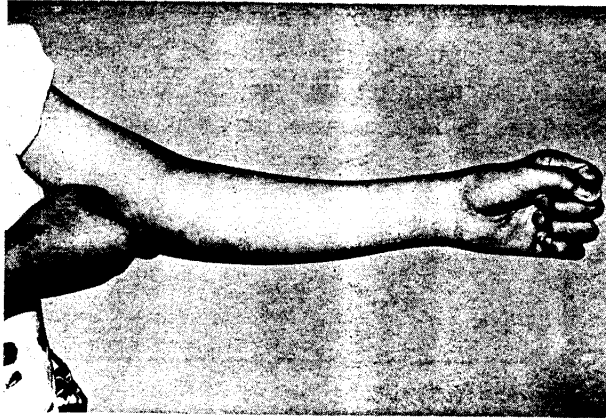


Fig. 14 Arthroplasty of the elbow joint (3)
Extension 3 weeks after the operation



Fig. 15 Arthroplasty of the elbow joint (4)
Flexion 3 weeks after the operation

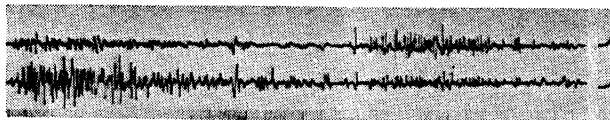


Fig. 16 Electro-myogram of the above case
35 days after the operation

The upper spindling is of the triceps and the lower for biceps, starting from right to left. These are the electrical discharge ranging from the maximum extension to the maximum flexion of the elbow joint. Despite ankylosis of the elbow joint of several years, duration, this case showed almost normal electro-myogram of the triceps and biceps even before the operation.

4. *Surgery of the hand* (Tsuge-Akamatsu). There are many deformations of fingers due to rheumatism and for these we use mainly Bunnell's method¹¹ for the restoration of the function (Figs. 17, 18).

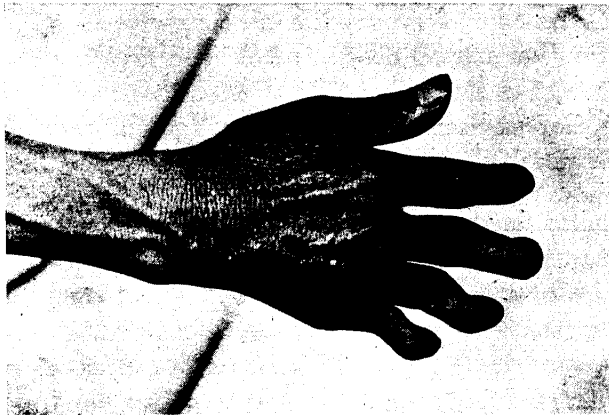


Fig. 17 Operation of the hand (case 7)

Rheumatoid arthritis of the right hand, duration 10 years, in a man of 46 years old. Flexion deformity of the metacarpophalangeal joints of both hands and hyperextension contracture of the proximal interphalangeal joints, showing so-called intrinsic plus deformity.



Fig. 18 After the operation of the above case
Bending of the fingers is improved, three weeks after the operation.

5. *Splinting of joints*. In the splinting of lower limb joints for the restoration of the function it is important to place a greater emphasis on weight-bearing without pain rather than on the movability of the joint. Consequently in the case of rheumatoid arthritis splinting of the joints is more frequently resorted to in Europe and America. There the mode of

living is such that they have chairs and beds and even at the lavatory they can sit down so that even if they have ankylosis of hip or knee joint so long as it is unilateral and in a fair position the inconvenience that may be encountered in daily life would not be so preponderant. In contrast to this, in Japan the every day life of house-wives is spent mostly sitting or squatting on matted floor, and even in lavatory and bath-room they require a high degree of bending of joints both in lower limbs and knee, making the ankylosis in any of lower limbs a great deterrent and handicap. Therefore, a sufficient care must be given to the adaptability before resorting to splinting of the joint.

6. OTHER MEASURES

1. *Salicylic acid metabolism* (MONDEN).¹² Now, comparing the estimation by salicylic acid with our results, the conventional method of the determination by salicylic acid has been by the ferric chloride method using 2 cc serum as the material. TERAOKA of our Department has confirmed that Hofstee's method, to be described in the following, of the estimation with the use of ultraviolet absorption spectrum (303 m μ) is simple in manipulation and that it gives a sufficiently accurate result with the use of only a small amount of 0.5 cc serum as the material (Tables, 12, 13).

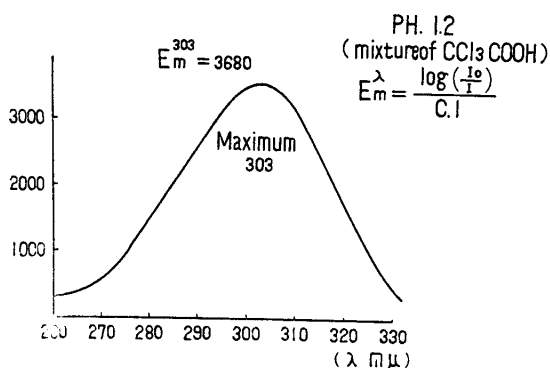


Table 12 Sodium salicylate solution (10⁻⁴M) ultra-violet absorption spectra

Table 13. Ration of the salicylic acid of blood in the ultra-violet and visible ranges (Teraoka, Monden)

method sodium salicylate	ultra-violet range (303m μ)	visible range (535 m μ)
10 mg%	10.0	10.3
20 mg%	20.1	17.5
30 mg%	28.8	27.5

Hofstee's method¹³⁾ : To 0.5 cc of serum is added 4.5 cc of 4% trichloroacetic acid, making the total volume 5 cc, and leave the mixture at the room temperature for 30 minutes. By filtering or centrifuging this solution, 3.5 to 4.0 cc of supernatant can be obtained, and by taking 1.5 cc of the supernatant in pipet and it is estimated by Beckman's spectrophotometer at 303 $m\mu$. According to the results obtained by MONDEN of our department, at first he used fully-grown dogs, but ever since the advent of the above mentioned microdetermination method, it has become possible to use rabbits and rats as the test animal. In addition, frequent examinations of human have become quite simple.

As for the amount of salicylic acid and its concentration in blood, there seems to be hardly any difference among human, dog, and rabbit. In the case of oral or peritoneal administration, the peak of the concentration is reached two hours after the administration, and the concentration has been found to give the value around 33—35 mg% in the case of 150mg/kg ; 10—20 mg% in 50 mg/kg ; and 5—10 mg% in 10 mg/kg. (Table 14)

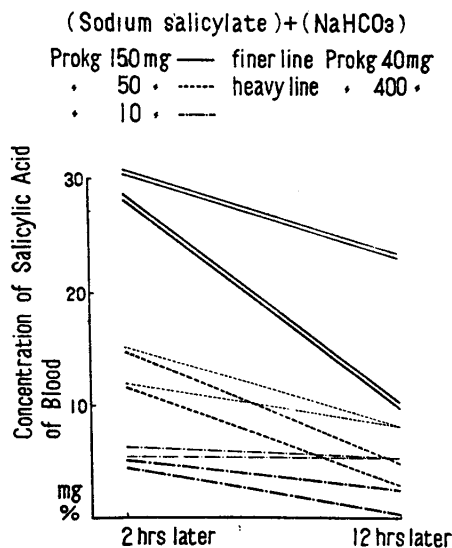


Table 14 Concentration of Salicylic Acid of Blood

In the case of Phenylbutazone to be described shortly shows a marked retention in blood, but in the case of salicylic acid administered continuously for two weeks in rat and human no marked retention can be recognized.

Next, in the case of the aspirin administration to human, its concent-

ration in blood is kept for a longer period of time when given parenterally rather than orally, although its absorption is somewhat prolonged.

In the observations carried on the effects of various other drugs administered concomitantly with salicylic acid, in the case of the administration of 40 mg/kg sodium bicarbonate solution, the salicylic acid concentration in blood after 12 hours is a little higher than that of the control, but with a large dose of 400 mg/kg soda, the salicylic acid concentration, on the contrary, falls (Table 14). In the case of drugs other than bicarbonate of soda, by administering such drugs as prednisolone (0.1 mg and 1.0 mg/kg); vitamin C (6mg and 60 mg/kg); and glucuronic acid (10 mg and 100 mg/kg), hardly any effect can be observed in the salicylic acid concentration of blood. Because approximately the same result can be obtained even in the continuous administration for two weeks with these drugs, in the country like Japan where the maximal dose of salicylic acid amounts to 2 to 3 g, would it not be reasonable to assume that the concomitant administration of 1—2 g sodium bicarbonate will raise the salicylic acid concentration of blood rather than just lowering it?

2. *Phenylbutazone* (Takaguchi). As for phenylbutazone, namely, the estimation method of Butazolodin, formerly Pulver's method had been in use, but Burns' method¹⁴ is superior as shown in Table 15, in which

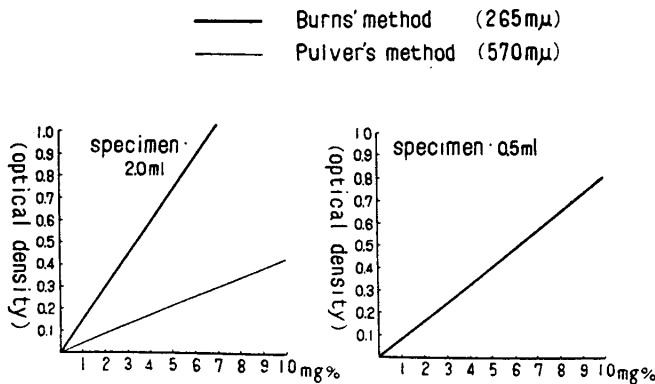


Table 15 Estimation for Phenyl Butazone (Na-salt)

even the estimation of as small as 0.5 cc of the material is possible.

By dividing patients with rheumatoid arthritis into two groups, we gave 100 mg or 200 mg Butazolodin once a day and periodically investigated its concentration in blood. The results, as shown in Table 16, were 1.7 mg% and 3.7 mg% six hours after the oral administration respectively, each showing the maximum concentration. Twenty-four hours after 7 days'

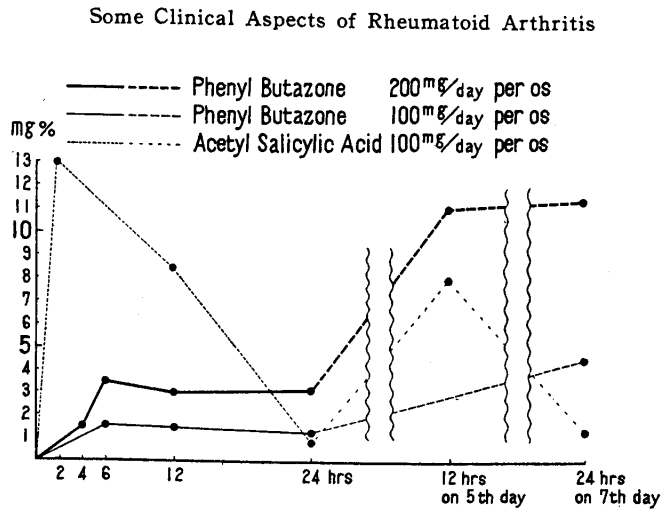


Table 16 Periodical Observation on the Concentrations of Phenyl Butazone and Acetylsalicylic Acid of Blood in Rheumatoid Arthritis

continuous administration it has been elucidated that this drug is retained in as high degree as 4.3 mg% and 11.2 mg% in the respective group. This proves to be entirely different from the result obtained by aspirin administration.

3. *Vitamin B₁* (H. Kodama). As shown in Table 17, the B₁-content

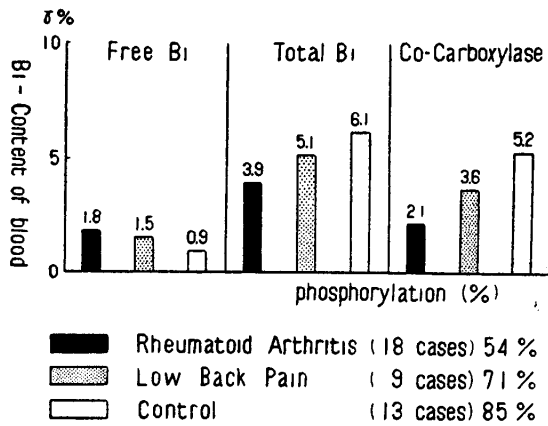


Table 17 B₁-Content of blood in Rheumatoid Arthritis

in the blood of a patient with rheumatoid arthritis a little over 1/2 that of normal person, and that of ester form B₁ is a little less than 1/2 of normal person. Consequently the rate of phosphorylation in the patient is as low as 54 per cent as compared with 85 per cent in normal person.

In the further observations of the patients divided according to Steinbrocker's classification, those in Stage 3 show the most advanced rate of the blood sedimentation, and inversely the rate of phosphorylation the minimal value of 47 per cent and the total B₁ content is also the lowest value of 3.0 $\gamma\%$, as shown in Table 18.

Table 18. Classification according to the Stage and Class, and the Relationship between Erythrocyte Sedimentation Rate and B₁ of Blood in Rheumatoid Arthritis (H. Kodama)

No. Cases	Stage	Class	E. S. R. (1 hr.)	Free B ₁ ($\gamma\%$)	Total B ₁ ($\gamma\%$)	Co-Carboxylase ($\gamma\%$)	Phosphorylation ($\gamma\%$)
6	1	1	18	0.8	5.2	4.4	85
3	1	2	24	1.3	3.1	1.8	58
5	2	2	90	1.3	4.2	2.9	69
2	3	2	101	1.4	3.0	1.4	47
2	3	3	37	0.4	4.7	4.3	91

Note: 1. each shows mean value.

2. classification is quoted from Steinbrocker.

4. *Liver glycogen* (Hirose). In the basic experiments conducted with liver glycogen, normal male rats are fed for 4 to 5 days on the artificial diet containing 40 per cent of protein, and the animals are sacrificed at the intervals of 1, 3, 6, 12, and 24 hours after the feeding. Then the estimation of liver glycogen has been carried out with the livers of these animals. As the result the glycogen content has been found to show the maximum value six hours after the feeding.

Next, with the same diet but with intra-peritoneal administration of 150 mg/kg sodium salicylic acid 4 hours after the feeding, animals are killed two hours after the injection and the amount of liver glycogen and the sodium salicylic acid concentration in blood are estimated. As the result liver glycogen has been markedly decreased as compared with the control. If the dose of sodium salicylic acid is under 100 mg/kg, no such a decrease can be recognized. Clinically this seems to be the phenomena correlated with the side-effect of the drug belonging to the salicylic acid group.

5. *Erythrocyte sedimentation and serum protein* (Kobayashi). After estimating the erythrocyte sedimentation rate in the patients with rheumatoid arthritis at the interval of 15 minutes, and the results are classified into three types of A, B, and C as shown in Table 19. In pursuing the proceeding cases, Type A seems to be at the height of inflam-

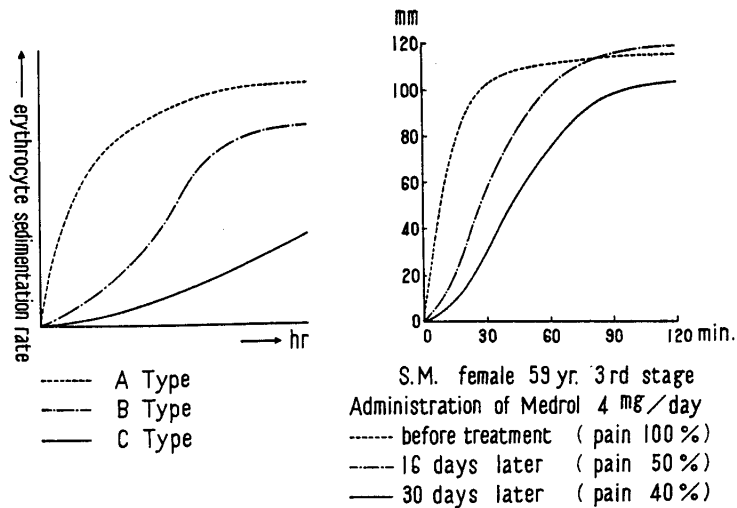


Table 19 Types of Erythrocyte Sedimentation Rate in Rheumatoid Arthritis

mation; Type B at the convalescent stage; and Type C at the dormant stage, as shown in Fig. 20. In this instance as can be observed in the figure, for the differential diagnosis of the severity of rheumatoid arthritis the estimation of the erythrocyte sedimentation at the intervals of 15 and 30 minutes is more accurate than the same taken at the intervals of one and two hours.

As for the sedimentations of serum protein, the tendency has been observed in which the increase in γ -globulin is marked; α^1 - and α^2 -globulin with a slight increase; and β -globulin at the normal or slightly lower level. It is significant to note that there is 5 per cent of the experimental error in the mutual relationship between the increase in γ -globulin and Type 3 of the erythrocyte sedimentation rate above-mentioned.

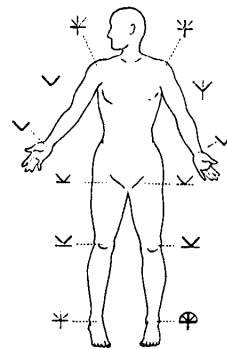
6. *The fragility of capillary blood vessels* (Kobayashi). As for the fragility of capillary blood vessels, we measure it with a petechiometer at -300 mm/Hg. We have examined the fragility of capillary blood vessels, serum prothrombin level, the duration of bleeding, and the liver function. As the result because the number of petechia are found to have increased to quite a high degree not only in rheumatoid arthritis, but also in other diseases as well as in normal person, the factors such as the individual constitution and heredity seem to play an important role.

In case the number of petechia are increased in rheumatoid arthritis, often the value of prothrombin is decreased. Also in the cases with decreased liver function the exacerbation of petechial number is especially

marked, and this condition will improve in parallel with the improvement in the liver function. However, protraction of the duration of bleeding is hardly observable. Next, when some re-inforcing agent of blood vessels is administered to the case with exacerbated petechial number, most of patients with rheumatoid arthritis turn for the better, while on the contrary almost no change can be brought about in those cases what appear to be of the constitutional origin.

7. *Rehabilitation.* Japanese people, especially women, spend much time squatting on the matted floor, and living in the house with the construction of lavatory and bathroom greatly different from that in Europe and America, it is of utmost importance for them to have a perfectly good articulation of the joints both in the lower limbs and knee. For Japanese women it is much more comfortable and convenient to be able to squat freely and move about the room on a wheel chair even if they can not walk unassisted only a distance of 10 meters.

When joints are impaired either by contraction or otherwise so that the patient can not stand up, we apply traction or perform operation. However, for the patient without hope for ever standing up stably but has no pain of the joint we give the rehabilitation training on a wheelchair specially adapted to the Japanese home and also we modify the construction of lavatory in such manner as most convenient for the patient (Figs. 19~21).



Case 8. at admission

Fig. 19 Case 8 Findings at the admission on July 13, 1956
A 36-year old female. Onset before 14 years, IV-stage, IV-class both wrists total ossal ankylosis, both knee joints and left ankle joints partial ankylosis



Fig. 20 Case 8 The wheelchair used in a Japanese room

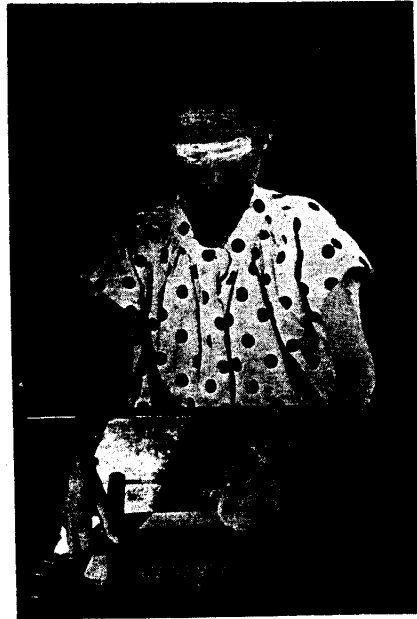


Fig 21 Case 8 Rehabilitation by a wheelchair (cooking in the kitchen)

SUMMARY

In our department we have been placing a special emphasis on the treatment and study of rheumatoid arthritis, and during the last four years we have handled about 1,600 cases visiting our outpatient clinic and approximately 100 hospitalized cases. Our experiences with these patients are only what might be called an introductory phase in the study and treatment of rheumatoid arthritis when compared with those in Europe and America. In estimating the incidence of rheumatoid arthritis in Japan from various available data, although it would not reach the level of England and U. S. A. , it will be about 100 cases per 100,000 population, matching more or less the incidence in the northern Europe. As regards sex and the predisposing age we find no great difference from those in Europe and America.

One striking difference that we find is the fact that patients in our country have very little resistance against salicylic acid drug used in treatment. Therefore, it is unreasonable to expect a good anti-inflammatory action by administering a large dosage of 5—10g of such a drug as aspirin per day. It must be limited within a comparatively small dosage of

1.0 to 2.0 g or with concomitant administration of prednisolone and aspirin in the hope of utilizing its analgesic effect. Furthermore, it is not feasible to introduce the results of studies made in Europe and America on the salicylic drug and its prescription all of them showing the concentration in blood 35 mg%, which is on the borderline of intoxicating dosage. This is only one example, and with some more experiences we shall undoubtedly encounter many dissimilar points. Therefore, it is essential that rheumatology specific to Japan needs to be established.

REFERENCES

- 1) KODAMA, T. et al.: The Classification and Physiopathology of the Chronic Arthritis, *J. Jap. Orthop. Surg.* 28, 362, 1954 (in Japanese)
 - 2) WATANABE, M. et al.: Atlas of Arthroscopy, Igakushoin, Tokyo, Japan, 1957
 - 3) POLLEY, H. F.: Experiences with Instrument for Punch Biopsy of Synovial Membrane, *Proc. Staff Meet. Mayo Clinic* 26, 273, 1951
 - 4) KODAMA, T.: Some Problems of the Rheumatoid Arthritis, *Saishinigaku* 12, 1528, 1957 (in Japanese)
 - 5) HENCH, P. S.: Rheumatoid Arthritis, *Ann. Int. Med.* 23, 67, 371, 1948
 - 6) STEINBROCKER, O. et al.: Therapeutic Criteria in Rheumatoid Arthritis, *J. A. M. A.* 140, 659, 1949
 - 7) CLEMMESSEN, S. et al.: Rheumatic Disease, Saunders Co. Philadelphia, 1952
 - 8) HENCH, P. S.: Medical Use of Cortisone, Lukens, 1954
 - 9) SHORT, C. L. et al.: Rheumatoid Arthritis, Harvard Univ. Massachusetts, 1957
 - 10) KODAMA, T.: Surgical Treatment of the Rheumatoid Arthritis, *Nihon Iji Shimpo*, No. 1794, 1958 (in Japanese)
 - 11) BUNNELL, S.: Surgery of the Hand, 3rd Ed., Lippincott Co. Philadelphia, 1956
 - 12) MONDEN, T.: Determinations of Salicylic Acid in Blood, *J. Jap. Rheum. Assoc.* 1, 140, 1958 (in Japanese)
 - 13) HOFSTEE, B. H. J.: Spectrophotometric Determinations Esterases, *Science* 114, 128, 1951
 - 14) BURNS, J. J. et al.: The Physiological Deposition of Phenylbutazone (Butazolidin) in Man and a Method for its Estimation in Biological Material, *J. Pharmacol. Exper. Therap.*, 109, 346, 1953
-