Dynamics of rheumatoid joint

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Abstract

In the present communication the recent works done by the Rheumatism Research Group of Department of Orthopedic Surgery, Okayama University, are described. The principal findings may briefly be summarized as follows. 1. Pathohistological pictures of the synovial membrane are clarified into six types. Among them, Fibrinoid type and Follicular-Fibrosis type are the representative ones of chronic rheumatoid arthritis. 2. For the evaluation of the systemic as well as the local activities in rheumatoid arthritis and for judging the therapeutic effect, some indices have been established. 3. Injection of steroid hormones into the local joints fails to give satisfactory results in advanced, chronic rheumatoid arthritis. In such instances the flushing of the joint with physiological saline solution is effective. 4. In the case of chronic rheumatoid arthritis where the inflammation of hand and phalangeal joints is marked, RA-test gives rapid and more intense reaction, and most of such cases are of Follicular-Fibrosis type. 5. When lymph follicles appearing in the synovial membrane are stained when methyl green pyronine, the arrangement of lymphoid cells and plasma cells becomes distinctly clear. By micro-autoradiographic observations it can be seen that \(^3\)H-thymidine injected into the joint cavity is mostly ingested by the lymphoid cells in lymph follicles. 6. In the observation by the fluorescent antibody method multinuclear leucocytes found in the joint fluid and in the peripheral blood react with 19S and 7S-gamma-globulins. 7. When the serum and the joint fluid of the patient with rheumatoid arthritis are fractionated, they separate into three peaks at 19S, 7S, and 4S. Both S. S. C. A.-test and L. F. T. tests reveal the peak at 19S. The serum of chronic hepatitis positive to RA-test and the serum of rheumatoid arthritis are found to react immunologically the same to anti-\(\beta_2\) M globulin sheep serum. 8. When the reticulo-endothelial system of rat is blocked by 900,000 molecules of poly-vinyl-pyroridon, the ability of antibody production is diminished. 9. Chemical synovectomy of injecting osmic acid is effective to FibrinoidCoating type. Its action mechanism lies in the complete cleaning of the surface of synovial membrane. 10. By radiating synovectomy with 193Au a fairly good result can be expected. 198Au is ingested by those cells in the surface layer of the synovial membrane and also by histiocytes in the synovial membrane. When 5 mc of 198Au are injected into the knee joint, a marked necrosis of the synovial membrane occurs. When 198Au is added to the ascites cells of rabbit during the tissue culture, in the concentration of over 14 \(\mu\)C degeneration of these cells can be recognized. 11. From the examination results of prognosis on those 25 cases with 41 rheumatoid knee joints after surgical synovectomy, it is considered that this method is

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indicated for Follicular-Fibrosis type. Ones with rheumatoid knee joint of Fibrinoid-Coating type
gold sol treatment should be resorted to. In the cases of hand joints, surgical synovectemy is to be
recommended at a relatively early stage.
1. Introduction

Studies on the pathophysiology of regional joints in rheumatoid arthritis are now being carried out vigorously. For instance, there are such works as concerned with Hollander's RA-cells, rheumatoid factor in the synovial fluid, those lymph follicles, lymphocytes and plasma cells that appear in the synovial membrane as well as the fluorescence immunological studies on them. On the other hand, attempts are being made on the treatment of rheumatoid arthritis by the flushing or rinsing the joint that responded well to the injection of steroid hormones, and chemical synovectomy, radiating synovectomy, immunological and surgical synovectomies as well.

The term, synovectomy, used in such instances seems to imply that in discarding the function of so highly differentiated a structure as the synovial membrane attempt is made to control the inflammation of the rheumatoid joint by bringing it as close to a simple connective tissue capsule as possible in order to minimize antigen-antibody reaction.

The treatment of rheumatoid arthritis may be analysed into systemic and local phases. In the rheumatism research group of Department of Orthopedic Surgery, Okayama University, we are studying on the pathophysiology of the rheumatoid joint, and the treatment of rheumatoid arthritis especially from the viewpoint of pathophysiological findings of the synovial membrane.

2. Histopathologic picture and prognosis of synovial membrane:

In the treatment of rheumatoid arthritis we make it a rule to take biopsy
Fig. 1 Diagrammatic drawing of the tissue elements in rheumatoid arthritis


Specimens of the affected joint as much as it is feasible, and we have so far encountered 250 cases. These have been classified into six types as mentioned in the following.

a. Synovitis simplex type (S): This is a type of simple inflammation of the synovial membrane having the proliferation of lining cells.

b. Arteritis type (A): This is the one which shows changes mainly in the arterial capillaries of the synovial membrane and in their vicinity, and also changes on the arterial wall and the infiltration of lymphocytes in the areas surrounding the affected vessel wall.

c. Fibrinoid type (K): This denotes the fibrinoid degeneration. In order to avoid the confusion with Fibrosis type the symbol “K” for Kollagen is used.

d. Coating type (C): This signifies the case where fibrinoid substances
cover the surface layer of the synovial membrane in a mossy formation.

e. **Follicular type** \((N)\): In this type there are observed lymphoid cells
aggregated in the synovial membrane in a lymph-follicular formation.

\(f.\) **Fibrosis type (F):** This is the type with proliferation of connective tissues.

These six types are not by any means existing independent of each other, and as the matter of fact many factors are accumulating and hence there are differences in the intensity of the proliferation, that is, some with marked proliferation, which is designated by capital letter and others with mild proliferation by small letter. And for the old lesions an apostrophe is added and the combination of these is represented as for instance as \(KcNFa'\).

As for the histological picture and the prognosis of these cases, the cases of Fibrinoid type vary considerably from mild to severe ones. In our experiences, in the case of Simplex type and Arteritis type, the systemic and local administration of steroids are effective. For Fibrinoid-Coating type, gold therapy is recommended. However, in the case of Follicular type, the surgical synovectomy is indicated.

3. **Evaluation of activity and therapeutic effects of rheumatoid arthritis:**

Ever since the establishment of the Rheumatism Clinic in our University in 1954, we have handled 3,300 cases of rheumatoid arthritis in these ten years. Among these patients it has been possible to follow up for the period of three years with 450 cases of them.

As for the evaluation of the activity of rheumatoid joints and the establishment of treatment regimen, there are not quite so satisfactory techniques available as mentioned by Steinbrocker, Lansbury, and Short et al. On the basis of our studies on the cases that we encountered we have also devised our original evaluation indices for systemic activity and regional joints and reported the results of our investigation at the Eighth Meeting of Australian Rheumatism Association in 1963.
Table 1 Evaluation of therapeutic effect (local) (KODAMA)

<table>
<thead>
<tr>
<th></th>
<th>0 unchanged</th>
<th>10 1 stage</th>
<th>20 2 stages</th>
<th>30 3 stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops, swelling</td>
<td>unchanged</td>
<td>-- aggrav.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local heat</td>
<td>unchanged</td>
<td>-- aggrav.</td>
<td>5 slight--none</td>
<td>8 marked--slight</td>
</tr>
<tr>
<td>Joint fluid</td>
<td>unchanged</td>
<td>-- aggrav.</td>
<td>5 slightly decreased of cells or fluid of joint</td>
<td>10 markedly decreased of cells or fluid of joint</td>
</tr>
<tr>
<td>Pain</td>
<td>unchanged</td>
<td>-- aggrav.</td>
<td>5 1 stage</td>
<td>10 2 stages</td>
</tr>
<tr>
<td>Function</td>
<td>unchanged</td>
<td>-- aggrav.</td>
<td>5 slightly improved</td>
<td>10 moderately improved</td>
</tr>
</tbody>
</table>

The symbol (--) denotes aggravator

The index of KODAMA is generally applicable to the cases of relatively more advanced type. However, it has been found that there is no appreciable difference between the results obtained by using LANSBURY index and KODAMA’s index so that we now make it as a rule to use the systemic index of LANSBURY. At the same time, we also use the index of KODAMA, as shown in Table, for the evaluation of therapeutic results. In this instance, we give 30 points to the swelling or edema, 20 points each to the nature of synovial fluid, pain and movability of the joint and 10 points to local heat for balancing the evaluation.

4. Some considerations on local injection of steroids for the treatment of rheumatoid arthritis:

Most of those cases visiting the rheumatism clinics with the advanced, chronic rheumatoid arthritis show only a temporary improvement after receiving the injection of steroid hormones and they will soon show the recurrence of swelling and severe pain, and they repeat this course for one or two years prior to coming to our clinic. In evaluating the results of the local steroid injection in such cases by KODAMA’s grading method it is obvious that there can be seen no effect either with prednisolone acetate or prednisolone TBA as shown in Table. Since the KODAMA grading gives at least 30 points for the effective case, such

Table 2 Effect of steroid injection into local joint

<table>
<thead>
<tr>
<th></th>
<th>A Cases</th>
<th>B Total joints</th>
<th>B/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone acetate</td>
<td>32</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>Prednisolone TBA</td>
<td>58</td>
<td>-15</td>
<td>-0.3</td>
</tr>
</tbody>
</table>
as the point of 0.3 signifies that there has been no improvement of symptoms after the treatment.

In Fibrinoid-Coating type debris is abundant in the synovial fluid, but

Fig. 5 Electron-microgram of debris of rheumatoid arthritis, 3 days after injection of $^{185}$Au
when this debris is incubated in Trypsin or Varidase for 24 hours, 30 to 40% of it remains undigested. When the knee joint is flushed with physiological saline solution by aspirating it with a big injection needle, a copious amount of debris oozes out of the joint, and this washing alone is quite effective. Such a flushing, given with care and scrutiny, is sometimes much better than the injection of steroids. When this debris is observed under electronmicroscope it will be seen that it is composed of various substances.

Table 3 The effect of flushing with physiologic saline

<table>
<thead>
<tr>
<th>Flushing only</th>
<th>Excellent</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing + Steroid injection</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

5. Rheumatoid hand and RA-test

Bland reports that among the cases of rheumatoid arthritis those showing positive rheumatoid reaction have rheumatic inflammation mostly in the hand. We have classified those presenting rheumatic inflammation mostly in hand

Table 4 Type of rheumatoid arthritis and RA-test

<table>
<thead>
<tr>
<th>Cases</th>
<th>RA-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>--+</td>
</tr>
<tr>
<td>Hand type</td>
<td>42</td>
</tr>
<tr>
<td>Knee type</td>
<td>21</td>
</tr>
</tbody>
</table>

Fig. 6 Lymph follicle in the synovial membrane of rheumatoid arthritis of wrist, ×100
joint as Hand-type and those in knee joint as Knee-type and further studied the relationship between the rheumatoid serum reaction and the histological picture. As the result we find a stronger rheumatoid serum reaction in Hand-type and the histological picture of the synovial membrane reveals predominantly Follicular type. In other words, hand joint inflammation shows pathologic conditions different from those of knee joint inflammation; that is, in the knee joint inflammation Fibrinoid-Coating type predominates but in the hand joint Follicular-Fibrosis type is relatively more numerous. We have found that in Follicular type, when lymph follicles appear in the synovial membrane, it is closely associated with rheumatoid factor.

Table 5 Type of rheumatoid arthritis and the histopathological findings of their synovial membrane

<table>
<thead>
<tr>
<th>Cases</th>
<th>Histopathological pictures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
</tr>
<tr>
<td>Hand type</td>
<td>53</td>
</tr>
<tr>
<td>Knee type</td>
<td>71</td>
</tr>
</tbody>
</table>

K: Fibrinoid type  
C: Coating type  
N: Follicular type  
F: Fibrosis type

6. About lymph follicles that appear in the synovial membrane:

When the lymph follicles that appeared in the synovial membrane are stained with methyl green pyronine, the central portion shows lymphoid cells stained blue and from the region surrounding the central portion to the surface
layer of the synovial membrane are observed plasmacyte-like cells positive to pyronine. In our previous attempt to ascertain whether or not there would be a communication between the synovial fluid and this lymph follicle, we injected colloid iron into the joint cavity and then resecting the synovial membrane, stained it with Berlin blue. As the result we found lining cells and histiocytes of the synovial membrane stained blue, but no reaction within the follicles. Next, $^3$H-thymidine was injected into the hand joint cavity and by resecting a piece of synovial membrane 20 hours later, it was examined by microautoradiography. Such microautoradiograms show numerous granules of $^3$H-thymidine within lymph follicles. There can be observed distinct proliferation of lymphocytes of thymus type in the secondary nodules of the follicle and lymphocytes of lymph-node type are seen in a close contact with the secondary nodules.

In any case, the synovial fluid has the communication with those lymph follicles formed in the synovial membrane and in addition, it has been demonstrated that lymphoid cells are actively undergoing cell division in situ.

7. Study on rheumatism by means of the immunofluorescent antibody:

With the advance in the concept of autoimmunity, recently this technique is also being extensively employed in the study of rheumatoid arthritis centering around the rheumatoid factor (ZIFF, MELLORS, MCCORMICK, RIDDLE, WEISS, BODEL,

### Table 6 Circulating anti-synovial tissue antibody

<table>
<thead>
<tr>
<th></th>
<th>Total cases</th>
<th>Positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Serum</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Serum</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
Svartz, and Hollander et al.\).

**Immunological reaction of rheumatoid synovial fluid to normal synovial membrane**:

According to the studies by Tsuji et al.\(^{18}\) of Department of Pathology, Okayama University, by means of the indirect method in which the normal synovial membrane is first incubated with the synovial fluid of rheumatoid arthritis patient, and then the membrane is stained with anti-gamma-globulin fluorescent antibody, it has been demonstrated that fluorescence is emitted by the lining cells of the synovial membrane and also by the blood vessel wall in the vicinity of these cells. In contrast, no such a fluorescence can be observed in the joint inflammation other than rheumatoid arthritis, such as in the case of osteoarthritis. In other words, these findings imply that there exists a certain immunological state between the synovial fluid of rheumatoid arthritis and normal synovial membrane.

**Studies on multinuclear leucocytes in synovial fluid and peripheral blood by means of the fluorescent anti-body technique (MIWA)**:

In their observations of leucocytes in the synovial fluid of rheumatoid arthritis patients under the light microscope, Hollander et al. (1961) reported that there were observed 1—20 granules of 0.5—1.5\(\mu\) in diameter in the cytoplasm. Later, by the investigations of Hollander himself, and others, it has been clarified that these granules are closely associated with the rheumatoid factor. More recently, Hollander et al. have proposed a postulate that these
Table 7 Immuno·fluorescent study on synovial fluid leucocytes of patient

<table>
<thead>
<tr>
<th></th>
<th>Fluorescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>29 ± 1 11</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>0 0 7</td>
</tr>
</tbody>
</table>

granules act in vicious circle on the rheumatoid inflammation and have designated those leucocytes that possess such granules as "RA-cells".

We have also followed up HOLLANDER's work. In the observations under the phase-contrast microscope the leucocytes in the synovial fluid of rheumatoid arthritis showed HOLLANDER's inclusion bodies in all the fifteen cases, and the leucocytes revealed one to twelve inclusion bodies in each cell. In the cases of osteoarthritis none showed inclusion body.

For the study with fluorescent antibody, anti-human β₂-macroglobulin sheep antiserum and anti-serum 7S gamma-globulin sheep antiserum (the products of Mann Research Laboratory) were used, and for the fluorescent material, fluorescein-isothio-cyanate was bound to the former and tetramethylrhodamine-isothio-cyanate to the latter. The results revealed that in the leucocytes of synovial fluid of rheumatoid arthritis the characteristic fluorescence was observed in
29/41 (70%) whereas in the case of osteoarthritis it was 0/7 (%). As for the leucocytes in peripheral blood, fluorescence was observed in 14/37 (3%) in the case of rheumatoid arthritis, those leucocytes emitting the fluorescence amounted to about 10% of the total leucocytes.

There can be recognized mutual relationship between the fluorescence of the leucocytes in synovial fluid and the result of RA-test of the synovial fluid. Similarly examining the leucocytes in peripheral blood, there can be seen no close relationship between the characteristic fluorescence of the peripheral blood leucocytes and the RA-test, but generally RA-test gives a higher value. In examining the synovial leucocytes and peripheral blood leucocytes of the same individuals in the similar manner, it is found that on the whole the incidence of fluorescence emission is higher with the synovial fluid. In the similar examinations conducted with two cases of osteoarthritis and one of joint tuberculosis all of them proved negative both in the synovial fluid and peripheral blood.

8. Relationship between the protein fraction in the serum and the synovial fluid on one hand and the rheumatoid factor on the other in rheumatoid arthritis (RA) patient (SENO):

The serum used was the pooled sera of several RA patients. As for the synovial fluid, in all the 11 cases it was pretreated with 1,000 units of hyaluronidase/3ml of the synovial fluid, and after centrifuging it at 2,500 rpm for about 10 minutes, the supernatant served as the material.

For the fractionation the gel filtration was employed with Sephadex G-200, and each fraction so obtained was subjected to S. S. C. A-test (by the method of HELLER-SVARTZ\(^{18}\)) and L. F. T. (by the technique of SINGER-PLOTZ\(^{19}\)). In this way the rheumatoid factor was investigated, and in addition, the assay was carried out with each fraction by the ultra-centrifugation.

Fig. 12 Protein fraction in the serum and rheumatoid factor
Dynamics of Rheumatoid Joint

The results of the gel filtration showed the appearance of three peaks both with the synovial fluid and serum of them. The first peak proved to be positive to both L. F. T. and S. S. C. A-tests. In the centrifugation assay the first peak corresponds to 19S, the second to 7S and third to 4S.

Next, a study was made on the immunological relationship between the serum of the patient with liver disease where the incidence of the rheumatoid factor is positive and the serum of rheumatoid arthritis. The sera from several patients with rheumatoid arthritis and likewise those from the patients with liver cirrhosis were respectively pooled together, and for this study anti-\(\beta_2\)M globulin sheep serum of Mann Research Laboratory was again used.

The results have demonstrated that the precipitation line of both rheumatoid arthritis and liver cirrhosis completely coincides with one another, either in the precipitation reaction in the gel by OUCHTERLONY's method or in the reaction by the immuno-electrophoretic method.

Tsuji et al. of Department of Internal Medicine, Okayama University, in their liver biopsy...
of the patients with liver diseases, have recognized the appearance of lymph follicles in the liver as observed in the synovial membrane of rheumatoid arthritis. It is quite interesting to note that there seems to be pathophysiology which is immunologically common to these two diseases.

9. Effect of RES-blockage on antibody production (Oobuchi):

Many works carried out by Coon's fluorescent antibody technique have clarified that lymphocytes and plasma cells are the antibody producing cells, and this fact has also made it clear that macrophages are the cells that ingest antigen and not the antibody producing cells. Consequently, there is none who dissents today about the fact that the information of the antibody production specific to antigen is handed from antigen ingesting cells to antibody producing cells. Fishman has suggested the existence of an m-RNA specific to this information but not

Fig. 15 Hemogram of rats received PVP and prednisolone injections, each curve shows the mean value of 5 animals.
all agree with such a postulate. We have studied the antibody productibility in the animals in which the antibody production is inhibited by experimentally injuring macrophages including the cells of the reticulo-endothelial system (RES), which lessens the production of the information-bearing substance. TOYAMA\(^{27}\) has demonstrated that by administering polyvinylpyrroridin (PVP) molecules to animals as much as 900,000 molecules over a long period of time, RES cells are made to ingest these molecules, which results in enlargement and degeneration, especially of the spleen and lymph nodes (lymphoblasts in particular), bringing about a severe destruction of the macrophage organ. Following up his techniques, we have succeeded in induction of blockage and degeneration of macrophages, mainly those of RES by injecting high molecular PVP subcutaneously or intraperitoneally into rats, and studied the antigen productivity in these animals. Namely, Wistar strain rats were divided into two groups; to one group were given 3\% PVP-physiological saline solution alone, and to the

![Graph of Hemogram of rats received PVP injection, giving mean values of five animals](image)
other the same PVP combined with 2.5 mg prednisolone were given. These injections were continued for 85 consecutive days. As the result it was found that macrophages were severely destroyed, and lymph nodes and the lymph apparatus of the spleen were atrophied, at the same time the number of peripheral lymphocytes was markedly diminished.

With Wistar rats similarly treated, the primary inoculation was conducted starting from the 63rd day of the treatment by the intramuscular injection of 2 mg bovine serum albumin (BSA) and 0.25 ml Freund's complete adjuvant with the interval of one week four times, and 5 mg of BSA were injected intravenously two weeks after the last injection. As shown in Fig. 17, there was observed weakening of the antibody production in either case whether PVP alone was injected or PVP combined with prednisolone when compared with the results of control groups. Although prednisolone was administered with the purpose to destroy lymphocytes, it was not possible to induce the destruction of the lymph tissues by the amount of drug administered. Histologically, in either case of the administration of PVP alone or PVP combined with prednisolone, there could be observed the swelling of systemic RES cells and the destruction

Fig. 17 Precipitation reaction of blood serum of rat received pretreatment of long-term PVP and cortisone injections every day for 98 days and sensitized with BSA. Each column shows the value observed in one animal. Dotted columns: Animals received pretreatment with PVP and steroid, Hatched columns: pretreatment with PVP only, Solid columns: pretreatment with saline solution. All the animals were sensitized with BSA. Method: See text
Fig. 18 A microscopic picture of a part of lymph node of the rat treated with PVP injection (40 g for 98 days)

Fig. 19 Bone Marrow of the rat treated similarly as in that appearing in Fig. 18: PVP ingested reticular cells in the center of the erythroblastic islet
Fig. 20 Liver of the rat treated with PVP injection (40g for 98 days): PVP ingested KUPPFER cells with atrophied liver parenchymal cells

of the spleen and lymph nodes, mainly the destruction of lymphoblasts, and at the same time the weakening of the lymphocyte production. After the sensitization, there was observed infiltration of plasma cells into spleen and lymph nodes, and this phenomenon did not materially differ from the sensitized control group where no blocking of the RES was tried.

TÖYAMA has not recognized any decrease in the antibody production by the PVP injection, and he interprets this phenomenon to be due to the preservation of the function of the reticulo-endothelial system and the proliferation of plasma cells. In our experiments, however, in spite of a marked proliferation of plasma cells, it has been demonstrated that the antibody production is decreased, and the resultant blockade of RES by PVP inhibits the propagation of information from the RES.

10. Chemical synovectomy by the injection of osmic acid (NARASAKI):

VON REIS and SWENSSON (1947) attempted the injection of osmic acid solution into the joint for the treatment of rheumatoid arthritis, and in 1959 BERGRAF used the combination of osmic acid and xylocaine injection to alleviate the side-effect. Later LEEVI tried injection of corticosteroids over a long period of time and reported favorable results.

We have also followed up these methods for the treatment of our patients. Out of 11 male patients (16 knee joints) of the age ranging from 11 to 68 years
old, and 14 female patients (16 joints), we selected 22 cases (29 joints) of classical rheumatoid arthritis and 2 cases (3 joints) of osteoarthritis for our study. All these cases were the ones who had failed to respond to the injections of corticosteroids into the joint over a long period of time. In this treatment we inject 4—10 ml of 1 % osmic acid solution and 5—10 ml of 2 % xylocaine into the knee joint after removing the joint fluid by needle puncture and washing the joint cavity with physiological saline solution. Immediately after the injection the inflammation of the joint is markedly aggravated for 2—6 hours; namely, there appear swelling, edema, fever and severe pain. At this instance, the knee joint cavity is aspirated with a big injection needle to remove the cavity fluid and the cavity is flushed well with physiological saline solution through the needle, and 20—30 mg of prednisolone solution are injected into the joint. The excreted brown colored fluid contains the debris of the surface layer tissue of the synovial membrane. As a rule, we repeat this aspiration of the fluid and the flushing of the joint cavity several times up to 24—36 hours after the chemical synovectomy. During this period of treatment, acute inflammatory symptoms and severe pain are gradually alleviated, and knee joint symptoms are improved within 2—7 days. However, there are some cases where we repeat the injection of steroids during this period. It is worthy of notice that four cases (4 joints) who had recurrence in the same joint after the first chemical synovectomy within 2—3 months but responded well or gave better results after the second synovectomy, indicate the feasibility of repeating such treatment.

In all cases we have tried the punch biopsy both before and after the synovectomy as much as possible.

The results of the treatment are graded into four groups: (A) effective, those who showed a marked improvement in swelling, severe pain, edema, and movement restriction, which lasted at least 1—6 months; (B) fairly effective, ones who showed a moderate improvement in their symptoms and there occurred gradual recurrent symptoms around one month after the synovectomy; (C) not effective, those who showed gradual recurrent symptoms within 1—2 weeks or those who showed no improvement whatsoever; and (D) aggravated, those cases where no improvement could be attained but showed development of hemarthrosis of unknown cause.

The evaluation of these results is made by the grading method of Kodama as illustrated in Table 1. Usually there develops an acute inflammation of the local joint with 24—36 hours of the synovectomy, but with the exception of four cases (4 joints), judging from the subjective symptoms of the patients as well as from our evaluation, 21 cases out of 28 showed a fairly satisfactory improvement of the joint. Even among (B) and (C) groups, classified as fairly
effective and not effective, there can be observed good result of repeated injections of steroids.

We have followed up the patients for the period of over 6—24 months after the chemical synovectomy and since in the treatment of rheumatoid arthritis systemic antirheumatic therapy is required, we have to give orally salicylic acid, steroids, antimalarials and the injection of gold sol for a long period of time. Therefore, it is quite difficult to give any definitive judgement at once on the follow-up results, but it seems that in those who were classified as (A) and (B) groups results of the chemical synovectomy coincide fairly well with those of gold sol treatment.

*Osmic acid synovectomy, and arthroscopic and pathohistological observations:*

Arthroscopic as well as pathohistological examinations with biopsy specimens are usually conducted before and after osmic acid injection whenever possible, and the results of such examinations reveal that the surface layer of the synovial membrane becomes necrotic and exfoliated but hardly any inflammation develops in the deeper layer. Even 6—12 months after the osmic acid injection the arthroscopy of the joint shows a dark brown color on the surface layer of the synovial membrane in some patients. Histological observation of such a case reveals epithelial cells and histiocytes in the connective tissue of deeper layer of the synovial membrane to contain brown granules believed to have derived from osmic acid. However, since there are no changes in the morphology of these histiocytes nor any changes in the tissue around these cells, the granules derived from osmic acid seem to have no biologic activity, but this point needs to be clarified by further study. From the whole aspect, it appears that chemical synovectomy with osmic acid effects a thorough cleaning...
of the surface layer of the synovial membrane.

11. **Radiating synovectomy by injecting $^{198}$Au:**

According to BYWATERS $500 \mu c$ of $^{198}$Au dissolved in 10 ml saline are injected into the knee joint. $^{198}$Au has the half life of 2.7 days and it emits $\beta$ and $\gamma$ rays, and $\gamma$ ray penetrates into the tissue about 1 mm. The total irradiation amounts to 480—1,000 $\gamma$ (about 690 $\gamma$ in average). In examining the synovial membrane with the biopsy specimens obtained after the injection, $^{198}$Au is deposited mostly in the fibrin agglutinated layer of the surface layer. BYWATERS tried it on 30 cases and obtained good result in 16 cases, some effect in 7 and no effect in 7 cases. He states that he will use $^{90}$Y in his future cases because it penetrates into the tissue as much as 3 mm.

MAKIN$^{30}$ also injected $^{198}$Au into the knee joint but he used a large quantity of 10 mc for the knee joint. In such instances the total irradiation reaches as high as 2,000—7,000 $\gamma$ (about 5,000 $\gamma$ in average) and it causes congestion of the synovial membrane, and it later leaves scars in the tissues underneath the membrane. He tried this radiating synovectomy on such cases as osteoarthritis, rheumatoid arthritis of hydrops type, and pigmented villous nodular inflammation.

We have also tried $^{198}$Au injection in the following manner:

**Materials:** All colloid $^{198}$Au, the product of Dianabot RI Research Institute.

**Properties of $^{198}$Au:** Half life is 2.69 days, it emits $\beta$ and $\gamma$ rays, and at pH 8—10, the diameter of the molecule is about 30 $\mu$, energy of $\beta$ ray is 0.96 Mev. and $\gamma$ ray 0.412 Mev.

All colloid contains 10 mg sodium acetate, 5 mg ascorbic acid, 3 mg gelatin, and 0.9 % benzyl alcohol.
As it emits $\gamma$ ray, it is possible to count its distribution in vivo from outside the body. The effect of radioactive energy on the first injection decreases down to its 6% on about eleventh day. In addition, the total energy of 500 $\mu$C of $^{198}$Au during one week amounts to about 60,000 $\gamma$.

By our methods for instance in the case of knee joint, first we aspirate and flush the joint cavity well with physiological saline solution. We sometimes perform chemical synovectomy with osmic acid prior to this flushing. Next, the solution of $500 \mu$C—5 mc $^{198}$Au dissolved in 20 ml physiological saline is injected into the joint. In taking the biopsy specimen 7 to 10 days after the injection, it is unavoidable to lose the injected solution at the time of biopsy and arthroscopy. In other cases, the joint is left untouched. After the injection some complain of fever, local hot sensation and aggravation of severe pain, but none excretes the injected solution in the meantime.

We have thus far tried this radiating synovectomy on 25 cases of 31 joints.

**Results:**

Grading the results of radiating synovectomy by KODAMA’s local index, the course of symptoms can be classified into four types: Type I shows swelling, edema, hot sensation and severe pain of the local joint 1—3 days after the injection but after it there is seen a noticeable improvement in the symptoms. Although there is some difference in points of grading, on the whole this type makes a good progress. Type II, differing from Type I, shows no local aggra-
The four types mentioned do show difference in the severity of symptoms, but they seem to be amenable to classification. To facilitate the representation the curves are drawn with less convexity, but actually symptoms are not so smooth as presented.

The classification of the four types is made as:

- Tape I ..... 4 joints
- Type II ..... 10 joints

Tape I and Type II are considered as Excellent.

- Type III ..... 5 joints
- Type IV ..... 7 joints

Type III is considered as Good, and Type IV as Fair.

Total ..... 26 joints.

On account of the follow-up period being short, there are three cases with 4 joints on whom the effective rating cannot be given.

Examinations after the injection:

1. By scintillation scanning the distribution of $^{198}$Au within joint is examined. Generally the distribution is found to be as shown in the figure. When this is measured by the scintillation scanning, though the amount of $\gamma$-ray decreases, the distribution pattern remains unchanged.

2. Findings of the joint fluid. In the measurements taken by the scintillation counter with the supernatant and the sediment obtained from the joint...
fluid on eleventh day and centrifuged at 2,000 rpm for 5 minutes, we get:
2,623 counts Natural count,
4,868 counts Fluid of opposite joint,
6,866 counts Supernatant, and
31,368 counts Sediment.

When this sediment is smeared on a slide glass and examined by the microautoradiography, these cells (believed to be leucocytes) in the joint fluid do not have granules. However, those irregular necrotic cells in the sediment that are not stained by a single hematoxylin-eosin stain show many granules. These cells seem to be the cells of synovial membrane that had become necrotic and fallen into the joint fluid. This indicates that having ingested $^{198}$Au, these cells of synovial membrane have become necrotic and exfoliated.

For the purpose to substantiate this supposition, the following examinations were undertaken: 1) With the joint fluid the counts are taken with scintillation counter and also its smear is examined by microautoradiography; 2) Next, the joint cavity is washed well with physiological saline and similar examinations of the joint fluid after the washing are conducted; and 3) Then 5 mg chymotrypsin are injected into the joint, and the joint fluid taken out 5 minutes later

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Scint. counts</th>
<th>Cell number</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97,476</td>
<td>705,000</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>4,444</td>
<td>1,450</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>12,543</td>
<td>4,050</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Table 9 Comparative results of the three joint fluids

Natural counts......4,600
is subjected to the same examinations.

As is obvious from this table, since the joint fluid, No. 3 obtained after washing with chymotrypsin, contains the cells of the surface of the synovial membrane, scintillation counts are greater than those of the fluid No. 2, and also by the micro-autoradiograph they show many granules.

3. Findings of arthroscopy. In the knee joint injected with 500 μc~1 mc of $^{198}$Au, there can be observed no change of color tone on the surface of the synovial membrane, villi and cartilages in the joint cavity as far as arthroscopic observation revealed before and after the injection. However, when the dose is increased to 5 mc, villi on the surface layer of the synovial membrane become necrotic.

4. Histological findings. We have carried out histological examinations
with biopsy specimens obtained before and 7—10 days after the injection of $^{198}$Au whenever feasible, but we find no morphological change with the dose of $500 \mu\text{c} = 1\text{mc}$. By the micro-autoradiographic examination of the synovial membrane tissue obtained on the third to tenth day,

Fig. 28 Microautoradiogram of synovial fluid after injection of $^{198}$Au $\times 400$

Fig. 29 Microautoradiogram of synovial membrane after injection of $^{198}$Au $\times 400$

Fig. 30 Microautoradiogram of synovial membrane after injection of $^{198}$Au $\times 400$
the surface layer cells and the histiocyes in the deeper layer of the synovial membrane show granules within the cells.

**Tissue Culture:**

In order to see the effect of $^{198}$Au on the cell *in vitro*, tissue culture was conducted.

**Materials:** Ascites cells of rabbit served for the purpose.

At first 20 ml fluid paraffin are injected into the peritoneal cavity of the rabbit to stimulate it, and 4 days later by opening the abdomen 100 ml Hanks solution and 1 ml heparin are poured into the open cavity and these with ascites are taken out. Next, this ascites is centrifuged at 3,000 rpm for 5 minutes, and the cells so separated are cultured. The extract of chick embryo 9 days old is mixed with rabbit serum and this mixture is used as the substrate.

![Fig. 31 Effect of $^{198}$Au on ascites cell of rabbit](image)

In each glass tube of about 2 mm in thickness and open at both ends, a drop each of the chick embryo extract and rabbit serum is mixed and in this substrate the ascites cells are cultured. In five concentrations of 3.5 $\mu$C, 7 $\mu$C, 14 $\mu$C, 21 $\mu$C as well as inactive $^{198}$Au are poured over five different cell groups in the glass tubes and morphological changes at 24-hour culture are observed under the phase-contrast microscope. As illustrated in the figure, at the higher concentration of $^{198}$Au there can be seen distinct morphological changes in the rabbit ascites cells.
Fig. 32 Effect of $^{198}$Au on the ascites cell of rabbit in tissue culture

A: control  B: 7μc  C: 14μc  D: 28μc  ×800

In our other experiments (Takatori33) $^{198}$Au labeled gold colloid was injected into the granuloma pouch of a rat, and the absorption from the pouch and distribution in the organs were studied. Another solution of Fe labeled chondroitin sulfate-Fe, $^{59}$Fe labeled ferric ammonium citrate, and $^{35}$S labeled chondroitin
sulfate was employed.

A comparison was then made between the absorption and organ distribution of this solution when injected into both the granuloma pouch and gluteal muscle.

When colloidal $^{198}$Au is injected into the pouch and injected into the gluteal muscle, the $^{198}$Au is phagozytozed by the reticuloendothelial system organs, the liver showing the largest uptake per gram among all organs. Also high radioactivity was seen in the spleen and kidney. In comparing the injection into the granuloma pouch with the case of gluteal muscle injection of colloidal $^{198}$Au, the absorption was very slow with peak levels of the liver, spleen and kidneys appearing 48 hours after injection.

Of course, distribution of gold in the body differs according to the method of administration, and also should differ with the type of gold compound used.

![Absorption and distribution of $^{198}$Au labeled gold colloid from the rat granuloma pouch](image)

**Fig. 33** Absorption and distribution of $^{198}$Au labeled gold colloid from the rat granuloma pouch

12. **Surgical synovectomy**:

It was Swett (1922) who first made a report on the surgical synovectomy
for rheumatoid joints. Later most of such synovectomy were performed not only for rheumatoid joints but also for the extensive chronic knee joint inflammations including villious joint inflammation. In the follow-up studies on these cases it is generally reported that about 60% of these operated cases show excellent or good results and other 40% failed to respond to the operation. In Japan recently this synovectomy is highly recommended by Professor Mori.33

Here our experiences with this operation will be presented. The number of the patients that we have been able to follow up over 4 years their prognosis amounts to 25 cases with 41 knee joints, and we find distinctly a marked improvement in walking ability and alleviation of severe pain in the local joint. Although there is 44% of the cases whose movability of the joint has worsened, they can sit on chair though they cannot squat on the mat as is the common customs with Japanese. Overall evaluation gives about 60% showing favorable results in this operation, which is a reasonable one as compared with the results
Fig. 35 Absorption and distribution of $^{59}$Fe labeled chondroitin sulfate-Fe from the rat granuloma pouch

Table 10 Effect of surgical synovectomy of rheumatoid knee joint

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>27</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Range of motion</td>
<td>6</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Function of walking</td>
<td>13</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Systemic condition</td>
<td>10</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Maintenance dose of steroids</td>
<td>13</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>E. S. R.</td>
<td>2</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Estimation by patient</td>
<td>14</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Notes: 25 Cases, 41 Knee joints
Age of patients 9 y. o—72 y. o.
Follow up 2 years—10 years
reported in foreign countries.

We did also surgical synovectomy of 67 wrist or finger joints. Eighty percent of these hand cases show excellent or good results.

As for the indication of this operation, at present we perform this synovectomy on those who have thickened joint capsule, the proliferation of connective tissue and infiltration of lymphoid cells in the follicular-aggregation form, what we call Follicular-Fibrosis type. In the following are presented histological pictures of the synovial membrane.

In the initial stage of rheumatoid arthritis there are two types, namely, one with the reaction of the arterioles of areolar connective tissue beneath the
synovial membrane (Arteritis type) and the other with fibrinoid degeneration (Fibrinoid type). As for the latter, Fibrinoid type, it develops in other collagen diseases such as nodular periarteritis, and even in the joint rheumatism where the inflammation is severe there can be observed fibrinoid degeneration and fibrin exudate of the surface layer of synovial membrane.

The Arteritis type, when it is simple one where there is no danger of nodular periarteritis development, responds readily to steroids and its prognosis is good. Fibrinoid type can likewise be improved by steroids and gold sol and these treatments can alleviate its symptoms more often than not, provided of course, there is no complication of other collagen diseases. In Fibrinoid type the synovial membrane is thickened and joint fluid accumulates. When steroid hormones are injected into the joint, the symptoms are alleviated temporarily but in most cases the joint fluid accumulates again within a few days. In this instance, the gold sol treatment is fairly effective, but those that do not show any improvement often tend to progress into Fibrosis-Follicular type. At this stage, the injection of steroids into the joint would no longer prove effective and as the inflammation of the joint capsule would adversely affect the muscles and tendons surrounding it, the surgical synovectomy is indicated.

Now there arises a question of an appropriate time for the surgical intervention, taking the knee joint as an example, it would be better to operate on before there is much atrophy of quadriceps muscle. In the case accompanied with capsular inflammation, there occurs reflex atrophy in those muscles attached to the joint capsule. When once this quadriceps muscle becomes atrophied, as in the general cases of rheumatoid arthritis, it is difficult to cure.

Therefore, for those who show severe symptoms in the knee joint as in the case of multiple rheumatoid arthritis we combine systemic administration and local injection of steroids, chloroquine as well as gold sol treatment, and wait and see the course for 3—6 months. In the case where the inflammation of the local joint does not subside and thickened synovial membrane remains unchanged even after this combined treatment, we ascertain it to be of Fibrosis-Follicular type by the histological examinations with biopsy specimens and recommend the patient to undergo surgical synovectomy as soon as possible.

13. Mud (or debris) located between the synovial membrane and the joint fluid:

At the surgical synovectomy of rheumatoid arthritis patient, on the opening the joint capsule, when the object glass is stamped on the surface of the synovial membrane and the stamp specimens stained, there will be found relatively healthy, multinuclear leucocytes, plasma cells, lymphocytes, necrotic synovial membrane cells, and viscous ground substances are mixed. I call this mixture.
as "mud" (debris) of the joint cavity. It is thought that within this "mud" layer is located the site of pathological conditions of rheumatoid arthritis, or at least the site of vicious circle.

SUMMARY

In the present communication the recent works done by the Rheumatism Research Group of Department of Orthopedic Surgery, Okayama University, are described. The principal findings may briefly be summarized as follows.

1. Pathohistological pictures of the synovial membrane are classified into six types. Among them, Fibrinoid type and Follicular-Fibrosis type are the representative ones of chronic rheumatoid arthritis.

2. For the evaluation of the systemic as well as the local activities in rheumatoid arthritis and for judging the therapeutic effect, some indices have been established.

3. Injection of steroid hormones into the local joints fails to give satisfactory results in advanced, chronic rheumatoid arthritis. In such instances the flushing of the joint with physiological saline solution is effective.

4. In the case of chronic rheumatoid arthritis where the inflammation of hand and phalangeal joints is marked, RA-test gives rapid and more intense reaction, and most of such cases are of Follicular-Fibrosis type.

5. When lymph follicles appearing in the synovial membrane are stained when methyl green pyronine, the arrangement of lymphoid cells and plasma cells becomes distinctly clear. By micro-autoradiographic observations it can be seen that \textsuperscript{3}H-thymidine injected into the joint cavity is mostly ingested by the
lymphoid cells in lymph follicles.

6. In the observation by the fluorescent antibody method multinuclear leucocytes found in the joint fluid and in the peripheral blood react with 19S and 7S-gamma-globulins.

7. When the serum and the joint fluid of the patient with rheumatoid arthritis are fractionated, they separate into three peaks at 19S, 7S, and 4S. Both S. S. C. A.-test and L. F. T. tests reveal the peak at 19S.

The serum of chronic hepatitis positive to RA-test and the serum of rheumatoid arthritis are found to react immunologically the same to anti-β₂ M globulin sheep serum.

8. When the reticulo-endothelial system of rat is blocked by 900,000 molecules of poly-vinyl-pyroridon, the ability of antibody production is diminished.

9. Chemical synovectomy of injecting osmic acid is effective to Fibrinoid-Coating type. Its action mechanism lies in the complete cleaning of the surface of synovial membrane.

10. By radiating synovectomy with ¹⁹³Au a fairly good result can be expected. ¹⁹⁸Au is ingested by those cells in the surface layer of the synovial membrane and also by histiocytes in the synovial membrane. When 5 mc of ¹⁹⁸Au are injected into the knee joint, a marked necrosis of the synovial membrane occurs. When ¹⁹⁸Au is added to the ascites cells of rabbit during the tissue culture, in the concentration of over 14 μc degeneration of these cells can be recognized.

11. From the examination results of prognosis on those 25 cases with 41 rheumatoid knee joints after surgical synovectomy, it is considered that this method is indicated for Follicular-Fibrosis type. Ones with rheumatoid knee joint of Fibrinoid-Coating type gold sol treatment should be resorted to. In the cases of hand joints, surgical synovectomy is to be recommended at a relatively early stage.

REFERENCES


Dynamics of Rheumatoid Joint


