

# *Asian* MEDICAL JOURNAL

Vol. 1 No. 1

October, 1958



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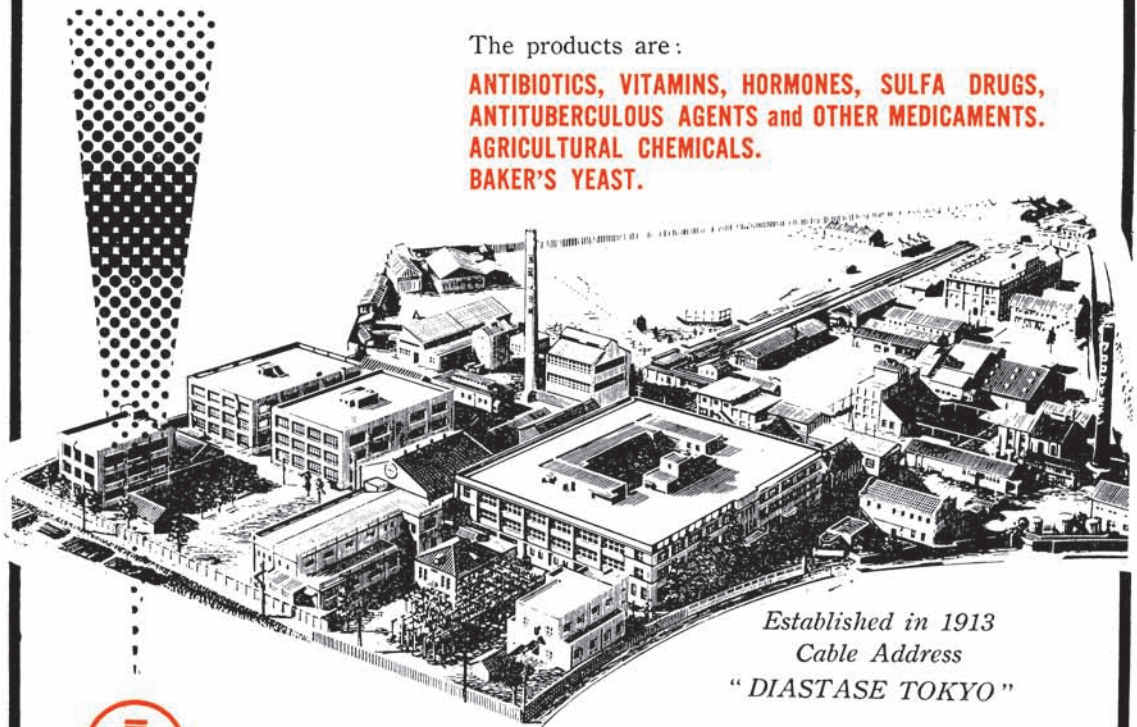
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## FOREWORD

Katsuma Abe

*Professor, Keiogijuku University*

The Japan Medical Publishers, Inc., which in the past has contributed so much to the exchange of medical knowledge between Japan and China through the Japan Medical Journal in Chinese, has now embarked on a wider program to realize medical exchanges among all of Asia through the issuance of the Asian Medical Journal in the English language. It is indeed a matter of the greatest pleasure for us to greet the new publication.



The countries of Asia all have some aspects in common in respect to customs, manners and living conditions. The same is true in regard to physical characteristics and disease. Thus any steps to enhance the exchange of information and knowledge concerning preventive medicine and therapeutic medicine must lead to the elevation of the health of all peoples of Asia. Such advancement of the welfare of the people, needless to say, is of primary importance.

The Chinese have an old saying, "Medicine is a benevolent art." It is only by taking in the highest form of modern medicine, however, that the "benevolent art" can be fully exhibited. To attain this state, it is of urgent necessity that the medical circles of the countries of Asia quickly and completely enter into the exchange of their greatest medical knowledges.

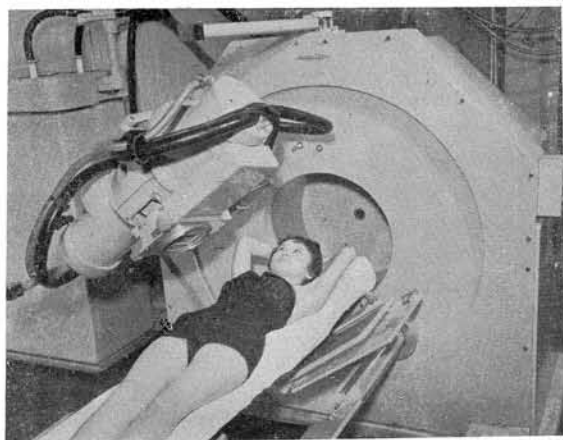
For this reason, I heartily welcome the appearance of the Asian Medical Journal. At the same time, I earnestly urge medical men of the Asiatic nations to contribute their articles to the publication as well.



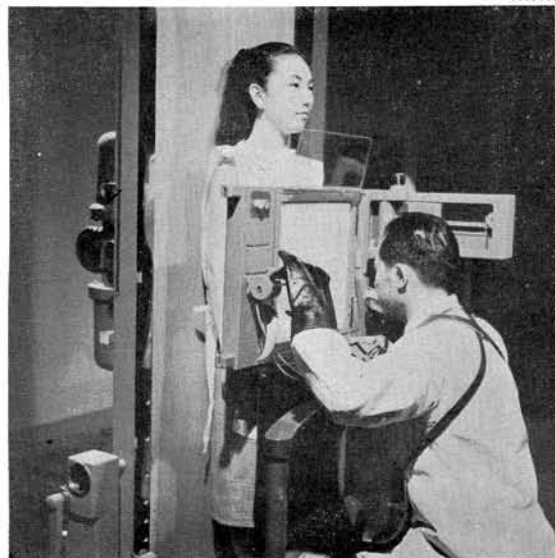
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A Journal of Medical Sciences of Japan and Asian Countries

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Photograph on the front cover shows general appearance of the Institute of Public Health of Japan.

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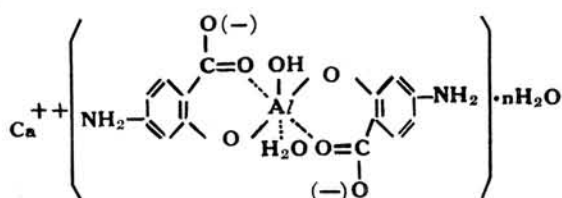
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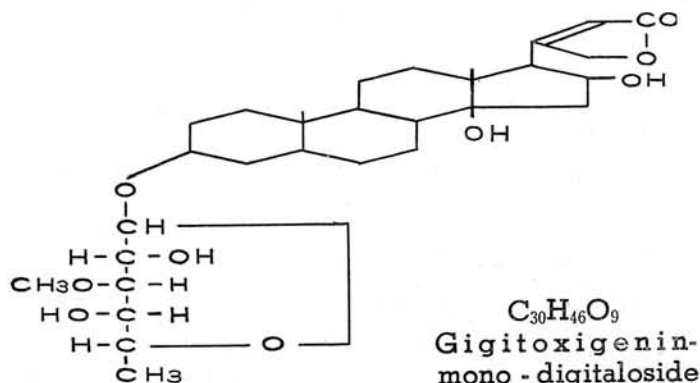
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## Message



Japan had interest on western medical science at her earlier stage of the modern history. As a result, the Japanese medical science today has been advanced to an appreciable extent.

Japan, which in the past had to learn from the Western countries in all aspects of medical science, has now firmly established an independent position in the field of medical science.

In view of the ever-progressing medical science, however, there will always be necessity for further improvement so that the people will ever enjoy health in the days to come.

It is indeed a matter for congratulation that all countries and peoples of Asia are making rapid national progress, and it can well be presumed that this progress is being accompanied by a big reform in the realm of health administration.

I firmly believe in this connection that these various nations of Asia can benefit a great deal from exchanging information regarding their respective ways of settlement for the common problems among them, and thereby contributing to the betterment of research in this field.

I as a Minister of State in charge of health administration for the Japanese people sincerely hope that the Asian Medical Journal just founded will serve, and prosper, as such a medium of informational exchange.

Ryugo Hashimoto  
Minister of Health & Welfare



## Message

The exchange of scientific knowledge among the nations and scientists of the world has become extremely active in recent years with the rapid progress made in the transportation and communication facilities. But there has always arisen the question of the language barrier, a factor which greatly limits the transferring of thoughts to others. As far as Asia is concerned, the language problem is particularly fraught with complications.



To our regret, even great scientific achievements are scarcely understood by scientists not only in other parts of the world but in other Asiatic countries, if they are published in an Asiatic language. It also prevents further exchange of information and wider propagation of such knowledge.

To overcome this difficulty, the Science Council of Japan, in addition to its Japanese publications, has issued in English such volumes as the Japan Annual of Law and Politics, Economic Series, Japan Science Review (Medical Science) and others for distribution to scientific circles in other countries.

At this time, the Japan Medical Publishers, Inc., has taken a step to overcome the language obstacle in the exchange of scientific knowledge through the publication of the Asian Medical Journal in English. By publishing these written in English by medical scientists in Asiatic countries, it has opened the way towards promotion of exchange of scientific information, beginning with the field of medicine.

As one of the scientists anxious to see a flourishing exchange of such information among the nations for the advancement of science, I feel the greatest joy at this event. I sincerely hope that the publication will continue to grow, and by contributing to the exchange of knowledge in its particular field, it will lead the way to the furtherance of amicable relations among the friendly nations of Asia.

*Kaneko Kamehige*

President, Science Council of Japan

## Message



Thirteen years have elapsed since Japan became the first nation in the world to suffer the diabolic blast of the atomic bomb, and the scars of that worst-ever destruction still remain, challenging the efforts of all men of medical profession both in Japan and abroad to wipe them off. I find it extremely significant to have the Asian Medical Journal founded on this memorable occasion and contribute a message to its initial number.

Tens of thousands of the Japanese people who were exposed to the dreadful radiation of the atomic bomb are still suffering from its intractable tragic effect. And the medical circles in Japan are exerting the best efforts to save these atomic patients from their unparalleled misfortune.

The Japanese Red Cross, for its part, has already established a specialized atomic clinic for atomic diseases in Hiroshima and Nagasaki and has tried everything possible for the treatment of the unfortunate sufferers. What could have been achieved so far, however, is not as satisfactory as is expected from the tremendous efforts rendered.

The more we know about the difficulty of making a success of this kind of medical treatment, the more strongly we hope that nowhere in the world will these atomic clinics be needed again in the future.

It will certainly add to its *raison d'être* if the Asian Medical Journal appeals to the good sense of the entire world with unbiased, accurate reports of the cold realities surrounding the atomic radiation, in addition to the various activities of the journal.

Let me say in conclusion that there is indeed a great deal to expect from the role which this newly founded Asian Medical Journal will play for the peace and happiness of the world.

President, Japan Red Cross Society

## Message

As we all know, medical science is concerned with the well-being of individual persons. But in the larger sense, it is concerned with the whole of society. It is a question which all mankind must consider seriously. It is herein that those who are engaged in medical research find their pride and joy.

If the medical circles of the world can freely exchange the results of their research without regard for national boundaries and political restrictions, I believe that a tremendous step will have been taken for the welfare of man. I have always thought of this as being absolutely necessary.

I congratulate the Japan Medical Publishers, Inc., on the publication of the Asian Medical Journal which can serve as a stepping stone to open the way to a greater exchange of medical knowledge among the nations of Asia.

It would make me only too happy to see the medical leaders of Asia will fully use the medium of this organ to promote the peace and welfare of the world.



田谷 隆雄

*Tamiya, Takeo*

President, Japan Medical Congress

## Message



The achievements of Japan's medical world have become known to the world in the past only through foreign language organs of various specialized fields and of institutions dealing with medical science. Abstracts have also been sent out in great numbers.

Outside of such specialized and school publications, however, except in certain instances, there have been no other means to announce such achievements and activities abroad.

Under these circumstances, it is worthy of note to see that the Japan Medical Publishers, Inc., has undertaken to issue the Asian Medical Journal with the epochal aim of spreading knowledge of Japan's medical science widely throughout the world. By introducing such information to China, Southeast Asia and other parts of the world, it may be expected that this new publication will come to occupy an important role in contributing to the progress of medicine.

Although the Japan Medical Association through its international committee has striven to maintain contact with other countries, I firmly believe that the new publication will be of tremendous aid in these efforts.

In this sense, I offer sincere congratulations to this publication which embodies such high ideals and pray for its success.

*Taro Takemi.*

President, Japan Medical Association

## Message

Science knows no national borders. The idea of free exchange of knowledges is particularly important in respect to the medical and pharmaceutical sciences which have in common the welfare of all mankind.

It is a fact that the peoples of Asia have aspects in common with each other in respect to history and environment. The medical and pharmaceutical sciences have advanced to the degree where they now cure diseases which were considered incurable in the past. Through this, man's life span has been greatly increased. It is necessary that all peoples should share in these benefits.



It is unfortunate that for long years, such exchange of cultures among the nations of Asia could not have been realized to a greater extent. Undoubtedly, one of the chief obstacles has been the problem of language.

It is to be regarded with the greatest of pleasure, therefore, that the Japan Medical Publishers, Inc., with the support of Japan's medical world, has decided to issue a publication in the English language.

Today, the output of pharmaceutical products comprises over 20 per cent of the entire production of chemicals in Japan. The Japanese people, indeed, are fortunate in being able to enjoy the greatest benefits of pharmacy.

Through the new publication, it is our hope that exchange of knowledges and information will be realized, not only in the field of medicine but in pharmaceutical science as well. In this manner, the welfare of all the peoples of Asia may be promoted by mutual effort.

I pray that hereafter that in the pharmaceutical field, the various countries of Asia will cooperate in advancing the welfare of the entire area through common endeavor. Toward this end, the new publication can play an important part.

*Morizo Ishidate*

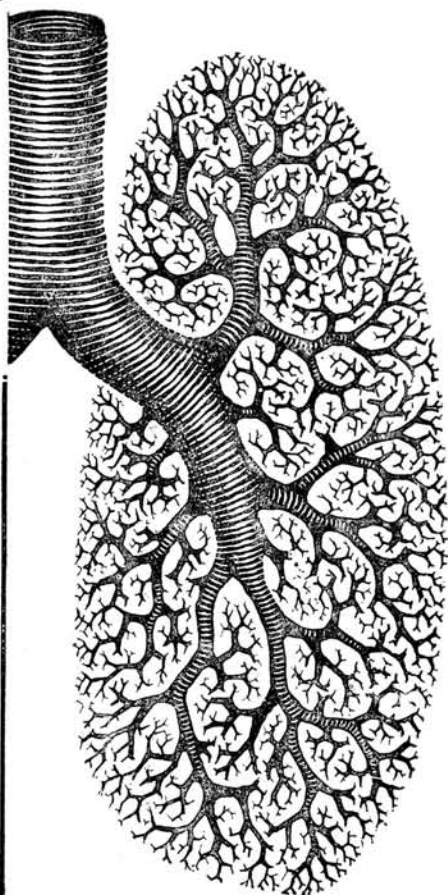
President, Pharmaceutical Society of Japan



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## Consideration on the Radical Operation of the Breast Carcinoma with Special Reference to the Significance of the Pectoral Muscles

Nobukatsu SHIMADA, Kunihiko ITO, Osahiko ABE and Toshikazu NOGUCHI

*Department of Surgery, School of Medicine, Keio University*

The patients of the breast cancer who visited our clinic during the past 13 years are 126 cases, all of which underwent some surgical procedures or other.

The recent 5-year survival rate after the

radical operation of the breast cancer is about 50%. The rate of our consecutive series of cases is 72.4%. This compares favorably with the recent rate of other reports, though our cases are comparatively scanty (Table 1).

Table 1. The 5-year survival rate after the radical operation of the breast cancer.

Reporter	Reported in	Interval of observation		5-year survival rate (%)
Stenstrom and Baggenstoss	1947	1927	1931	41.0
Nicolson	1948	1930	1942	35.9
Haagensen	1949	1935	1942	58.2
Harrington	1951	1910	1941	51.2
Lewison	1953	1935	1940	47.1
Kuru	1954	1941	1953	48.1
Shimada	1958	1945	1958	72.4

Indeed postoperative results of simple mastectomy reported by McWhirter is fairly good, but such kind of operation is indicated to most cases disregarding the development of the original disease (Table 2). The trouble is that some involved axillary lymph nodes are clinically silent and others are swollen without pathological metastasis (Table 3). Of course the prognosis of the cases with axillary metastasis is unfavorable. Therefore, simple mastectomy above described as the radical operation of the breast cancer is considered to be the less significant until the method by which correct diagnosis is performed, before operation, whether axillary glands are involved or not (Table 4).

As the radical operation of the breast cancer, Halsted's principle has been adopted for about half a century. We have had a question as to the significance of removal of the pectoral muscles. Our tentative conclusion is that removal of both the major and minor pectoral muscles is not so important

Table 2. The 5-year survival rate after simple mastectomy of the breast cancer

Reporter	Cases	5-year survival rate (%)
McWhirter	1609	40.8
Saugmann Jensen	41	66.0
Filzwilliams	76	68.4
Mustakallis	6	83.3
Nohrmann	43	58.1
Winz	97	51.5
Maisin	216	53.6
Deaton	30	63.3
Haitmann	117	61.5
Shorogge	129	55.9

otherwise than in making the clearing technique of axillary lymph glands convenient, because not only the pectoral muscles per se are rarely involved but also their existence enables adequate postoperative radiation.

As a matter of fact, the pectoral muscles

Table 3. Metastasis of axillary lymph glands—comparison of clinical signs with histological findings

	Group without removal of the pectoral muscles		Group with removal of the pectoral muscles	
	Clinically lymph nodes palpated	Clinically lymph nodes not palpated	Clinically lymph nodes palpated	Clinically lymph nodes not palpated
Histologically metastasis demonstrated	18	8	21	0
Histologically metastasis not demonstrated	3	25	3	11

Table 4. Swelling of axillary lymph nodes and prognosis

Swelling of axillary lymph nodes	Group without removal of the pectoral muscles		Group with removal of the pectoral muscles	
	Cases	Death due to recurrence	Cases	Death due to recurrence
Not palpated	38	0	17	1
Palpated	24	5	35	19
Unidentified	2	0	7	0
Total	64	5	59	20

per se do not hinder the operator from clearing axillary lymph nodes. Accordingly, they may not be removed until their existence makes it difficult to clear the metastasized infraclavicular lymph nodes. From these viewpoints mammary amputation, axillary clearance and resection of the pectoral fascia with removal of neither major nor minor pectoral muscles are performed on a group of cases

Table 5. Our cases classified by Steintal's grade

Grade of Steintal	Group without removal of the pectoral muscles	Group with removal of the pectoral muscles	Total cases
I	17	7	24
II	47	31	78
III	6	18	24
Total	70	56	126

among those which belong to Steintal I~II and the follow-up results are observed (Table 5).

Though the original reason is different from ours, this type of operation is already reported by Bryant and Murphy etc. at the beginning of this century. Postoperative results of such kind of operation have also been reported by Holman recently (Table 6). Kuru proposes the partial excision method of the major pectoral muscles and Orr proposes the method by which resection of the minor pectoral muscle alone is performed, though their standpoints are different from ours.

As postoperative treatment we expect much from radiation therapy for the effect of prohibiting recurrence. According to Dr. Yamashita of our medical school, we apply X-ray and Radium or Cobalt from the earliest pos-

Table 6. The 5-year survival rate after the radical operation without removal of the pectoral muscles

Reporter	Time of operation	Mode of operation	Steintal I %	Steintal II %	Steintal III %
Holman	1930   1942	Without removal of the pectoral muscles	83	42	55.3
Shimada (Surgical Dept., Med. School, Keio Univ.)	1946	Without removal of the pectoral muscles	100	85.8	89.2
	1958	With removal of the pectoral muscles	100	60.6	72.2

sible time after the operation (i.e. 5 6th day). X-ray therapy is performed by tangent radiation to the axilla from antero-caudal, postero-caudal and sometimes cranial direction. The dose of 300r is radiated at a time so that the total doses to the focus amount to 5,000r within two months. Radium and Cobalt 60 are given by surface radiation to the supraclavicular region, marginal region of the sternum and the operative scar on the anterior chest

wall. A total dose of 10,000~12,000 mg/hour is radiated to the former two with 4 cm distance, while 6,000 mg/hour to the latter one with 2 cm distance (Table 7).

Among our 126 cases, 70 underwent the radical operation without removal of the pectoral muscles, while 56 received the operation with removal of the pectoral muscles. Of course more developed cases are encountered in the latter group. Statistically the 5-year

Table 7. Postoperative treatment in our clinic

Postoperative treatment	Group without removal of the pectoral muscles	Group with removal of the pectoral muscles
X-ray	19	21
Radium or cobalt	1	2
Carzinophilin*		1
Nitromin*		1
X-ray+radium	34	19
X-ray+hormone		1
X-ray+radium+carzinophilin	2	
X-ray+radium+sarcomycin*	1	
X-ray+radium+hormone		1
Without postoperative treatment	9	4
Unidentified	4	6
Total	70	56

\* antitumor substance

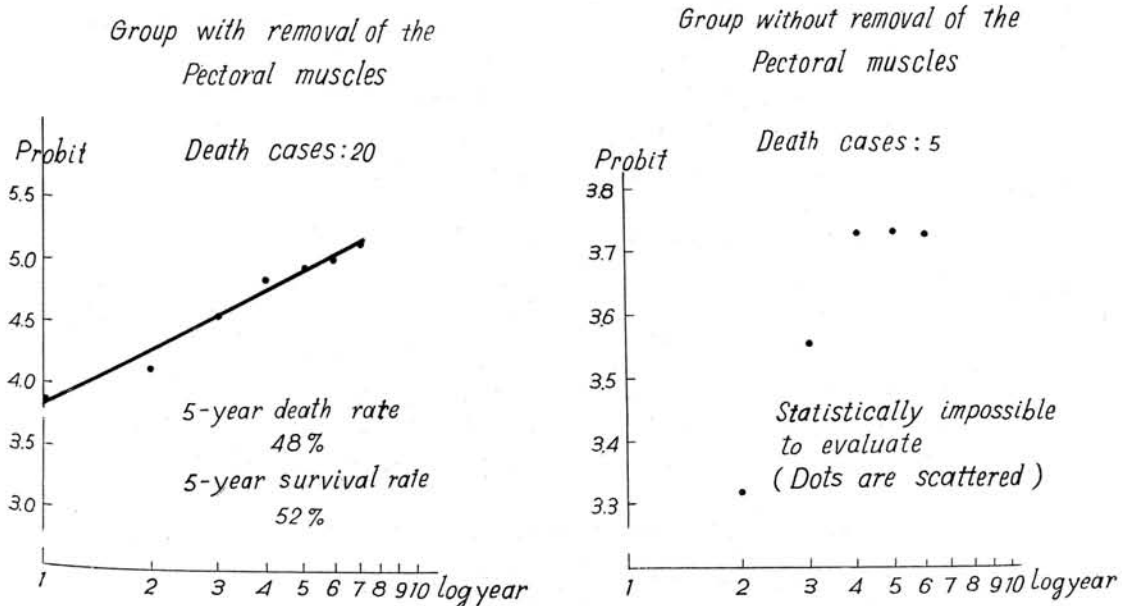


Fig. 1. The 5-year rate of our total cases

survival rate of the group is 52% which is almost equal to other follow-up results. But the 5-year survival rate of the group without removal of the pectoral muscles is so satisfactory that it cannot be calculated statistically. Only 5 deaths have been encountered in this group (Fig. 1). As far as the cases of Steintal I~II are concerned, the 5-year survival rate of the group with the pectoral muscles removed is 61.5%, but that of the group without removal of the pectoral muscles is 90%, only 4 deaths being encountered (Fig. 2). What makes difference between the two groups

is not yet clarified, but both surgical procedures and postoperative radiation therapy are considered to have much to do with it.

The duration of the disease before operation is somewhat shorter in cases with removal of the pectoral muscles than in those without removal of the pectoral muscles. Concerning the location of the primary tumor, cases of which the tumors are originated in the medial side of the breast are considerably evidenced in the group without removal of the pectoral muscles. No particular relation is found between location of the primary tumor and

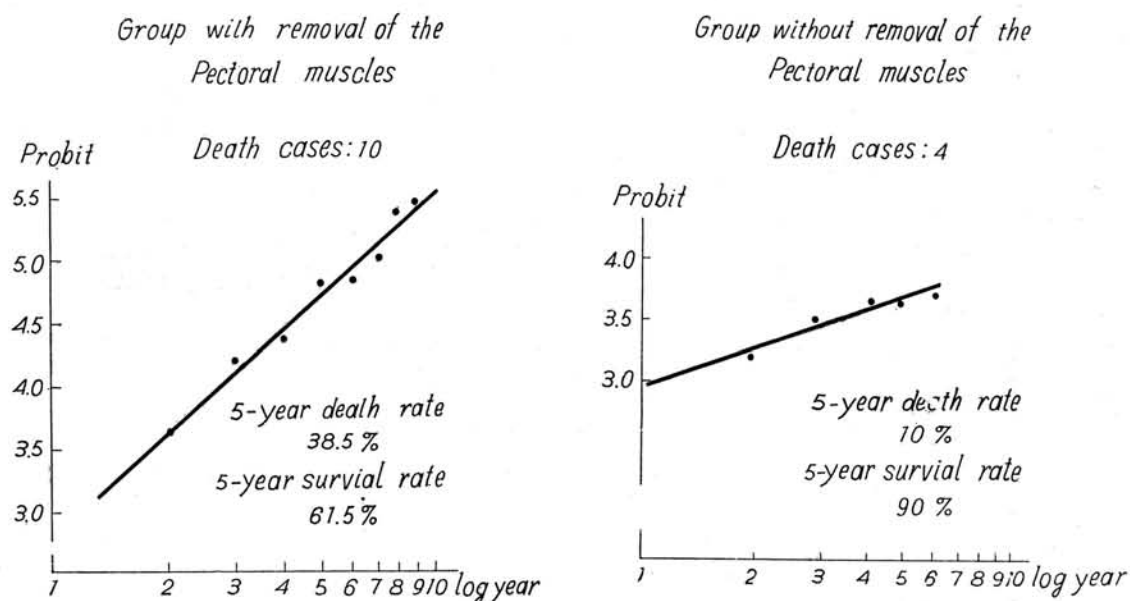


Fig. 2. The 5-year rate of the cases of Steintal I and II

Table 8. Cases of postoperative lung metastasis

No.	Steintal	Site of the original tumor (quadrant)	Mode of operation (Removal of the pectoral muscles)	Postoperative radiation	Interval between operation and onset of pulmonary symptom	Interval between operation and death
1	II	Lateral-upper	Without removal	Incomplete	28 months	34 months
2	II	Internal-upper	With removal	Incomplete	12 months	12 months
3	III	Lateral-upper	With removal	(—)	Demonstrated at the time of operation	
4	III	Lateral-upper	With removal clearance of the clavicular region	Complete	9 months	16 months
5	II	Internal-upper	With removal	Incomplete	56 months	80 months
6	II	Lateral-upper	With removal	Incomplete	Not clear	3 months



death due to metastasis. The tumors of the death cases are located in the lateral-upper or medial-upper quadrant or the central portion of the breast where the breast cancer is frequently encountered clinically. Observation of the 6 cases which are definitely diagnosed on lung metastasis after the operation reveals that the primary tumors are mostly located in the lateral-upper quadrant. It is a noteworthy fact that 5 of these 6 cases including one which belongs to the group without removal of the pectoral muscles have not received adequate postoperation radiation therapy. As far as the cases of Steintal I~II which are submitted to adequate postoperative radiation are concerned, not a case of lung metastasis has yet been encountered after the operation whether the pectoral muscles are removed or not (Table 8).

Considering these points, the problem on the metastasis through the internal mammary glands reported by Handy is indeed important, but it is a difficult question to decide whether the partial or total resection of the pectoral muscles is more reasonable than the non-removal method of the muscles with adequate radiation or not.

This is a matter left for further study judging from our follow-up results. Considerable effect of X-ray treatment can be expected as far as the cases of Steintal I~II are concerned. Details will be reported by further study.

No particular findings are obtained from the investigation of the relation between the size of the mammary tumor and the prognosis of 5-year-survivals. Statistical studies of the relation between the adhesion to circumferences and prognosis are as follows. The 5-year survival rate of the cases without adhesion is 56%, whereas the rate of those with adhesion is 27.5%. That is to say, the cases of which the primary tumors are adherent to either the overlying skin or the base show very poor prognosis. Among the 5 death cases in the group without removal of the pectoral muscles, adhesion to the skin is demonstrated clinically in 4 cases. We consider, therefore, that the operation without removal of the pectoral muscles should not be indicated to those cases of which the mammary tumors are adherent to surrounding tissues (Fig. 3). Cases without swollen axillary lymph nodes on the first consultation are more frequently found in the group without removal of the

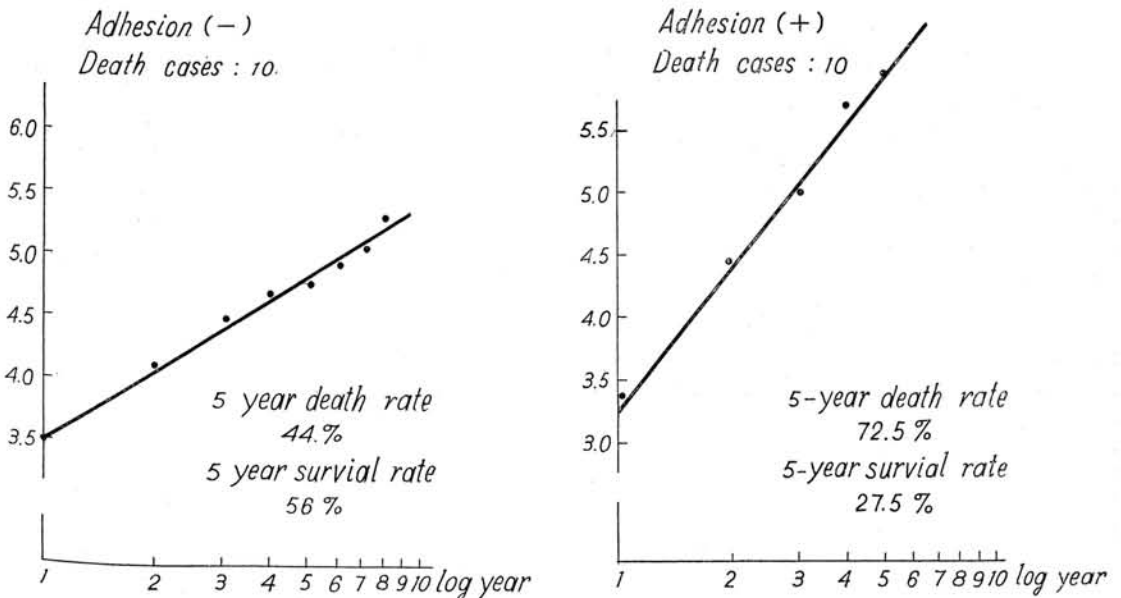


Fig. 3. Adhesion of the primary tumor and prognosis in the group with removal of the pectoral muscles

Table 9. Histological axillary metastasis and prognosis

Metastasis of axillary lymph nodes	Group without removal of the pectoral muscles		Group with removal of the pectoral muscles	
	Cases	Deaths due to recurrence	Cases	Deaths due to recurrence
Not demonstrated	33	0	13	2
Demonstrated	27	5	22	9
Unidentified	10	0	21	9
Total	70	5	56	20

pectoral muscles than in the group with removal of the muscles. But death is more frequently encountered in cases with swollen axillary glands all over the cases, particularly among those of which metastasis of the axillary lymph nodes are histologically demonstrated, despite the mode of operation (Table 9).

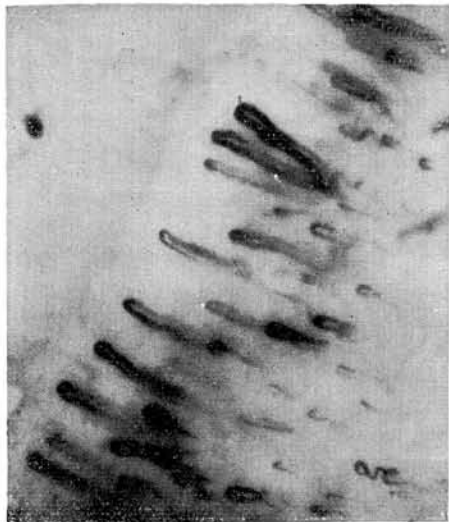
In the present report a few considerations are made on the operation without removal of the pectoral muscles, which has been performed in our clinic on condition that adequate postoperative radiation therapy should be begun as early as possible. We believe that this mode of operation is worthy of much clinical application as a radical operation of the breast cancer provided correct indication is performed.

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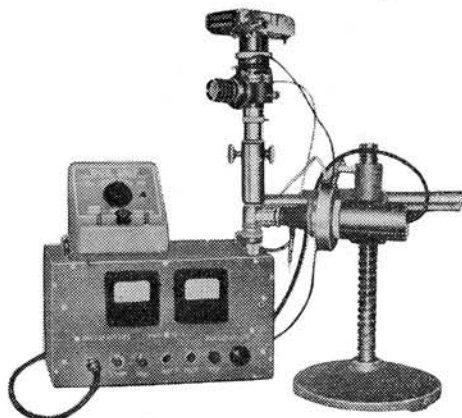
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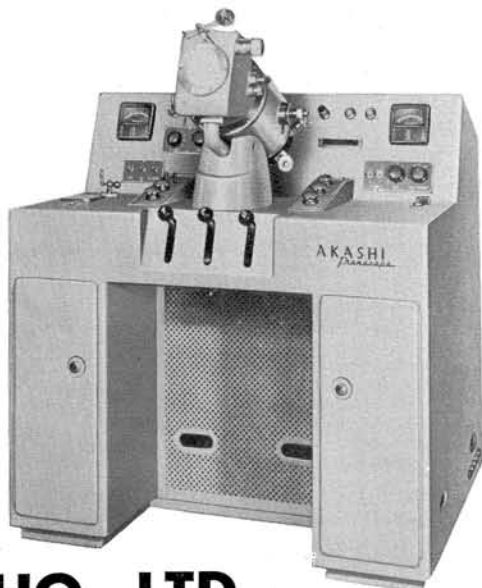
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## Electron Microscopy of Japan

Masanaka TERADA, M. D.

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### Introduction

Looking back upon the course in which human beings have hoarded up extensive knowledge in various fields, we can see that they have devoted themselves to find some media for observations of things that were invisible to the naked eye.

In order to make it possible to make astronomical observations and to study microbe, they finally devised an astronomical telescope and a light microscope, of which the latter had been widely used as the best and only medium for unravelling a mystery of the microbic world, and yet there were the limitations to its performances.

In 1876, Dr. Abbe, a well-known scientist of Germany, announced that the objectives, a distance of each of which is under  $0.2\mu$  ( $1\mu=1/1000$  mm), could not be clearly seen in separate with the light microscope, because of the limitation to its resolving power.

In 1931, as the results of efforts made by numbers of researchers and technical experts, an electron microscope was completed, but its resolving power was lower than that of the light microscope. However, during 1940-1942, the electron microscope worthy of its name was revealed and it moved into the limelight. At the same time the extensive studies were made for widening the sphere of its applications, and this has greatly contributed to further development of the electron microscope. It was proved that the electron microscope could be utilized for the studies of the surface of metals, formations and nature of pulverized matters, structures of microbe, etc.

Here in Japan study of the electron microscope was started in 1939, and the first one was completed in 1942. It is to be noted that our researchers and technical experts announ-

ced in 1943 the revolutionary electron microscope, the resolving power of which reached as high as  $10\text{ m}\mu$  ( $1\text{ m}\mu=10\text{AU}=1/1,000,000$  mm), in other words, its performance was better than that of the light microscope by 20 times, and thus Japanese made electron microscope has become the object of worldwide attention. It was in those days that among the nations concerned there was a quickening of scientific exchange with priority given to the electron microscope.

The meetings were held in both the United States and England in 1942 and in Germany in 1949, in which the scientists from various countries freely discussed many problems and fully exchanged their opinions concerning the electron microscope. In 1956, the First Regional Conference in Asia and Oceania on Electron Microscopy was held, and the delegates from Cambodia, China, India, Indonesia, U.S.S.R., U.S.A. and Germany including Japanese delegates, got together in Tokyo; and exchanged the results of their research works, and it was agreed and announced they would contribute their share to welfare of human beings through the microscopy. In the Conference it was revealed that the limit of resolution of Japanese made electron microscope extended to  $0.8\text{ m}\mu$ , which was approximately 250 times that of the best light microscope and in terms of magnification approximately 4,000,000 times. Believe it or not, our researchers have now raised the limit of resolution as high as  $0.6\text{ m}\mu$  (6 AU), which is about 300 times that of the light microscope.

Here, let me explain briefly about the structure and contrivance of the electron microscope.

As the electron microscope employs electron beams as its light source, one must be master

of the nature of the electron beams, so that he will be able to manage them satisfactorily just same as in the case of light beams.

First, a tungsten filament is heated and the electron beams are generated, which are accelerated by employing such high voltage as 50,000–100,000 V. Unlike the light beams, the electron beams are electro magnetic waves which consist of grain with mass of  $9.107 \pm 0.00022 \times 10^{-28}$  gr., and therefore they can not pass straight through the air. This is very reason that the inside of microscope column be kept vacuum to the extent of  $10^{-4}$ – $10^{-5}$  mHg.

As means of emanating and condensing the electron beams, electromagnetic lenses are employed. In the early days of invention of the electron microscope, 2-stage lens system was adopted, which consisted of the objective and projector lenses, but now these days 4-stage lens system, the condenser, objective, intermediate and projector lenses, has often been employed even for the small type of the electron microscope. Moreover, completion of 6-stage lens system has now widened the sphere of application of the apparatus, which consists of: 2 stage condenser lens, 2-stage objective lens, intermediate lens and projector lens. The images formed by such lens systems are projected on a fluorescent screen, which will freely be observed through 3 viewing windows. So highly stabilized electric circuit ( $10^{-4}$ – $10^{-5}$ ) and selected parts are employed that the stabilized images will be always obtained. Moreover, it is so designed that operation of such electric circuit will cause no danger to operators.

Well then, I am going to introduce to you general features of the Japanese made electron microscopes.

The electron microscopes with different functions are used according to purposes of its application, for instance, for studies of: the surface structure of metals, the nature of pulverized matters, the structures of pulp and fibre, bacteria, virus, etc. It is to be proud of, however, that the universal type electron microscope has now been manufactured in Japan in order to make it more usable for

various studies. This type of apparatus has been exclusively made in Japan, which stands alone in every respect, especially in high resolving power. By employing specially devised Cooling and Heating Attachments with it, specimen can be observed while it is being cooled and heated ( $-140^{\circ}\text{C}$ – $1,000^{\circ}\text{C}$ ) in the microscope column. Fig. 1 shows the sensational universal type JEM-5G Electron Microscope, magnification of which is 4,000,000 times.

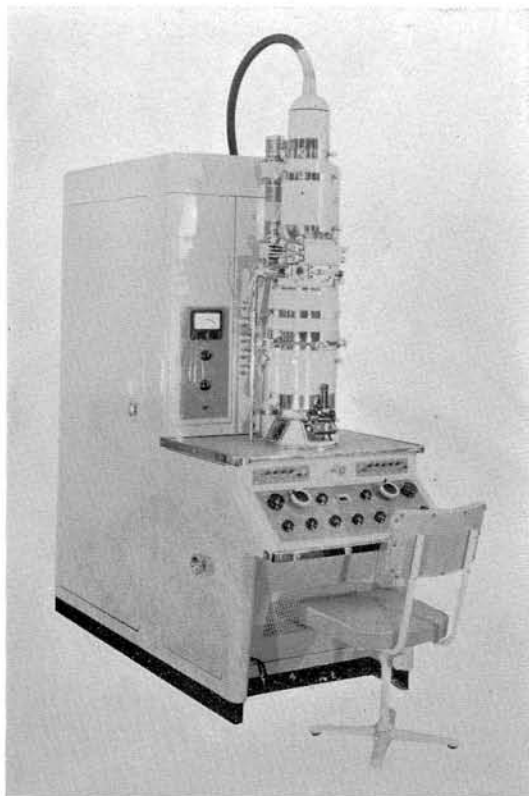


Fig. 1. JEM-5G Type Electron Microscope.

In Japan the electron microscopes have been manufactured by four makers, such as Hitachi Works, Ltd., Shimadzu Seisakusho, Japan Electron Optics Laboratory Co., Ltd., and Akashi Works, Ltd.

Japan Electron Optics Laboratory Co., Ltd. also manufactures such standard type TEM-T4 as shown in Fig. 2. Though it is compact and simple in its operation, its resolving power has been recorded as high as 2.0–2.5  $m\mu$  (20–



25 AU) and its magnification has reached 300,000 times, and moreover, it is capable of being used as electron diffraction device. Besides the above, more compact one has been hitherto supplied to a quite number of factories and schools, see Fig. 3, the limit of resolution of which extends to  $5\text{ m}\mu$  and its magnification reaches 100,000 times. This apparatus is also capable of being used as the electron diffraction device.

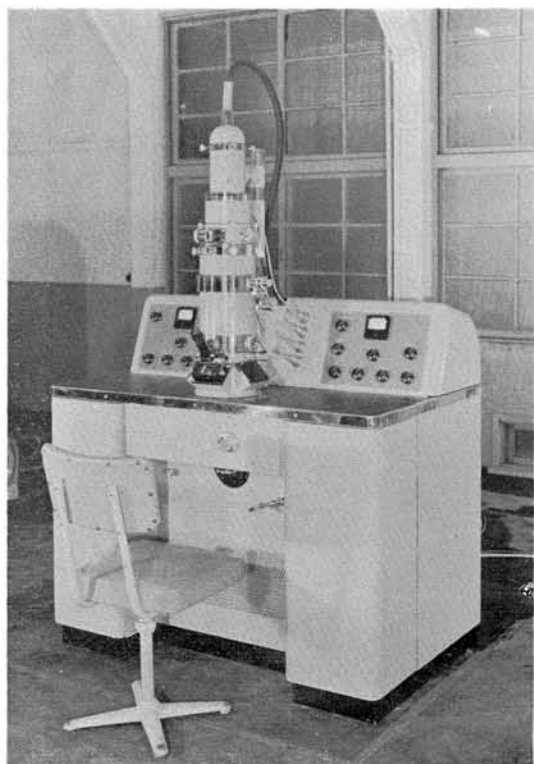


Fig. 2. JEM-T4 Type Electron Microscope.

When the electron microscope is used as the electron diffraction device, it is possible to study the crystal lattice of metals and formation of inorganic substances. That is why the electron microscope is used today in various fields such as scientific, medical, biological and agricultural fields in order to make a thorough study of the microbic world where the X-ray diffraction device could not reach.

Reverting to the cooling and heating of specimen, see Fig. 1, I dare to say that such

methods have made the electron microscope more useful. In order to make the electron microscope perform optical diffraction and reflection same as in the case of light microscope, the inside of the microscope column must be kept vacuum, so that the electron beams can pass straight through the lens system.

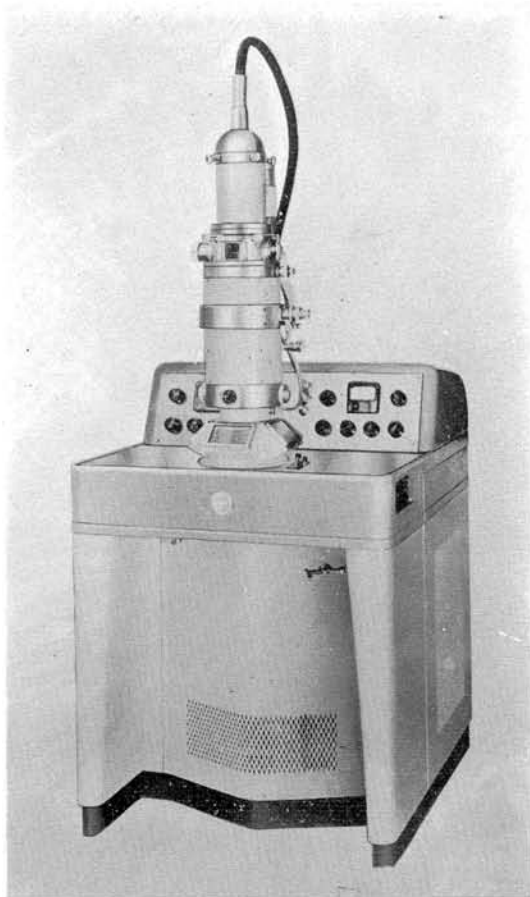


Fig. 3. JEM-T2 Type Electron Microscope.

Consequently, moisture contained in matters be evaporated, and when the electron beams are projected specimen be burnt up, by employing the Cooling Attachment, such materials as ice, mercury, microbe, etc. can freely be observed even under low pressure. Furthermore, it is also possible to study the changings of metals in formation and structure owing to treatments made both in high and low temperature by using the Cooling and Heating

### Attachments.

It is to be noted that utility value of the electron microscope has been fully recognized in metallurgic circle since Dr. Mahl revealed Replica method in 1940, which has enabled one to re-produce very closely the surface structures and/or formations of metals, non-metals and microbe. Influenced by further development of reproduction technique, the electron microscope has become more popular and been widely used at factories for the purposes of inspecting parts as well as the quality of materials.

It is well known that the pulverized or fibriform substances have been often used as specimens for the electron microscope, and in these days it is possible to make observation of the specimen even while it is being treated by chemicals and cooled or heated in the microscope column.

Speaking of a recent remarkable trend, the metallurgic circle has now been paying its attention to a method of direct observation of metals with the electron microscope. For this purpose, thin film is prepared in the following ways, through which electron beams are transmitted, viz., by electrolysis, ion bombardment, melting, by applying a corrosive agent and by evaporated film method. In

industrial field, Extraction Replica method has been adopted, in other words, by evaporating carbon film on the surfaces of metals and also by making it corrosive, the surface is replicated, and at the same time inclusion or precipitation of specimen is identified by means of electron diffraction.

In order to study the micro-structure of bacterial cell, virus as well as animal and plant with the electron microscope, it is necessary to cut specimen as thin as 100-200 AU, and for this purpose, Ultra Microtome is used. Fig. 4 shows JUM-5 Ultra Microtome manufactured by Japan Electron Optics Laboratory Co., Ltd. This apparatus is well known for superiority in its performance and

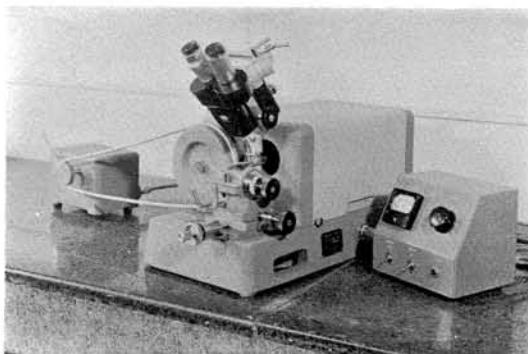


Fig. 4. JUM-5 Type Ultramicrotome.

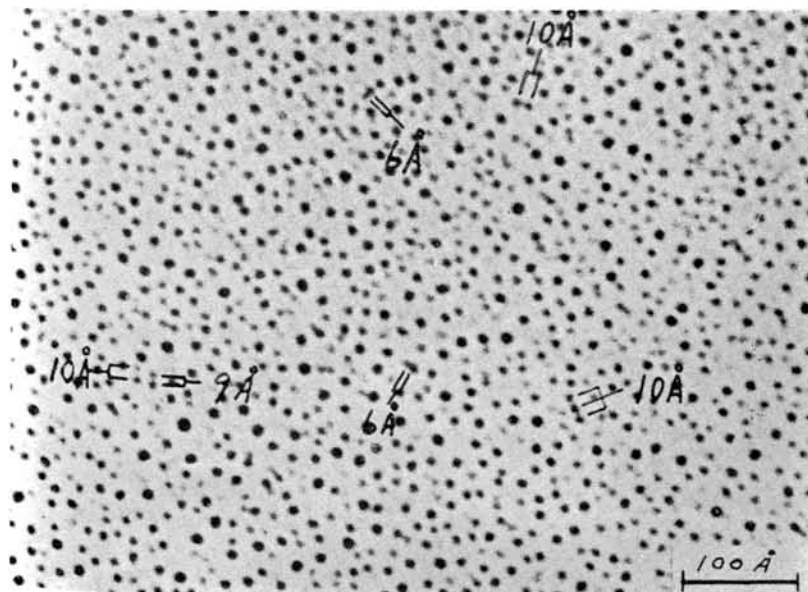


Fig. 5. The evaporated film of Pt-Pd alloy prepared for measuring a resolving power.

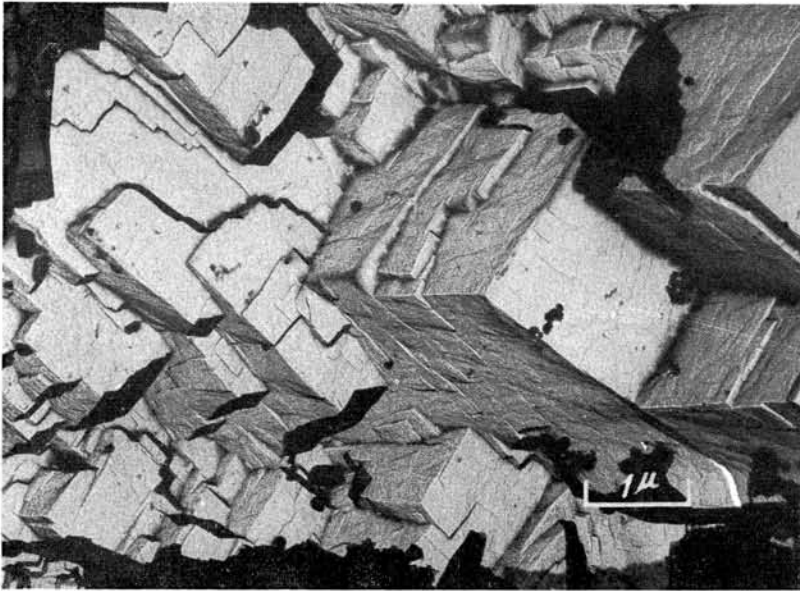


Fig. 6. Observed monocrystal of Aluminium by the Replica method.

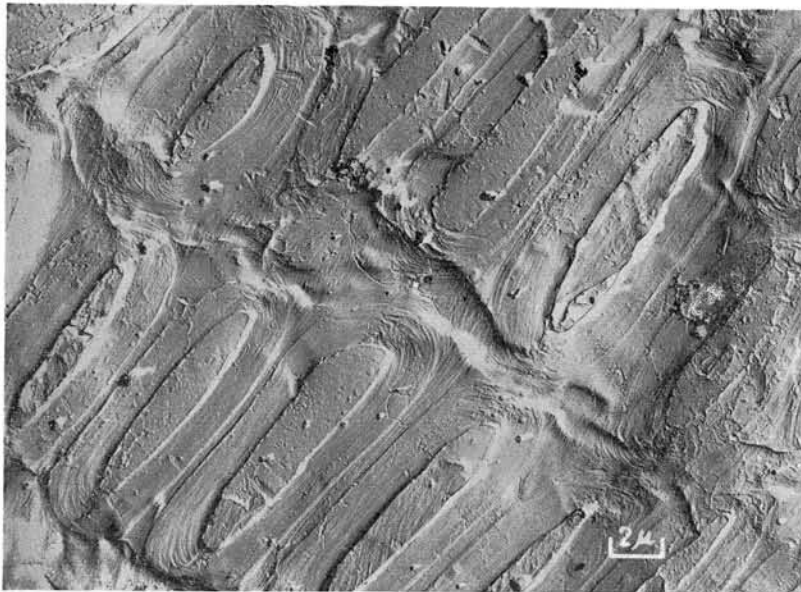


Fig. 7. Pulp made of pine tree.

simplicity of operation. It is so designed that specimen can automatically be cut in train in the shape of ribbon.

#### **The Application of Electron Microscopic Studies in the Field of Biology**

In Japan the electron microscope was first manufactured in 1939, at the time when the German and American scientists had already succeeded in taking electron microscopic

pictures of microbes. Although it took several years in order to create Japan's original electron microscope during the war under poor circumstances, in 1943 its resolving power and direct magnification had reached a level of  $5m\mu$  and 5,000—10,000x, respectively. With the aggravation of the war studies along this line were inevitably discontinued until the end of the war, and it was in 1947 when biological materials first became to be studied

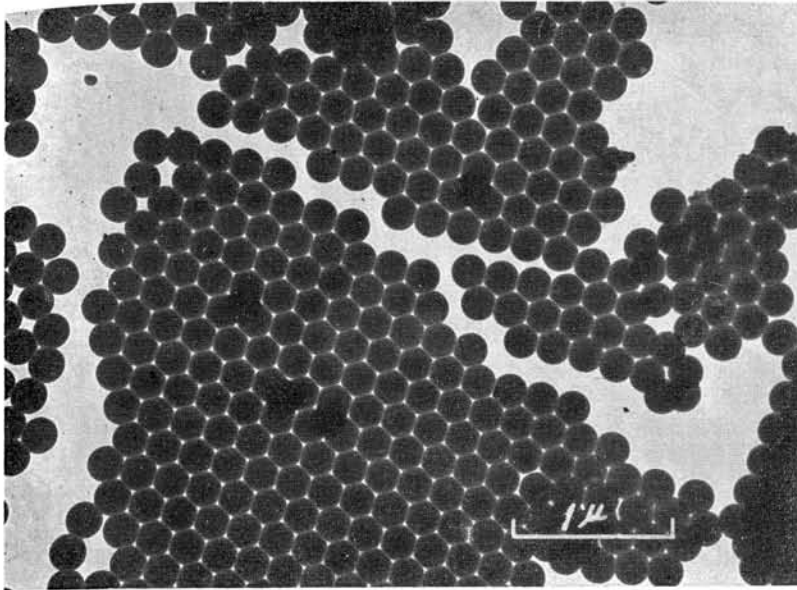


Fig. 8. Mono-layer Dow latex particles array.

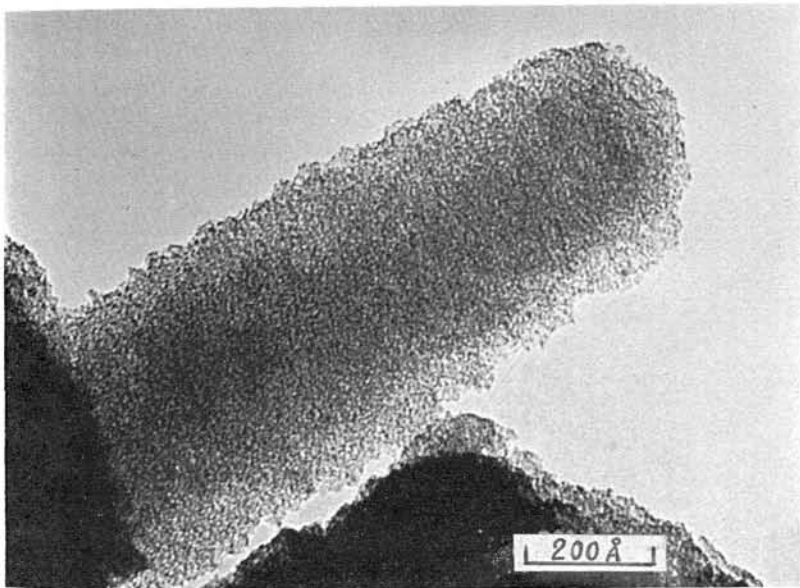


Fig. 9. Fine structure of active carbon.

with the Japanese electron microscope. The Japanese Society of Electron Microscopy was established in May, 1949, and since then the electron microscope has become to be applied in various fields of natural science. Electron microscopic studies on virus and those applying the ultra-thin sectioning method are some of the outstanding research works in the field of biology. During this period of 10 years morphological studies with the electron

microscope and studies in clarifying the biological character corroborating these and furthermore, studies in clarifying their genetic relationship have made great progress. Their rapid progress and results have contributed much to natural science throughout the world.

#### Studies on Virus

From light microscope to electron microscope;

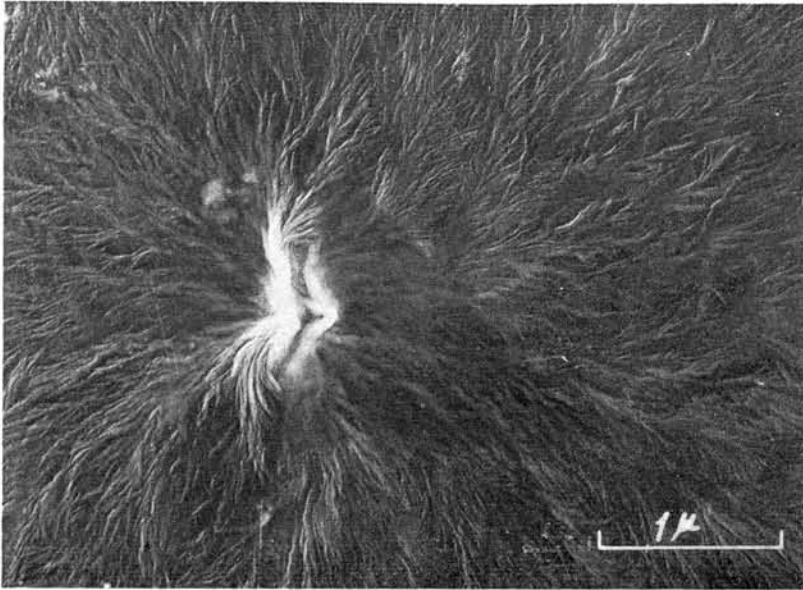


Fig. 10. Spherulites of Nylon 6. (Amylan in Japan).

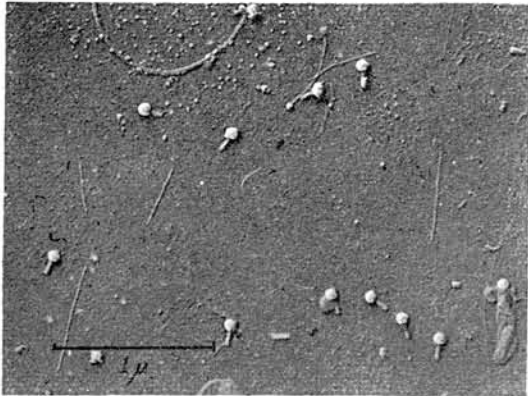


Fig. 11. *Sh. flexneri Ia* phage. Typical form with head and tail.

this means that a new world from  $200m\mu$  to  $1m\mu$  has opened before us, and viruses, colloid and high molecular protein, hitherto invisible to the eyes have become some of the top subjects. Many of our colleagues in Japan have spent most of their time for the discovery of viruses under the electron microscope during the early to intermediate stage. We have also been indulged in various electron microscopic studies during the past 10 years and have carried out studies on animal virus or plant virus and bacterial virus (bacteriophage), with special stress layed on studies concerning bacterial virus. Twently odd new kinds of

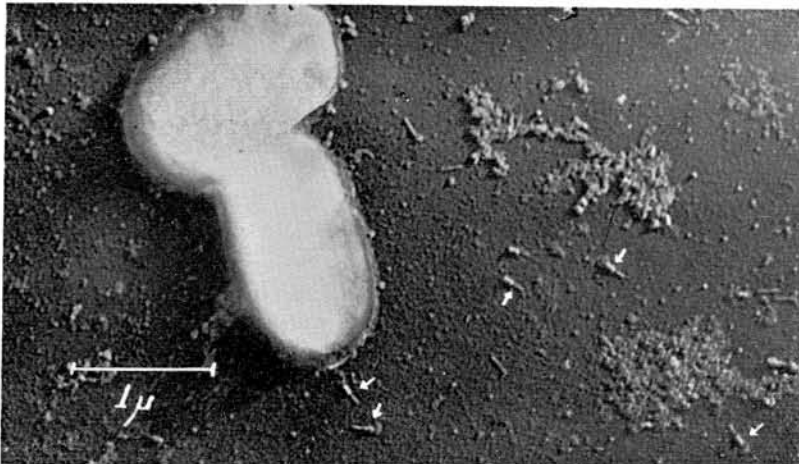


Fig. 12. *Sh. sonnei* R-form (Tanaka strain) phage marked by white arrows. Typical form of *Sh. sonnei* R-form (Tanaka strain) phage consisting of the crest like head, the rod shaped body and tile, are scattered. Also, viruses consisting of only the rod segment are seen.



bacterial virus have been confirmed up to date with the electron microscope. These studies were further carried out and since the relation between their morphology and function has been proven from a genetic stand point, I should like to introduce here some of our studies along this line and stress the importance of electron microscope in research work of natural science.

The host cells of the 20 odd kinds of the phages confirmed by us are bacteria of the Salmonella, Shigella and Escherichia, Staphylococcus, Actinomyces and plant-pathogenic

bacteria. Their shapes are similar to those already reported having a sperm-like form with a head and a tail. (Fig. 11). The sh. sonnei R-form Tanaka strain phage indicated in Fig. 12 has an entirely different shape as compared to the afore mentioned ones. It is composed of a crest-like head, rod-shaped body and a tail, and it is different from any one of the various phages hitherto reported. The sizes of the phages differ from those having a head of a hundred odd  $m\mu$  to those such as Staphylococcus phage having a head of about 30  $m\mu$ . Not only electron microscopic but also

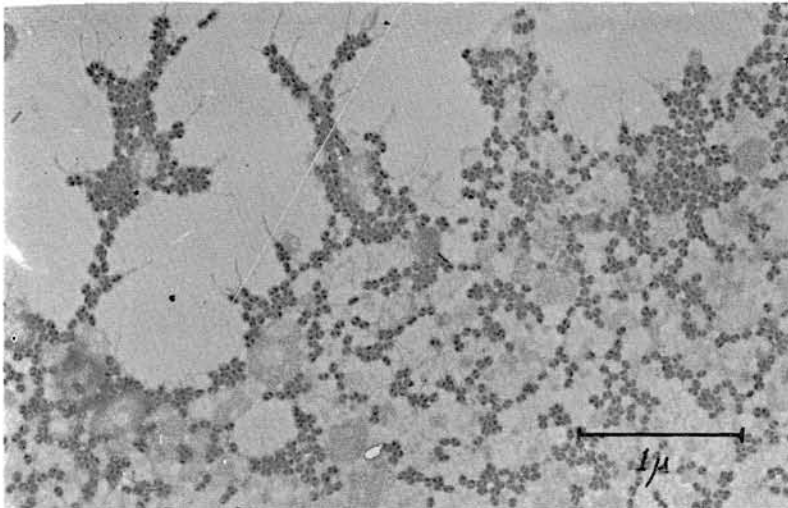


Fig. 13. The head of Actinophage showing the diplococcus-like internal structure.

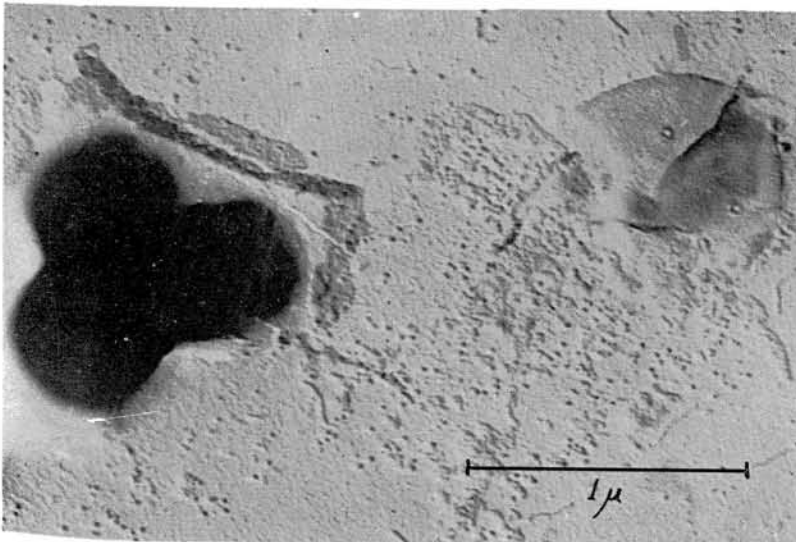


Fig. 14. Staphylococcus (209 P strain) phage. The bacterial body that has already been ruptured by the viruses. As a result of the destruction of the bacterial cell, the viruses were scattered to and fro.

detailed biological, serological and genetic studies have been carried out on these phages. (M. Terada; Studies on Bacterial Viruses, Naya Publishing Co. Ltd., 1956). One of the important studies among those on bacterial viruses is the one on mechanism of multiplication, which is considered to be one of the fundamental problems in the study of virus. The internal structure of the head (Fig. 13), tail structure and ghostphages were studied in detail with the electron microscop and some investigations on the mechanism of multiplication of phages were made from the electron

microscopic side of view. Although the mechanism of multiplication will be discussed later, there are also the electron microscopic studies with the ultra-thin sectioning method by Dr. N. Higashi, who first induced the ultra-thin sectioning in Japan.

Among the phages discovered in our country several kinds of phages of *M. tuberculosis* have been recently isolated from soil. Phages causing bacteriolysis of tubercle bacilli of human type, bovine type and avian type and non-pathogenic acid-fast bacteria have been discovered.

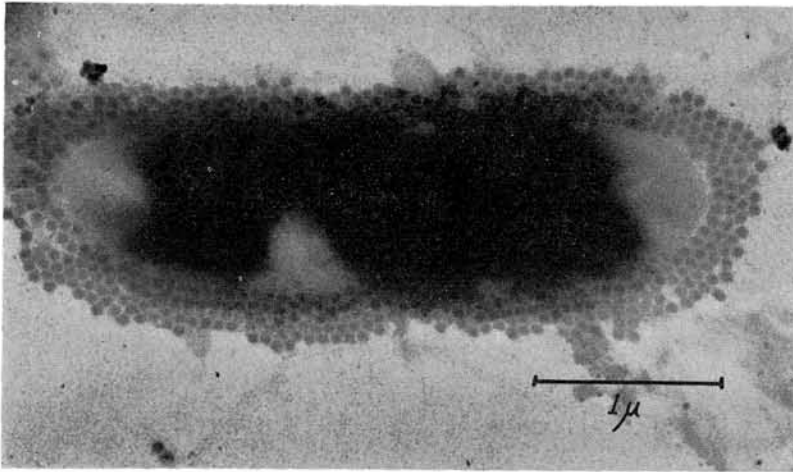
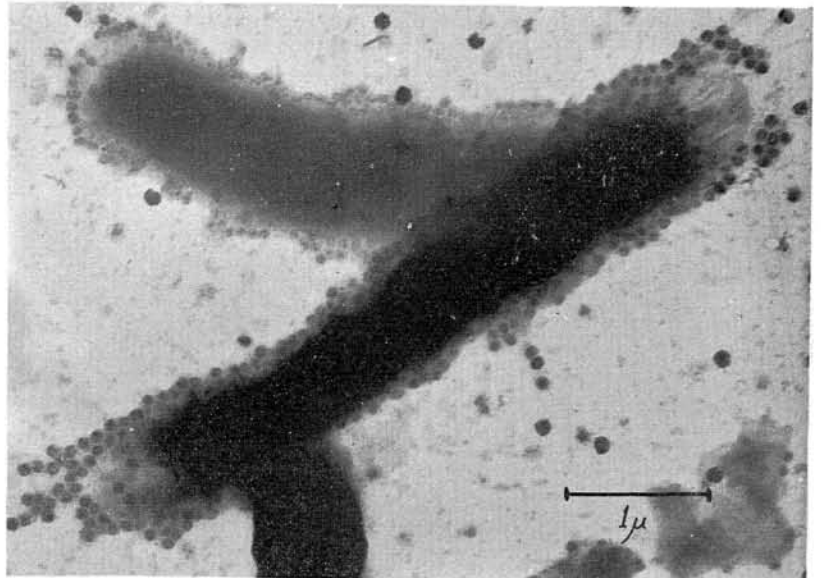


Fig. 15. *A. cloacae* phage S  
A great number of 5 phage are in layers adsorbed to the host cell.

Fig. 16. *S. enteritidis* (S. 64 strain) phage.

The strong-contrasted bacterium on the lower side adsorbs a few viruses. As the swelling and lysis progresses, the bacterium on the upper side, attacked by a large numbers of virus particles, is about to burst; consequently the bacterial internal contents have almost been consumed and show us weak-contrasted image of the bacterium to be destroyed. The viruses attacking the host cell are of a small type and the internal structure can be seen very distinctly. There are large and small types around the bacteria.



Some of the interesting bacterial viruses studied by us are shown in Fig. 14—19. The specimens have been prepared by our original method, and this method is simple and through it not only can the shapes of the phages be grasped but the relation between host bacteria and phages can also be readily confirmed.

Studies on animal virus: Fig. 20 shows the *Molluscum contagiosum* virus mingled among the collagen fibres. Some interesting studies concerning relatively large animal viruses are being carried out. Many papers concerning the mechanism of multiplication of pox group viruses together with ultra-thin sectioning have

been reported. In relation to the purification of virus the ultra-centrifuge is indispensable for the study of virus, especially animal virus. Ultra-centrifugation, ultra-thin sectioning and electron staining are influential weapons in forwarding electronmicroscopic studies.

It is regreted that the appliance of the **ultracentrifuge** was at a late stage in our country. At the present Spinco L type and E type have been imported, and although an ultra-centrifuge similar to L type which is manufactured in Japan is being widely used, it was in 1951 when the Sharples type super-centrifuge was first used in Japanese laboratories. At that time trial production of

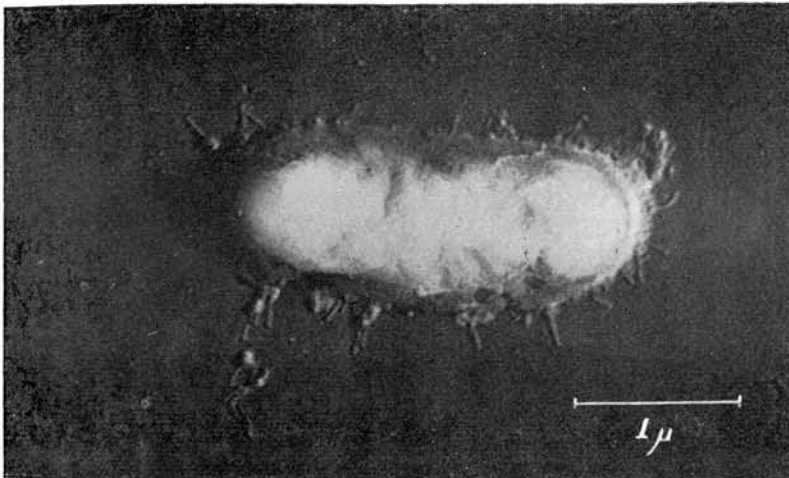


Fig. 17. Actinophage Ku-1

Attacking hostcell, *Actinomyces griseus* Ku strain. This phage was isolated during the mass-production of to prevent the intermingling of actiophage in the process of streptomycin production.

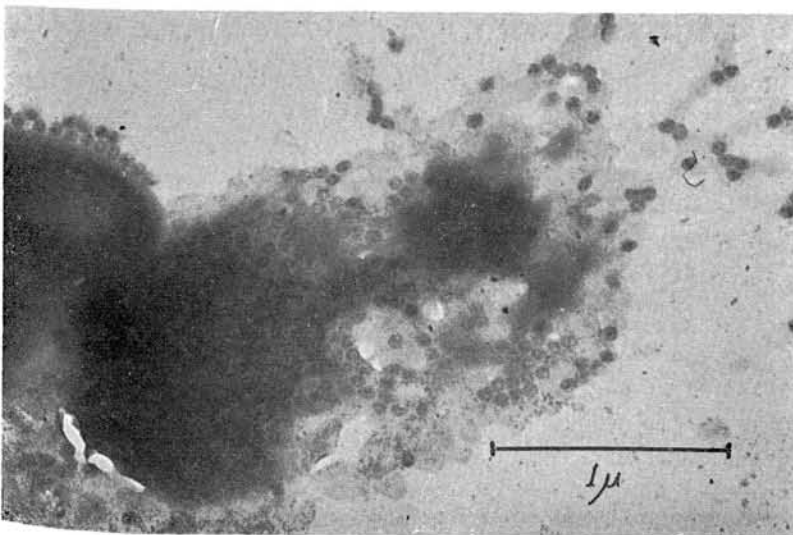


Fig. 18. *S. pullorum* (Y.S. 6) phage

The internal structure of the head of the multiplying viruses in the host cell.

ultra-centrifuge was just being carried out in Japan. The ultra-centrifuge had already been applied in 1933 in Europe and America, and electronmicroscopic studies followed afterwards. Studies along this line have made great progress, and together with the advance in studies concerning purification of viruses beautiful electron microscopic figures of Dengue fever virus and Tobacco stunt virus have been obtained. Physicochemical analysis of purified virus and furthermore, the biology and immunology of virus have given fruitful results. Purified viruses with Sharples super-centrifuge are indicated in Fig. 21 and

Fig. 22. With the advance in purification of viruses electron microscopic studies on Izumi-netsu virus and Japanese B encephalitis virus, which are both characteristic diseases in Japan are being completed. Difficult studies on rabies virus, hepatitis virus and measles virus have already started.

Wonderful results concerning microbes, in general, are also being obtained; flagella of bacterial cells, capsule, spore, polar-body, cell wall, cytoplasmic membrane, bacterial nucleus, etc. Furthermore, application of the electron microscope in the field of immunology may some day be of help in clarifying the mecha-

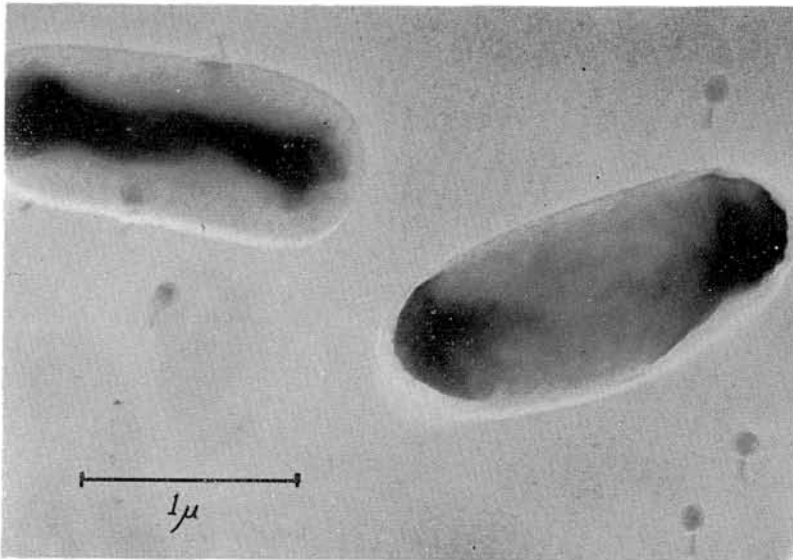


Fig. 19. *Erwinia carotovora* (ginger) phage

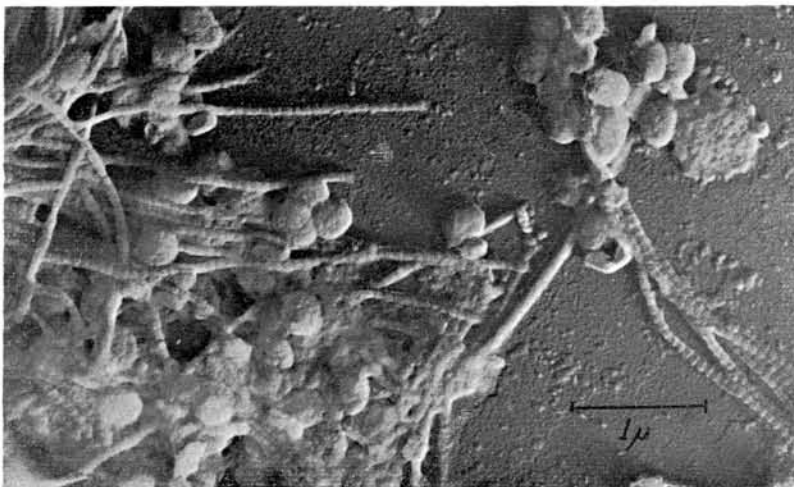


Fig. 20. Molluscum contagiosum viruses and collagen fibres.

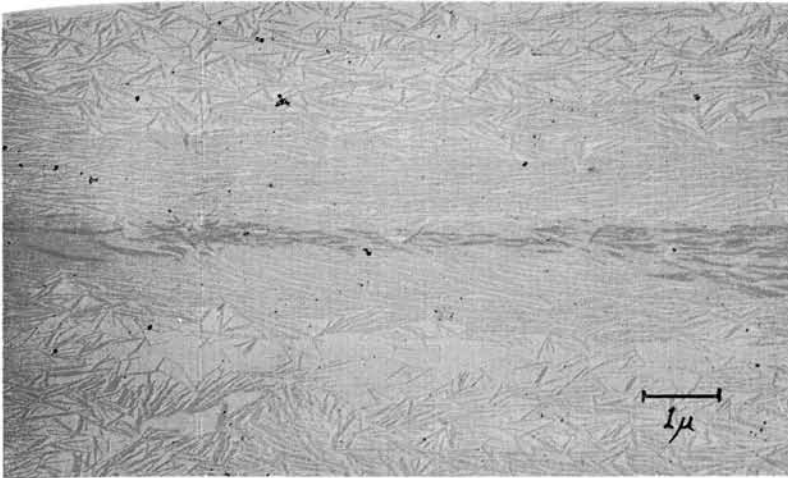


Fig. 21. Tobacco mosaic disease virus, concentrated and purified with Sharples Super-centrifuge.

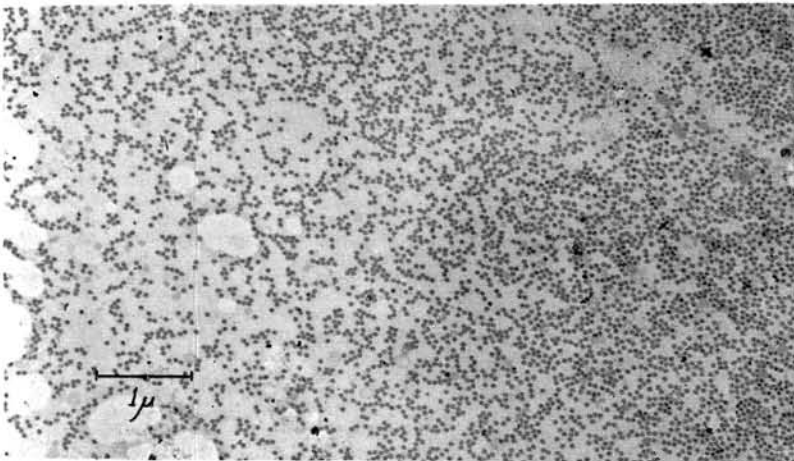


Fig. 22. *S. gallinarum* Akita phage, concentrated and purified with sharples Super-centrifuge. This material was used for the immunological and enzymatic studies of this virus.

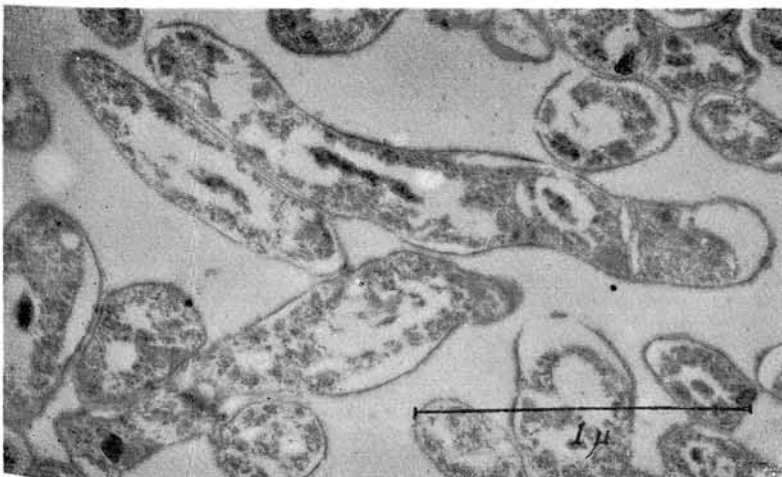


Fig. 23. Ultra-thin sectioning of *M. tuberculosis*.

nism of microimmune reaction.

**Studies with Ultra-thin Sectioning.**

As in foreign countries, the present trend in electron microscopic studies is the application of ultra-thin sectioning. We owe much to Pease and Baker who in 1948 contributed much to its development. Spencer type ultra-microtome was first imported into our country in 1952, and thereafter technical studies along this line have made great progress. With the import of various types of ultra-microtomes, ultra-microtomes of a high level have also been manufactured in Japan. Dr. Higashi after his return from U.S.A. has been one of the

pioneers in this field. Its application in histology and pathology has remarkably increased, and a new field in microhistology and micropathology is about to be established. Wonderful results in the study of the mechanism of muscle contraction are being obtained. In the field of oncology, not only the already known tumor viruses but also a pursuit for viruses in Yoshida sarcoma is being carried out. Furthermore, electron microscopy is being applied for the etiological studies of cancer and sarcoma. On the other hand, in the field of genetics electron microscopy is being applied for studies of genes in chromosomes. In the field of microbiology ultra-thin sectioning has

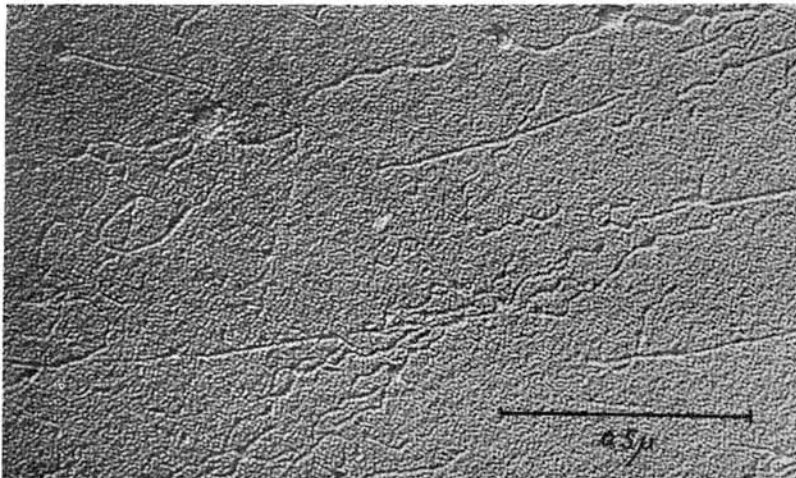


Fig. 24. Elementary fibers of DNA extracted from acid-fast bacterium Kedrowsky strain. Cr. shadow, Direct magnification 20,000 x

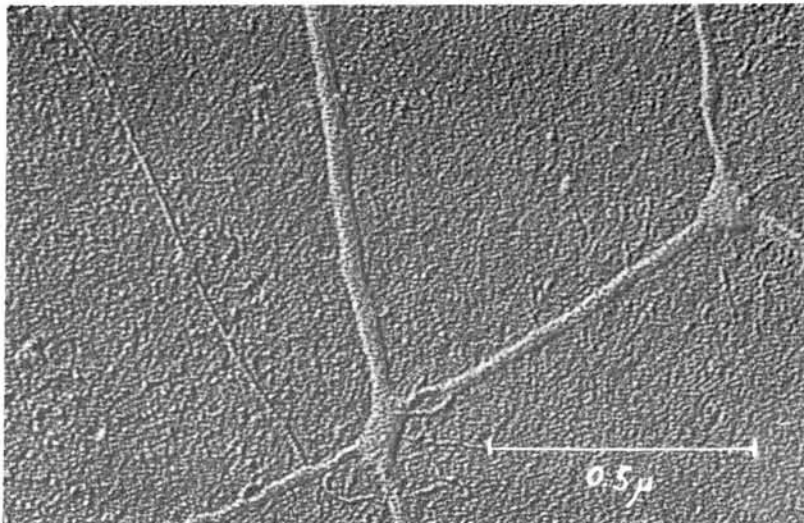


Fig. 25. Elementary fibers of DNA extracted from acid-fast bacterium Kedrowsky strain. Cr. shadow Direct magnification 20,000 x



played a great role in the discovery of trachoma virus and studies on the multiplication mechanism of pox group viruses. Recently a mitochondria-like structure has been discovered in the body of *M. tuberculosis* (Fig. 23). Studies with ultra-thin sectioning will probably continue to play a large role in electron microscopical studies for the time being.

### Electron Staining

Studies along this line are just about being started. The difficult technic of adding a strong contrast selectively is of special importance in the histological observation of ultra-thin sections. This difficulty will probably be overcome in the near future.

### Studies on DNA and RNA

In closing I should like to introduce our recent studies on DNA and RNA obtained from biological materials.

To analyse the biological activity physico-chemically in a macromolecule dimension has become the central theme in modern biology.

Especially the progress in the studies on nucleic acids is most remarkable.

The role played by nucleic acids in genetics, protein synthesis or so-called self reproducing system has been proven to be very important. For instance, since it has been revealed that chromosomes are chiefly composed of nucleoprotein, the existence of genes which have been advocated from a functional standpoint

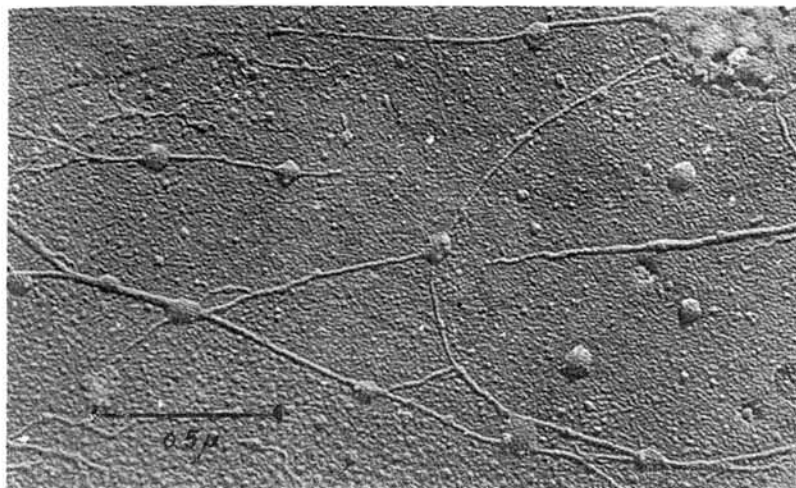


Fig. 26. DNA extracted from *S. sendai* phage Krh strain.

Both associated-micellized and singly separated fibers are observed.

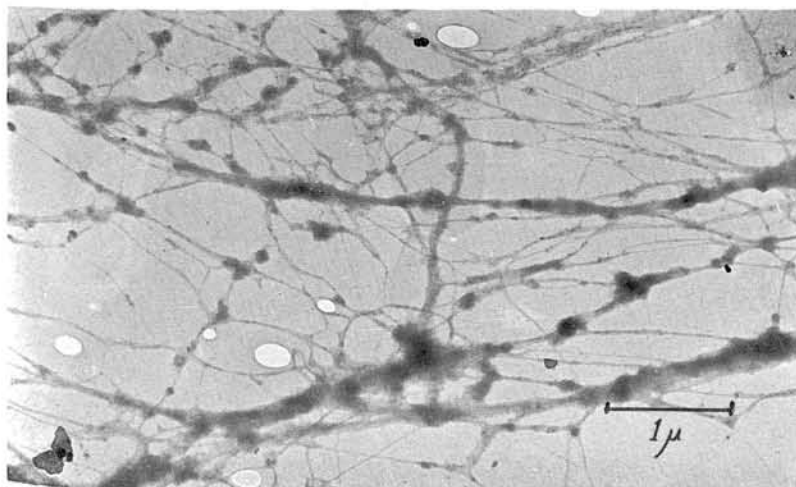


Fig. 27. Fine fibers of Kedrowsky DNA electron-stained with  $\text{AgNO}_3$ .



has been attempted to be clarified from a materialistic standpoint. The correlation between genes and deoxyribonucleic acid (DNA) is about to be clarified.

Along this line the morphological study on nucleic acid is naturally required to be fulfilled. There is every possibility that the application of electron microscope with the resolving power reaching a level at which a few Å may be calculated could now provide the most powerful clue for the resolution of this problem.

We have carried out the electron microscopic studies on nucleic acids (DNA and RNA) obtained by purification of extracted materials from

bacteria and bacterial viruses.

Some interesting findings in our experiments will be described somewhat in detail.

Fig. 24 and 25 show an elementary DNA fiber of non-pathogenic acid-fast bacterium Kedrowsky strain, and Fig. 26 that of *salmonella sendai* phage.

The diameter of these elementary single fibers is presumed to be 20-25 Å, according to our calculation from the actual figure of a single fiber shadow. This value shows good accordance with the theoretical value 20 Å postulated by Watson & Crick from the X-ray diffraction figure of DNA and also approximately

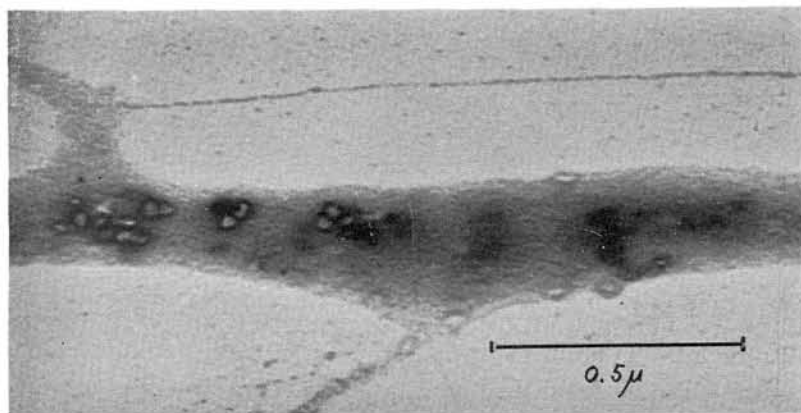


Fig. 28. Electron staining of Kedrowsky DNA with  $\text{La}(\text{NO}_3)_3$ .

DNA fibre bundle with a helically coiled figure can be seen in upper part.

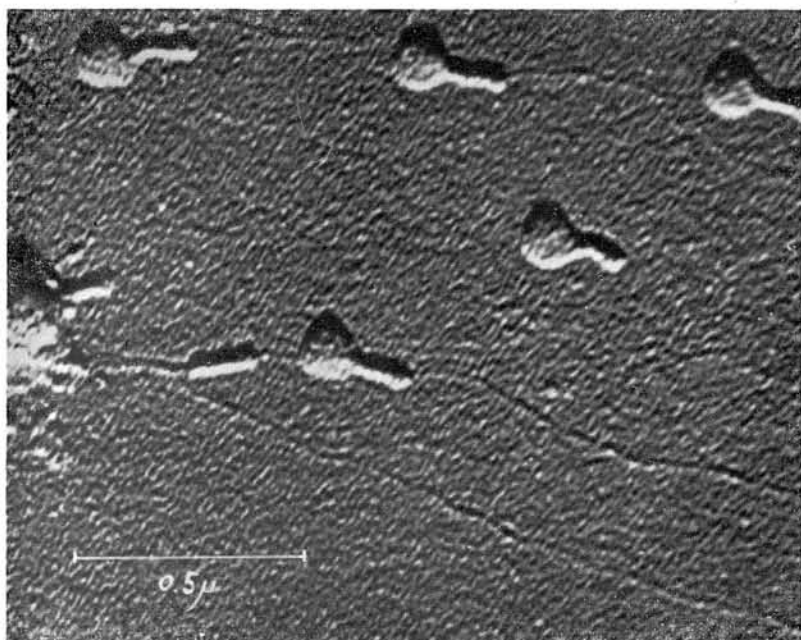


Fig. 29. Purified material of *S. gallinarum* phage Zt strain stoked in a refrigerator for 2 weeks. DNA fiber released from the tail of a phage.

with the value reported by Williams and Kahler on electron microscope picture of calf thymus DNA.

Fig. 27 and 28 show the electron stained pictures of DNA. We employed  $A_6NO_3$  and  $La(NO_3)_3$  as the electron stain.

Fine fibers of DNA are caught under a good contrast without any shadowing.

It will be our most important study to decide whether these chemical substances are also effective or not for the specific differential staining between DNA and RNA or other high molecular substances such as protein.

On the other hand, it is very interesting

that DNA fiber shown in the upper part of Fig. 28 demonstrates a helical figure. Of course this is not a physicochemical double helical structure of DNA fiber itself advocated by Watson and Crick. But this physicochemical structure makes an associated bundle of elementary fiber of DNA to take such a helical form which may also be assumed as a sub-structure of chromosome.

Fig. 29 also provides an interesting image on the relationship between the mode of infection and the chemical composition of phage. Long and fine DNA fibers released from the tail of phage can be seen. It is enough to

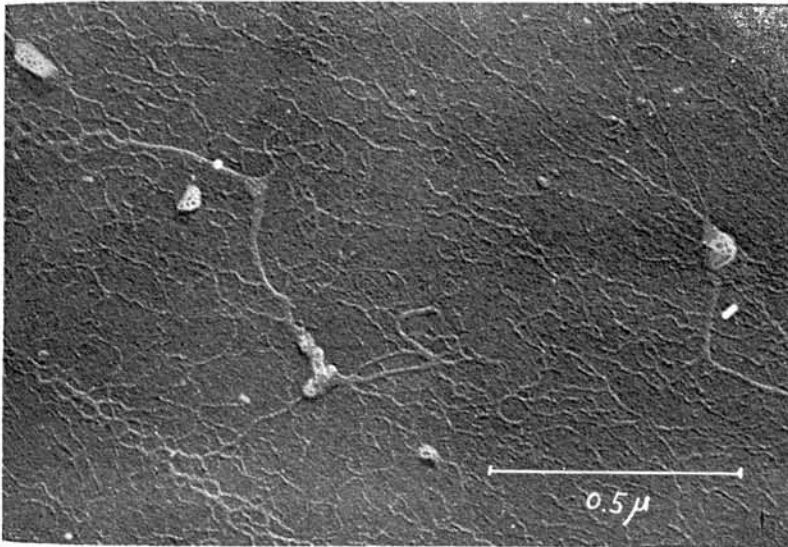


Fig. 30. Elementary fibers of RNA extracted from acid-fast bacterium Kedrowsky strain. Cr. shadow, Direct magnification; 20,000 x

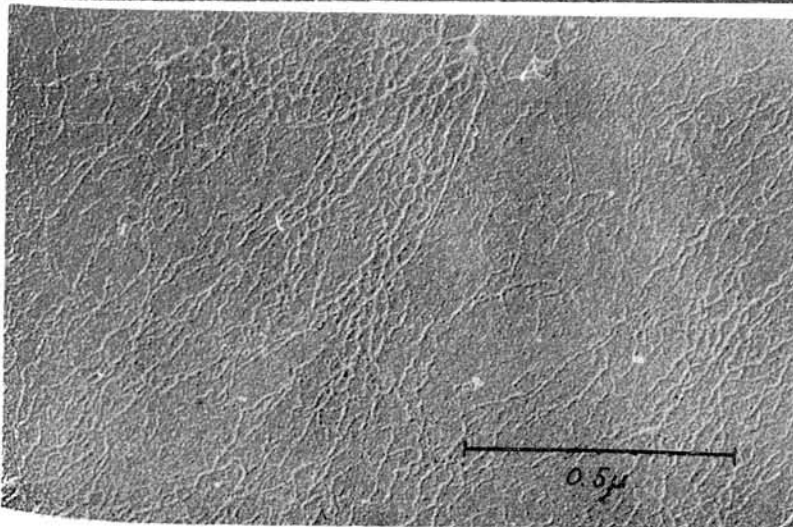


Fig. 31. Elementary fibers of RNA from Kedrowsky strain.

confirm the schema described by Pollard: DNA is coiled in the head of a phage and it is injected into the bacteria from its tail when invading the host bacteria.

Fig. 30 and 3i show the fiber-like configuration of RNA of Kedrowsky strain. They are similar to the figure of DNA, but they are found to be bent in more various directions showing a random coil. The diameter of the elementary single fibre of RNA is calculated to be between 15–20 Å from the actual estimation of shadow length of a single in these electron-photographs. Incidentally, Dr. Watanabe has reported the diameter of RNA fibre to be 16 Å from physicochemical analysis.

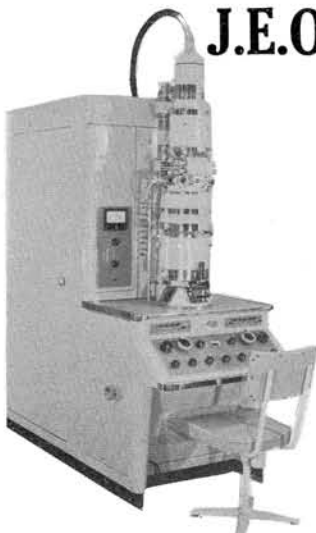
The high purity of all the above mentioned materials for microscope specimen were proven by physicochemical identification such as cystein-, diphenylamin-, orcine- or protein-reaction, UV spectrum, analytical value for N, P and atomic ratio N/P, etc.

It was also enzymiologically confirmed with


electron microscope that the specific figure, above mentioned, completely disappeared after the treatment respectively by DNase or RNase.

Moreover, the genetic activity of these materials were biologically confirmed. For instance, the DNA material extracted from Kedrowsky strain which produced a yellow colony was mixed into the fluid culture medium for the Elly strain which was also non-pathogenic acid-fast bacterium belonging to the same serological subgroup as the former, but produced a white colored colony. In the progeny from such a cultivation, a mutant strain was obtained, which produced a slightly yellowish colony.

It is presumed that the transformation was successfully carried out in which a part of the ability to produce a yellow colony could be transferred even by purified DNA extracted from the donor strain Kedrowsky into the recipient strain Elly.



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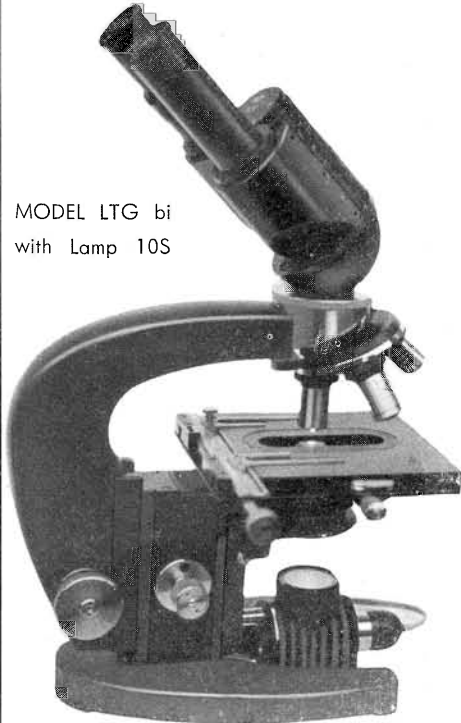
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## Studies on Colistin

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*Shimizu Surgical Department of Tokyo University*

In 1946 Dr. Fujimasa of Kobayashi Bacteriological Institute isolated *Bacillus polymyxa* var. *colistinus* from the soil in Fukushima Prefecture, extracted a new antibiotic from its culture broth and named it as colistin. It was proved to possess strong antibacterial activity against gram negative bacteria. This paper presents some experimental results as well as the clinical observation of surgical infections with colistin.

### Experiment on Antibacterial Activity

#### Materials

Colistin was used 500,000 units (Lot No. 39) supplied by the discoverer, and the test organisms were *B. coli communis*, *B. paracoli* and *B. pyocyaneus* offered from Bacteriological Laboratory, Tokyo University and gram negative bacteria isolated from the patients in ours.

#### Methods and Results

##### 1. Antibacterial test

Antibacterial activity was determined by the dilution method. One oese of each strain, incubated on the bouillon medium for 24 hours, was inoculated to 3 cc. of bouillon containing colistins at various levels, maintaining at 37°C for 24 hours. The activity was measured according to the inhibitory concentrations against these diluted organisms for 24 hours. The bouillon medium was usually composed of beef extract 0.5%, peptone 1% and sodium chloride 0.5% at pH 7.2. Colistin was samely effective to *B. coli communis*, *B. coli acidi lactici* and *B. para-coli* and next to *Aerobacter aerogenes* 327, *B. coli communior* and *B. pyocyaneus* in order (Table 1).

After 4 hours' incubation of *B. coli communis* on bouillon, colistins at various levels were allowed to act the bouillon prepared so

as to give the final concentration by 10,000 times for 1.5, 3, 6, 12 and 24 hours, respectively. They were transferred to the agar plate media and incubated for 24 hours. Then, the mode of numbers of bacterial cells was observed as illustrated in Figure 1.

Table 1. Inhibitory concentration against various gram negative bacteria in 24 hours.

Organism (Bacteriological Laboratory, Tokyo University)	Colistin u./cc
<i>B. coli communis</i>	30
<i>B. coli communior</i>	100
<i>Aerobacter aerogenes</i> 327	50
<i>B. acidi lactici</i>	30
<i>B. paracoli</i>	30
<i>B. pyocyaneus</i>	>100

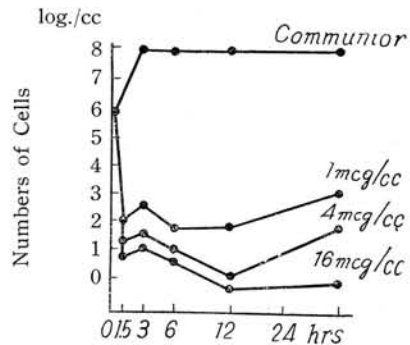


Fig. 1. Influence of colistin to increased numbers of *B. coli communior*.

- 1) Colistin acted bacteriostatically against *B. coli communis* at least at 10 units/cc.
- 2) At 10-40 units/cc, the numbers of organisms tended to increase after 1.5-12 hours.
- 3) At more than 160 units/cc, organisms eventually disappeared, so this was considered to be equal to the final value.

**2. Bacterial amount test**

Using as the stock solution one oese of *B. coli communis*, which was incubated on bouillon for 24 hours, the inhibitory effect of colistin was examined to each bacterial amount from  $10^{-1}/cc$  (numbers about  $2.5 \times 10^7$ ) to  $10^{-8}/cc$  (Figure 2). When inoculated to  $10^{-8}/cc$  it was less than 1.25 units/cc in 16 hours and less than 2.5 units/cc in 24 hours, increasing the inhibitory concentration as the amount became larger. With  $10^{-1}/cc$ , it was less than 10 units/cc in 16 and 24 hours.

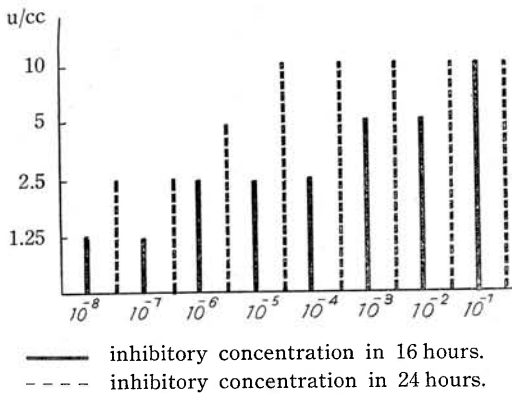


Fig. 2. Inoculated amount of bacteria and inhibitory concentration.

**3. Blood level and its preliminary experiment**

The blood level of colistin was determined using the vertical diffusion method. The preliminary experiment thereof was conducted under the following conditions on medium and its pH:

Medium: The hemi-coagulated agar medium was employed, giving variety to its constituents. Colistins at various levels dissolved in physiological saline solution were diffused to the *B. coli communis* solution finally cocentrated  $10^{-4}/cc$  after 24 hours' incubation.

On the medium No. 1 A the growth zone was indistinct with unfixed boundary, and on No. 1 B decoloration was not uniform. Both No. 2 A and No. 2 B were possible of usage (rf. Table 3). No. 3 and 4 produced small spores, especially No. 4 B showing large colonies and incomplete decoloration.

Influence by pH of medium in the vertical diffusion method: When colistin dissolved was diffused on the media No. 2B at pH 6.6, 6.8, 7.4 and 7.8 respectively, on acidic side the inhibition zones were distinct and completely decolored, while on alkaline side non-decolored zones remained despite of presence

Table 2. Constituents of hemi-coagulated agar media.

Constituents	No. 1A	No. 1B	No. 2A	No. 2B	No. 3A	No. 3B	No. 4A	No. 4B
Peptone	0.2%	0.2%	1%	1%	1%	1%	1%	1%
Dextrin	0.1	0.1	—	—	1	1	1	1
Beef extract	0.1	0.1	1	1	—	—	1	1
NaCl	0.2	0.2	0.5	0.5	0.5	0.3	0.5	0.5
Agar	0.7	0.7	0.7	0.7	0.7	0.5	0.7	0.7
1% NaNO <sub>3</sub>	1	1	1	1	1	1	1	1
0.1% methylene blue	—	4	—	4	—	4	—	4
pH	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6

Table 3. The inhibition zones (mm) on the media No. 2A and No. 2B.

	Control	u/cc					
		80	40	20	10	5	2.5
No. 2A	0	2	1.5	0.5	0	0	0
No. 2B	0	4.5	3	1.85	1	1	0.5

of colonies, so that the inhibition zones must be measured depending upon the existence of colonies on boundary (Table 4).

Blood concentration: In case of examining the level in body fluid, the influence by such as serum or urine comes into problem. Various diluted colistins in distilled water, 0.85% physiological saline solution, serum or

Table 4. The inhibition zone (mm) when varying pH.

pH	Control	u/cc							
		2560	1280	640	320	160	80	40	20
6.6	0*	10.0	9.5	7.0	5.5	6.0	3.75	2.75	2.5
6.8	0	14.0	13.0	10.0	10.0	9.5	6.5	4.0	4.0
7.4	non-decolored	17.5	14.0	12.0	14.0	12.0	17.0		
7.8	non-decolored								

\* Units: mm.

inactivated serum were diffused on the media No. 2B for comparison. The result was indefinite with the serum as it is but definite usually when inactivated it. Thus, the blood concentration was measured using inactivated serum and medium No. 2B.

The blood concentration obtained from the hospitalized patients to our Department, who received intramuscular colistin of 50,000 units/kg, is presented in Figure 3. It showed 45-90 units/cc 1 hour after injection, decreased gradually to about 15 units/cc after 6 hours and became undetected after 12 hours.

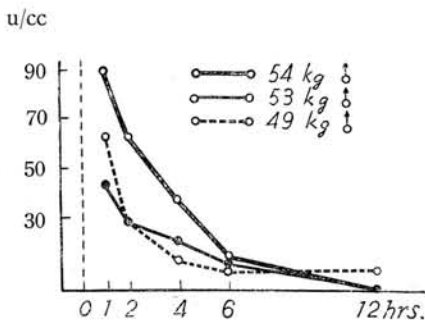


Fig. 3. Inactive blood concentration following 50 units/kg intramuscular injection.

### Clinical Studies

Of the instances treated with colistin in Shimizu Surgical Department, the 5 cases will be introduced as described below. Besides them, colistin in combination with operation or post operation was used for 7 cases consisted of 1 peritonitis due to perforation, 1 intestinal obstruction, 1 hepatic abscess, 1 stomach cancer and 3 brain tumors. Four cases were given 250,000 units once or twice daily by topical instillation, eight 250,000 or

500,000 units four times daily by intramuscular injection, and 500,000 units as a rule for operation.

### Case reports

1. Uchida, 20-year-old woman, with appendical regional peritonitis: One hundred and twenty hours after the outbreak, she admitted to hospital with temperature 37.8°C, pulse 96 and leukocytes 7,400. Following appendectomy the wound was closed primarily, receiving 200,000 units penicillin and 500,000 units colistin intraperitoneally at the operation. Afterwards, the injections, penicillin 50,000 units and colistin 250,000 units four times daily respectively every day, dropped her temperature to 38-39°C in 6-9 days and below 37°C in 10 days after operation. Penicillin amounted to a total dosage of 2,200,000 units and colistin to 10,500,000 units. From the pus at operation *Pseudomonas aeruginosa* were isolated (minimum inhibitory concentration 80 units/cc in 24 hours). There was no evidence of side reaction due to antibiotics. Effectiveness (+).

2. Shimahashi, 55-year-old man, with stomach cancer: November 10, 1950 he entered hospital because of a hen's egg size tumor at upper abdomen. For pre-operation, gastric resection and partial resection of pancreas were performed on November 27, but next day a symptom of peritonitis appeared. The laparotomy tried on November 30 showed necrosis of pancreatic tissues, pus-corpuscle, small gram negative bacteria and diastase by albumin test. Despite of much secretion there was complete suture, and the wound was closed with gauze drain. Thenafter, to check

much secretion colistin was administered to the site 250,000 units twice daily from December 6 to 11 while continuing penicillin medication. As secretion decreased gradually and general conditions got better, he retired hospital on December 12. There was noticed no side reaction due to antibiotics. Effectiveness (+).

3. Tsukada, 30-year-old woman, with rectal cancer: The resection of the rectum was done by sacral approach on December 15, 1950 and further the incision of the sacral wound on December 16, she was given 250,000 units colistin locally and 500,000 units penicillin systemically. Secretion became less and wound improved well without any side effect. Effectiveness (+)

4. Ezaki, 37-year-old man, with perianal abscess: He had an attack of disease on October 13, 1950, admitted to hospital on the 17th day and received resection on the 27th day in the same month. From that day systemical penicillin and topical colistin began to be administered a daily dose of 200,000 units each for successive 5 days. Granulation on wound improved rapidly, and the number of bacteria thereon, which were counted 1030 per one oese at resection, reduced to 16 four days later. From the pus at resection staphylococcus and gram negative bacteria (24 hours' inhibitory concentration 20 units/cc) were found. Side reaction was none. Effectiveness (+).

5. Okada, 62-year-old man, with abdominal fistula post appendicectomy: On November 16, 1949, appendicectomy way made, and

suppurated abdomen formed fistula. At re-operation on November 20, 1950 the wound was sutured after scrapping fistula with instillation of 200,000 units penicillin. For subsequent every 5 days systemical penicillin of 200,000 units and colistin of 250,000 units into the wound were administered twice daily. Colistin totaling 2,750,000 units failed to produce satisfactory effect without any side reaction. Effectiveness (+).

### Conclusion

1. Colistin is bacteriostatic at least at over 10 units/cc and bactericidal at over 16 units/cc against *B. coli communis*. Its minimum inhibitory concentrations after 24 hours are 30, 30, 30, 50, 100 or more than 100 units/cc against gram negative bacteria; *B. coli communis*, *B. acidi lactici*, *B. para-coli*, *Aerobacter aerogenes* 327, *B. coli communior* or *B. pyocyaneus*, respectively.

2. In order to maintain effective blood level against *B. coli communis* by intramuscular injection, at least 50,000 units/kg of colistin must be administered as a single dose 4-6 times per day. The patients tolerated at least to a single dose of colistin without any side effects.

3. Concerning prophylactic or therapeutic effect against infections, the effective cases are 4, the doubtful 5 and the ineffective 3 among 12 cases. For these purposes colistin might be still more effective if used in association with penicillin. No side reactions were experienced locally nor systemically.



## Making Third Tour in South-Eastern Asia

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Lecturer of Showa Medical School (Pediatrics Section)

It might be perhaps in December last year that I unexpectedly received a formal information from the Japanese Pediatrival Society to the effect that the 1st Asian Pediatrival Congress would be held under the auspices of the Malaya Pediatrival Society in Singapore. As I had a reminiscence of taking advantage of General Hospital there to be allotted to the assembly hall as a part of our laboratories during the war times, and was one of the members of the Japanese Pediatrival Society having deepest relation with the coming Congress in the past I had strong wishes for participation, availing myself of this chance to see personally present situation of medical education and hygiene in South-eastern Asian countries. It was happily decided for me to participate as one of Japanese delegates on the recommendation of the Society, and thus I was given third opportunity to visit South-eastern Asia.

The session of the Congress lasted for five days from 26th May to 30th. The Journey in a short period of three weeks in which I visited firstly Loochoo, then Hongkong, Bangkok, Malaya, Java, Sumatora and other territories, was chiefly due to the fact that I could obtain visa from Indonesian Government in only two days by means of valuable advice and cooperation of medical students in Tokyo sent to Japan from Indonesia with whom I was always on intimate terms through the International Medical Association. It might probably be the first instance for Japanese physicians that I could get permission for tour in Indonesia in such short period.

### Outlook of 1st Asian Pediatrival Congress

The Congress opened in auditorium of General Hospital attached to Malaya Univ. on

26th May was attended by delegates from the Societies in more than twenty countries, including participants from 18 countries in South-eastern Asia, observers from Switzerland, America, and by resident delegates of respective countries (ambassadors and ministers). They sat together in the hall decorated with national flags and the Congress was opened for five days until 30th by the opening address of Chief Minister of Singapore. All varieties of countenance and costume seen there aroused an atmosphere different from that in internal congresses, and I was strained in the first international congress I had ever attended. Just then the Asiatic Olympiad was in progress in Tokyo, and so whenever delegates sat together, their talks were focused upon proceeding of the games rather than upon themes of the meetings. There were from two to seven delegates from each country, and presence of Professor Funconie of Türich University in the capacity of the honorary lecturer from the opening of the meetings contributed much to the internationality of the Congress. I thought that it was especially one of the great results throughout the Congress for Japanese delegates to have heard personally a lecture of this professor who had been introduced either by text-books or by professors in all fields of the science. All lectures were made in English and separately in three halls. Ten or twenty minutes were apportioned to each lecture under selected chairmen and vice-chairmen, and after four or five lectures were over, there were additional interpellations and discussions by persons twice or treble as many as the lecturers. The discussions took a hot aspect unimaginable in the internal congress.

In a short period of five days 51 subjects

were published and a symposium on baby nutrition problem took place. As to these, impressive items would be cited as follows.

The first day's program of the Congress centered about problem of the infantile tuberculosis. "Tuberculosis encephalopathy with and without meningitis" published by Dr. P. M. Udanis of India showed many sick-instances and invited our attention to the presence of tuberculosis encephalopathy without meningitis.



Writer photographed at the Institute for Medical Research, Kuala Lumpur.

On the second day considerations were bestowed upon both the clinic and technique of infantile nutrition. Professor Funconie's "Metabolic disorders and malnutrition" indicated the relation of hypophysis cerebri with malnutrition systematically and cogently, and this favorite side of his research aroused a great emotion among auditors. In the meanwhile "Kwashiorkor" reported by Dr. Poey Seng Hin of Indonesia was one of undernutrition approximate to the disease due to excess of flour in the diet, and he tried to make detailed investigation on many sick-instances. The abundant content of his lecture appealed to me. In the afternoon of the day infantile surgery was debated. "Surgical ascariasis" reported by Dr. A. E. Desa of India denoted an interesting sick-instance.

In the morning of the third day blood and rheumatic diseases were discussed. Hot discussions were made of spleen-extraction in the time of thalassaemia and haemoglobinopathy.

Themes of the parasites and chiefly of virus diseases were taken up respectively in the afternoon of the same day and in the morning of the fourth day. On these occasions Japanese delegates expressed their own opinions. Inquiries from more than ten persons were made of treatment of influenza A 57, detailed method of using Pans No. 610 for Japanese summer encephalic's polio in Japan. After these publications discussions were recommenced about medico surgical and child health service problems. From 5 o'clock p.m. publications were made chiefly of acute infectious diseases, epidemic hepatitis and typhoid diseases. In the morning of the final and fifth day reports were made of liver diseases, especially of liver cirrhosis in infancy and all varieties of jaundice, and then there were reports concerning acute infectious diseases, diphtheria, colitis, infantile diarrhea treated by neomycin, and megaloblastic anemia. Fifty five reports in all were disposed of orderly and interestingly in the period of five days, and more discussions than themes could be finished, tactfully, as expected, under the good leadership of chairmen and vice-chairmen. All attendances recognized that the



Nurse Hostel, Malaya University.

above-mentioned results were mainly due to assiduous efforts the Pediatrical Society of Singapore concerned, though few in the number, had paid to the preparation of the 1st Congress.

#### As to Pediatrical Hospitals in South-eastern Countries

During this tour I was blessed with chances

to call on paediatric schoolrooms of five universities, and I found remarkable progress in their accommodations in comparison with those I had visited five years ago. For instance, there were established in Bangkok the National Paediatric Hospital, having more than 300 beds and about 20 consultation rooms. This magnificent hospital of course furnished perfect nursing and diet, and it had great rooms partitioned with glasses between beds, and also it had milk preparation rooms and recreation rooms fully equipped. I found there babies being carried to perfectly isolated lactation rooms and suckled by mothers. The Paediatric Hospital attached to Malaya University which was said to be founded by the will of a millionaire had about 300 beds and the Paediatric Hospital accessory to Djakarta University also was furnished with as many beds. They were both packed to their utmost capacity, and had such a prosperous aspect as a physician had to diagnose more than 100 baby outpatients in the morning. There were government hospitals in Penang of Malaya, Kuala Lumpur and Jeohol, where paediatric departments were provided with about 100 beds. As the number of physicians in the above-mentioned countries was further few than in Japan, there were very few paediatric specialists even in big cities, and consequently each country seemed to give great enthusiasm towards the establishment of paediatric hospitals. Among patients in hospitals most of them were mainly afflicted with infantile diarrhoea, exsiccosis resulting from marasmus, inflammation of the intestines, pneumonia, all descriptions of meningitis, encephalitis, far advanced tuberculosis, liver diseases, and contagious diseases such as diphtheria and tetanus. Especially the frequency of tetanus in newly born babies was impressive to me. I was indicated with three instances of patients attacked by gangrenous stomatitis in Djakarta University, who were all in far advanced stage despite of many doses of penicillin, and whose cheeks turned to be mortified. I thought it strange to find many cases of diphtheria in hot territories, but it seemed to be due to the lack of the preventive inoculation. The type of the disease was analogous to that in Japan,

and the diseases of malignant and laryngeal type were found. There were instances of mixed vaccine of diphtheria, whooping cough and tetanus being inoculated in cities, and among encephalitis Japanese encephalitis seemed to be prevalent.

All above mentioned universities had connection with some universities in America and obtained material helps from them. Most of aborigines were sent to some universities in America, and after they returned, they entered the staff. Thus almost all establishments were managed by native people, and compared with what it was five years ago, this improved greatly.

In Thailand, Indonesia and everywhere, not to mention Malaya, hospital staffs could speak English as much fluently as their own tongue, and I accepted their neat explanation and guidance with envy and admiration. In these hospitals the therapy and inspection of all kinds of diseases were near to the first rank, and antibiotics, adrenotrophic hormone and blood transfusion were used correctly and boldly. Especially in administering rehydration to patients from infantile diarrhoea and marasmus there was no operation, excepting that the limbs were fixed upon 'siene', and sight of difficult drip phlebotomy thus being applied to several patients impressed me. In-patients had appearances similar to those found in Japan about twenty years ago. In central hospitals there was the latest therapy in practice. Most of hospitals had milk preparation rooms completely equipped, and in Djakarta University Hospital those were magnificent, where more than ten persons served, and indicative of decent milk factory.

#### Calling on Dr. Utojo

I heard from the Japanese Embassy that there served in the Internal Medicine Department of Djakarta University Dr. Utojo, who graduated from Kyoto University and studied in the internal medicine there, and visited his own residence. He married with a Japanese woman from Kyoto and had a boy. As he studied in Kyoto University after completing the course there, he was a fluent speaker of Japanese and had a detailed knowledge of

things in Japan. Dwelling upon the hygienic condition of Indonesia, he pointed out that the Indonesian Government were applying for foreign physicians (chiefly from Germany, Italy and Swiss) for the sake of supplementing absolute shortage of them and that Japanese

physicians of ability would be given the same treatment as foreign ones. But it was understood that they must serve in government medical establishments for the first three years and then they would be given a license for the medical practitioner.

### As to the surgical field of Japan

The leading part of the medical science of course lies in the surgery. The Surgical Society of Japan contains approximately 9,000 members and has already reached the international level in its substance. Several topics of the meetings held in April this year are cited as follows.

Keeping pace with recent development in the heart surgery, results of exogenous circulation, especially of artificial heart and lung machine have improved greatly. The problem concerning balance of blood absorption and transmission, and the subject as to flux have generally been solved, and most of these theories have been turned to practice on the clinic. Thus specialists have gone with the research on random stoppage of cardiac motion. Random stoppage of cardiac motion in the operation under direct seeing can decrease the quantity of bleeding. Accordingly this can eliminate troubles resulting from voluminous blood-transfusion and solve consequent problems. There are consequently easy manipulations of the operation. Methods of potassium citrate (by Dr. Kimoto in the Surgical Department of Tokyo Univ.), acetylcholine (by Keio Univ., Tokyo Women's Medical Col. and Kanazawa Univ.) and A.T.P. (by Nagoya Univ.) being injected to the muscular origin of aorta by way of drugs causing heart stoppage have been published in the meetings of the Surgical Society of Japan this year.

Further research must be made of, which of them has superior effect, or of final results of the method of heart resuscitation.

At any rate the application of the artificial heart and lung apparatus has not yet brought

about 100 percent success. Cases of death produced by lung hazards after the operation and acidosis (by Osaka Univ.) resulting from excessive use of bubble elimination medicine, air embolism and superfluous supply of oxygen have been indicated in present reports.

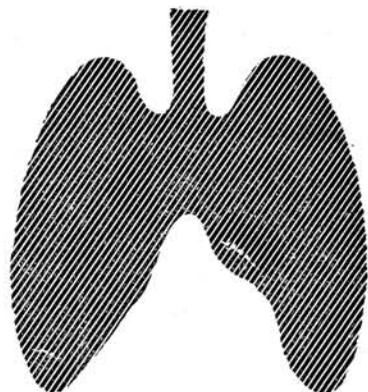
Professor Iguchi of Kyushu Univ. has pointed out the advantage of alcoholized blood vessels being disposed of in chrome salt by way of grafting flakes in the transplantation of blood vessels.

Especially the efficiency of the apparatus of piecing up blood vessels initiated by him has invited attention. This machine makes it possible to join together blood vessels of more than 3 mm. in diameter. Details of the apparatus in question made in Soviet Russia have been introduced by Professor Kimoto of Tokyo Univ. This is very elaborate, and makes it possible to piece up blood vessels as fine as diameter of 2.5 mm. The possibility of joining together such thin blood vessels will bring about remarkable revolution not only in the domain of angiological surgery, but in the operation of far advanced tumor.

Delivering a lecture on "some new problems as to the newly established operating-room,—especially effects of the personnel in the room upon investigation of electroencephalogram, and education of the operation by means of colour television", Professor Kazuo Takeuchi of Tokyo Univ. has indicated that causes of hindrance for the electric measurement are due to the superfluous staff in the operating room, and thus he has given out a noticeable question as to the numerous personnel necessary for the operation of heart.



# DRIVE AWAY TUBERCULOSIS



WITH

LATEST ANTI-T.B. AGENT

## NEO-ISCOTIN

(Sodium Isonicotinyl Hydrazide Methanesulfonate)

*It's superior therapeutic activity has been reported at the symposium on "Prevention from Relapse of T.B. with Hydrazide and it's derivatives," held in 1958 under the auspices of the Japanese Association for T.B. According to this report, they succeeded to reduce the number of relapse-patients to one sixth of that in the past.*

*Many superior characteristics of Neo-Iscotin are as below:*

- *Longer lasting concentration in the blood.*
- *Most suitable for a treatment with a large dosage.*
- *Scarcely any side reaction and formation of resistant strain.*
- *Easy to take a dosage.*

*Also reported at the symposium that they could get good results in treating with a large dosage of Neo-Iscotin for serious T.B. patients.*

(Catalogue on request)

Powder; 25gm., 100gm., 500gm., kg, 10kgs.  
Tablet (100mg.); 50's, 100's, 500's, 1,000's



### DAIICHI SEIYAKU CO., LTD.

3-Chome, Edobashi, Nihonbashi, Chuo-ku, Tokyo, Japan

## Roentgenography and Contrast Media

Seiichiro SEKI, M.D.

*Technical Officer to Ministry of Health and Welfare of Japan*

There are bronchography, cholecystography, pyelography, angiography and so forth for the roentgenography applied in Japan, and there are also various specimens of contrast media used for their respective purposes. The myelography was originated by Dr. Sicard Forestier using lipiodol in 1923, and in Japan bronchography was introduced to the clinic immediately after this technique was initiated in 1925. And the cholecystography invented by Dr. Graham Cole in 1924 was also immediately introduced to the Japanese roentgenology. In addition the lienography using thorium dioxide sol was invented in Japan in 1929. But, as there have been a few cases of the cholecystic diseases in our country, the cholecystography has not so much spread. Consequently it was only in 1950 that Japan was self-supplied by the contrast media for this radiography in the form of Phentetiothalein sodium. On the contrary, Sugiuron (Disodium methyl-3.5 diiodopyridone-2.6 dicarboxylate) was already completed in 1932 for the pyelography, and it marked a remarkable progress in the diagnosis of urinary system. At present the pervasion of the roentgenography in this field means a common sense to the Japanese medical world, and as to the drugs used for this purpose we do not depend on their import from foreign countries. In 1951 Pyraceton (Chlorinate diethanolamine of 3.5 diiodo-4-pyridone-N-acetic acid) was manufactured in Japan, and then Urokolin (Chlorinate natorium of 3-acetylamio-2-4-6-triiodo benzoic acid) was produced in 1952 for the sake of urinography. Further use of this medicine has been extended to the angiography.

Apart from the above mentioned radiographies, the technique, of which the efficiency is now most highly estimated in Japan, and which contributes much to routine diagnosis, is the bronchography. Since this method of

diagnosis was introduced to Japan, it has undergone the climax of vogue two times. The first opportunity took place soon after the method in question was introduced, and now is the second chance.

For the first time the method was conducted by means of iodoil (Moliiodol), but at present mainly has been manipulated by using Urokolin oily suspension. As the bronchography in its primary stage was simply directed towards observation of morphological structure of the bronchea, and the surgical therapy for pulmonary tuberculosis had not made much progress, there was not fully popularized this method. The fact that some quantity of iodided oil remained in the lung for long time after iodided oil had once been injected there, stood in the way of X-ray diagnosis after the operation, and gave considerable hindrance to the development of this method. According to the author's experiment, the iodided oil has remained on the surface of alveoli of the lung, forming thin stratum, for one year after the iodided oil was injected into the bronchea.

The chief object of therapy for pulmonary tuberculosis in Japan can be now found in combined effects of shortening treatment days by focal resection and preventing the relapse, and thus it is to improve the therapeutical efficiency. So that there have been frequent cases of the lung operation. Keeping pace with this tendency, instances of bronchography have been increasing yearly. Cases of the surgical operation administered to the lung in the National Sanatoria in 1952 were 2.2% of the number of patients, but increased to 17.3% in 1955. Still more for the daily average of 57,550 patients, 50,573 cases were mainly bronchographically radiographed during the same year. These instances endorse the above described conclusion. One reason for the

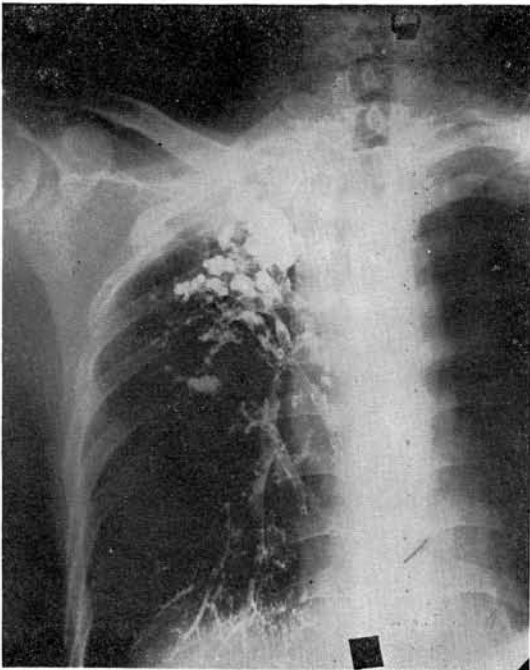
present spread of bronchography in Japan can be chiefly looked for in the possibility of repeated X-ray diagnosis of the lung due to the fact that the contrast media does not radiologically remain in the alveoli of lung. Additional combination of Moliadol sulfamine bringing about easy expectoration has been initiated. In addition it is testified by experiment that the Urokolin (3-acetylamino-2-4-6-toriiodo-benzoic acid) compounded into vegetable oil at the rate of 60% is found effective and adequate for the bronchography, and it improves the further prevalence of this technique.

According to experiment made by the author, the Urokolin, even though it may enter the digestive system, brings almost no hazard to the stomach and the intestines, and possesses no poison, and it is after all excreted through the urinary system. When the Urokolin has been injected into the bronchea, it is expectorated within 48 hours in 85% of cases administered, and especially within only 8 hours in early cases to the extent of its remains being unconfirmed in the lung radio-

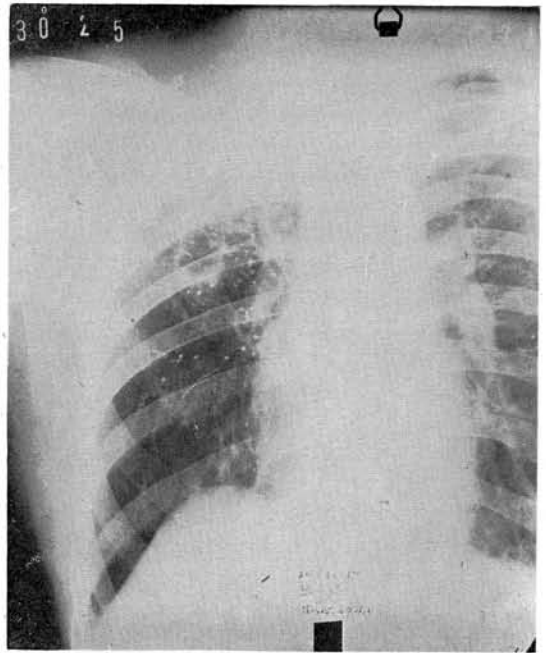
graphically.

In instances where the oleous Urokolin has been injected into the lung for a week at the longest, the presence of the medicine is affirmed in the lung. This phenomenon simply means the roentgenographed reflex against foreign body, and gives no obstacle to the radio-diagnosis. It is verified by experiment that, even when the Urokolin injected into animals cannot produce the roentgenogram, the medicine remains on the surface of alveolus of lung, forming thin oil stratum. But iodine cannot be isolated from the oil stratum chemically. The stratum is yet apparent for three months after the Urokolin has been injected, but no effect cannot be found on the alveolus of lung. Reference is made to Fig. 1 and Fig. 2.

When this medicine has been administered to patients by injection apparatus of 2-4cc in the bronchography, they continue to respire calmly, and thus the medicine can be transmitted evenly to the end of the minute bronchea as described in the third figure. The drug may be applied not only to the diagnosis



A: Immediately after inoculation



B: 24 hours after inoculation

Fig. 1. Bronchography with Urokolin oily

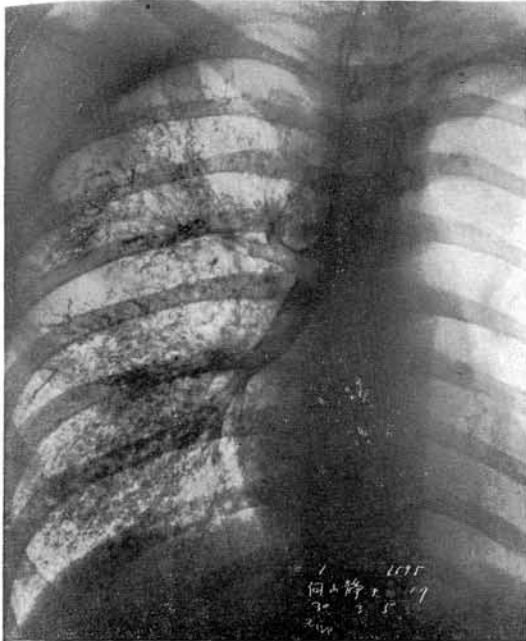


Fig. 2. Immediately after inoculation of 4 c/c Urokolon Oily shows not only bronchial structure, but the fein structure of alveolus.

of divarication of bronchea, condition of the wall of great bronchea, bronchiostenosis, but also to the azinography.

**All varieties of contrast media manufactured and used clinically in Japan**

**MOLIODOL** 5%, 20%, 40%

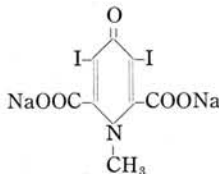
Iodol compounded in vegetal oil organically.

Date of Permission to be manufactured. August, 1931.

Scope of Application, Radiography of spinal cord, bronchea, vesica and womb.

**SUGIURON** 10 g in 30 cc

Disodium 1-methyl-3,5 diiodo-4-pyridone-2,6 dicarboxylate (U.S.P. Sodium Iodomethamate)

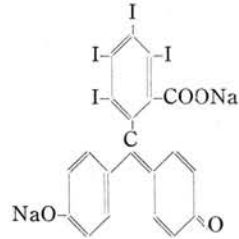


Date of permission to be manufactured. December, 1932.

Scope of Application. Radiography of pelvis of the kidney, kidney, ureter, vesica and urethra.

**PHENTETIOTHALEIN SODIUM** 'Daiichi',

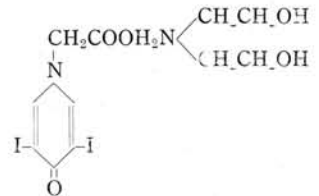
2.5 g in a tube, Phenoltetraiodophthalein Sodium. (chemical term)



Date of Permission to be manufactured. December, 1950.

Scope of Application. Cholecystography, function test of the liver.

**PYRACETON** 35%, 70%



Chlorinate diethanolamine of 3,5-Diiodo-4-Pyridono-N-acetic acid

Date of Permission to be manufactured. April, 1951.

Scope of Application. 35%; Radiography of kidney, pelvis of the kidney, ureter, vesica and excretory urethras. Cerebroangiography, general angiography. 70%; Cardioangiography.

**PYRACETON-C** 60%

Pyruceon 60% solution contains C.M.C. 3% and J. P. hydrochloric procaine 0.5%.

Date of Permission to be manufactured. October, 1953.

Scope of Application. Radiography of bronchea, womb and urethra.

**BARYAN**

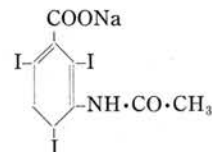
Barium Sulfate (Baryan, micabarium)

The main compound is barium sulfate

Date of Permission to be manufactured. September, 1940.

Scope of Application. Radiography of stomach, esophagus, small intestine, large intestine, rectum and digestive organs.

**UROKOLIN** 30%, 60%



Chlorinate natorium of 3-Acetylamino,-2,4,6-triiodobenzoic acid

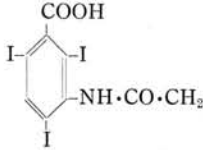


Date of Permission to be manufactured. 30%; May, 1952, 70%; December, 1953.

Scope of Application 30%; Radiography of kidney, pelvis of the kidney, ureter, vesica, excretory and retrograde organs. Cerebroangiography, general angiography.

60%; Radiography of kidney, pelvis of the kidney, ureter, vesica and excretory organs. Radiography of abdominal aorta. Radiography of pelvis and vein.

UROKOLIN OILY SUSPENSION 60%.



3-Acetylamino 2·4·6 triiodobenzoic acid

Date of Permission to be manufactured. November, 1954.

Scope of Application. Bronchography

Most of contrast medias used in Japan at present are produced by Daiichi Seiyaku K.K. (Daiichi pharmaceutical Company Ltd)



## *Eisai Theophylline Preparations*

### **Cardiac Diuretic**

#### **Neophyllin**

Theophylline Ethylenediamine

#### **Neophyllin M**

Dihydroxypropyl Theophylline

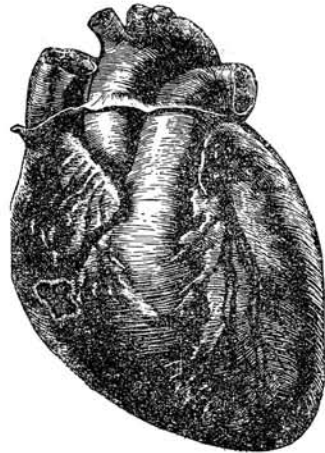
#### **Theocolin**

Theophylline Choline

### **Antasthmatic**

#### **Asthphyllin**

Neophyllin M, Papaverine  
HCl, Noscaphine, Ephedrine HCl,  
Diphenhydramine HCl.



## **Eisai Co., Ltd.**

Bunkyo-ku, Tokyo

## Introduction of Hydronsan

Seiichiro SEKI, M.D.

In Japan there are almost same descriptions of therapeutic drug for pulmonary tuberculosis as those in other foreign countries. SM, PAS and INAH including its Compounds are principal ones, and Pyrazinamid, Biomycin, and recently Kanamycin are used. Two or three of these drugs are used together at the same time, and there are few cases of the specified drug being used separately. For instance, out of 91,357 patients treated at public expense (in March, 1958) 89,293 cases (98%) were given so-called combined treatment, but only 2,064 ones (2%) received treatment by the specified drugs, and most of them (1,161 persons) were subject to the exclusive remedy by INAH, and its Compounds. In the meanwhile about 4,980 kg. of Dihydrostreptomycin, 930 kg. of SM, 3.4 tons of INAH, 128 tons of PASCa and 32 tons of PASNa have been manufactured for antituberculosis.

But one of slightly peculiar phenomena to be found in Japan is the frequent use of INAH Compound which has been produced for the sake of decreasing subsidiary ill effects of INAH. It is not to check the continuous use of INAH in order to improve the efficiency of therapy. For example, the dosage of INAH used in the National Sanatoria in April, 1958 averaged 0.29 gr. per a patient daily, the number of patients administered averaging 37,072 cases daily. Compared with the above-mentioned, the dosage of INAH Compound averaged 0.9 gr. per a patient, the number of patients amounting to 6,492 cases daily on the average. Thus the general tendency has endorsed this unique phenomenon.

Theoretically one of therapeutic agents for tuberculosis administered in this way lies in extermination of the disease by eradicating parasite from the host in view of the drug-parasite-relationship. But it can be understood fully from recent development of chemotherapeutics for pulmonary tuberculosis that it is impossible for parasites to be removed from the host entirely, as above mentioned, by dint of the drug.

The necessity of introducing this new theory to the therapy is hoped for in the present chemotherapy. In addition to INAH acting upon the bacteriostatic, it has the special property of being easily manufactured into the compound together with other matters. Accordingly, if the chemical matters turns to be the compound, which has affinity with specified histology and acts strongly upon the viscera having important relation with life, or which has the virtue for maintaining efficacious concentration of INAH in blood for long time and has special properties advantageous for the therapy, the virtue of these drugs by way of antituberculosis medicine is not only effective in the parasite-drug relationship, but also in the host-drug relationship, that is to say, from the standpoint of the new theory.

When present chemotherapy of tuberculosis reaches a deadlock in the drug-parasite relationship, searching for a new way, and the host-parasite relationship is given serious considerations, nothing more than appearance of the antituberculosis drug viewed from the host-drug-relationship must be congratulated.

The experiment testifies universally that the sodium glucuronate improves the detoxicant action for liver, and it is also common sense from the biological standpoint that the nature of this antidotal action in itself is the detoxicant action contained in this thing.

It is noticeable that sodium glucuronate isonicotinyl hydrazone (commodity name; Hydronsan), a new compound formed by chemical combination of glucuronic acid and INAH, has been favorably used in Japan for the drug against tuberculosis. The effective property of Hydronsan for the anti-tuberculosis medicine becomes apparent after satisfactory results have been obtained from the treatment of tuberculosis made by specialists in the Japanese National Sanatoria.

Hydronsan are produced by Chugai Seiyaku K.K. (Chugai Pharmaceutical Company) in Japan.

## Alinamin Administration in Pulmonary Tuberculosis

Yuichi YAMAMURA, Katsuhiko OGURA, Chozo HAYASHI,  
Mie WATANABE, Shiro IMAZU, Masatami YAMAGUCHI,  
Yae OGAWA and Haruo YAKUSHIJI

*National Sanatorium, Toneyama Hospital*

It was first advocated by Dr. Watanabe, director of the Toneyama Hospital, that a state of vitamin B<sub>1</sub> (abbr. B<sub>1</sub>) is present in tuberculosis and clinically B<sub>1</sub> administration is required in the treatment of tuberculosis. The administration of B<sub>1</sub> in tuberculosis cases showing increased urochromogen excretion in the urine results in a marked reduction and it was shown than in cases where urochromogen is experimentally increased by administration of tryptophan the administration of B<sub>1</sub> will promptly bring about a decrease. It was suggested from these facts that B<sub>1</sub> plays an important role in the treatment of tuberculosis. It was shown later by Fujino, under the supervision of Watanabe, that urinary urobilin content decreases with administration of B<sub>1</sub> in tuberculosis patients and Yamanaka has reported that urinary urochromogen and urobilin decrease with administration of B<sub>1</sub> in tuberculosis and the decrease is greater when B<sub>1</sub> is given together with anthranilic acid or nicotinic acid.

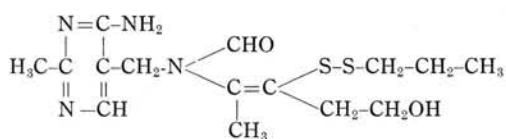
It is said that in tuberculosis, the more serious the condition, the smaller is the quantity of B<sub>1</sub> excreted (Iwasaki, Sugiura) and the urinary excretion of B<sub>1</sub> following loading decreases parallel with severity of the disease.

Yamamura and his associates have recently measured the free and ester forms of B<sub>1</sub> in whole blood in 16 moderately ill pulmonary tuberculosis patients and found that there is no significant difference from the values in normal healthy controls. It was found that when administration of B<sub>1</sub> was totally suppressed during the rainy and summer months and only the food prepared in the hospital given, the blood B<sub>1</sub> level dropped markedly. The urinary B<sub>1</sub> was measured following loading with B<sub>1</sub> in 4 tuberculosis patients and

it was found that in the 2 cases with manifestations of beriberi, there was a greater excretion in the urine but the blood B<sub>1</sub> level was lower compared to the other 2 cases and it was suggested that there was a metabolic disturbance of B<sub>1</sub> in some tuberculosis cases.

As stated above, the relationship between B<sub>1</sub> and tuberculosis has been noted since quite some time ago. In this study the results of administering TPD (Thiamine propyl disulfide-Alinamin) made available by the Takeda Pharmaceutical Industries, Ltd., in tuberculosis patients with manifestations of beriberi are presented. A group of patients in which B<sub>1</sub> was totally withheld and a group in which a set quantity of ordinary B<sub>1</sub> was given were taken as controls. The period of the study covered the rainy and summer months.

TPD is a derivative of B<sub>1</sub> recently synthesized by Fujiwara, Matsukawa *et al.* and possesses the following chemical structure.



It is stated that absorption from the intestines, rise in blood B<sub>1</sub> concentration and clinical effect, is superior to B<sub>1</sub>.

### Experimental Method

Moderately ill tuberculosis patients hospitalized in the Toneyama hospital were divided into following 3 groups of 10 patients each (5 male, 5 female). Group 1 consisted of patients given 10 mg. TPD (Thiamine propyl disulfide) a day orally. Group 2 was given 10 mg. B<sub>1</sub> every day orally and in Group 3, B<sub>1</sub> preparations were withheld completely and 1 gm. potato starch administered as a placebo.

Administration was in three divided doses after meals. The period of the study was from June to July, 1953. The beriberi manifestations were examined prior to and after administration by the method of Omori. That is, palpitations, dyspnea, abnormal pulse, accentuation of the 2nd pulmonic sound, drop in diastolic pressure, auscultation of the crural sound, dermatographia were examined as circulatory disturbances (C symptoms) and headache, dizziness, lassitude especially of the legs, numbness, exaggerated or weak knee reflex, tenderness of the calf muscles, hyperesthesia as neural disturbances (N symptoms) and edema of the legs examined for nutritional disturbances of the tissues (O symptoms).

Blood was also collected prior to, 15 days after commencement of and 24 hours after termination of administration, and the free

and ester form B<sub>1</sub> measured by the Bromcyanide method.

## Experimental Results

### 1. Effect on Beriberi Manifestations

As can be seen in Table 1, there was improvement in the palpitations, lassitude and tenderness of the calf muscles in a large number of cases in both the TPD and B<sub>1</sub> groups and there was a greater number in the TPD group in which the abnormal 2nd pulmonic sound and knee reflex disappeared compared to the B<sub>1</sub> group. It is worthy of note to observe that there was disappearance of objective symptoms unrelated to the remarks of the patients. In general, a greater number of cases showing alleviation of beriberi manifestations were found in the TPD group compared to the B<sub>1</sub> group. There

Table 1.

Classification of condition	Symptom	TPD (10 mg.)				B <sub>1</sub> (10 mg.)				Control			
		Improved	Without symptom*	Ineffective	Exacerbated	Improved	Without symptom*	Ineffective	Exacerbated	Improved	Without symptom*	Ineffective	Exacerbated
Circulatory disturbance (C)	Palpitations	5	2	3	0	4	3	2	1	1	5	3	1
	Dyspnea	3	5	1	1	2	6	2	0	2	6	1	1
	Abnormal pulse	0	10	0	0	0	10	0	0	0	9	1	0
	Accentuation of the 2nd pulmonic sound	4	1	5	0	2	3	5	0	0	3	7	0
	Drop in diastolic pressure	3	7	0	0	2	7	0	1	0	5	2	3
	Auscultation of the crural sound	2	8	0	0	0	10	0	0	0	10	0	0
	Dermatographia	1	6	0	3	1	6	1	2	0	6	3	1
Neurological disturbance (N)	Headache	3	5	1	1	2	5	2	1	1	4	3	2
	Dizziness	2	6	1	1	2	6	1	1	2	5	0	3
	Lassitude	7	3	0	0	4	3	3	0	0	3	5	2
	Numbness	0	7	2	1	0	8	1	1	0	4	4	2
	Lassitude of the legs	5	2	2	1	5	2	1	2	1	6	1	2
	Abnormal knee reflex	6	2	2	0	2	3	5	0	1	0	7	2
	Tenderness of the calf muscles	7	1	2	0	5	1	3	1	1	2	4	3
	Hyperesthesia	1	9	0	0	1	9	0	0	0	9	0	1
Edema	0	10	0	0	0	10	0	0	0	10	0	0	
Total	49	84	19	8	32	92	26	10	9	87	41	23	

\* means the symptom is not present from the beginning.

was either no charge or a worsening of the symptoms in the majority of the patients in the control group in which B<sub>1</sub> was withheld.

## 2. Blood Concentration of B<sub>1</sub>

As shown in Table 2, there was a marked rise in total B<sub>1</sub> concentration of the blood following administration in the TPD group (measured in more than 10 patients) and it reaches a value approximately twice the original level and even 24 hours after

administration is terminated, a high level is maintained. That is, the average B<sub>1</sub> level was 5.7 $\gamma$ /dl, 10.33 $\gamma$ /dl and 8.56 $\gamma$ /dl prior to, during and after termination of administration respectively. Statistically by the t test, the difference between the preadministration value and the value during administration is highly significant (P=less than 0.01) and the difference in values between pre- and postadministration is also significant (P=0.01-0.02). The increase was mostly in the ester form

Table 2. Blood B<sub>1</sub> Content of T. P. D. Administration Group ( $\gamma\%$ )  
(period: 1 month)

	Before administration			15 days after starting treatment			24 hours aft. termination of administration		
	F	E	T	F	E	T	F	E	T
S. T. 43 ♂	2.4	0.6	3.0	2.6	5.8	8.4	2.0	7.0	9.0
F. M. 38 ♂	1.0	4.2	5.2	0.6	7.8	8.4	0.8	7.0	7.8
M. H. 32 ♂	1.6	6.2	7.8	1.0	7.8	8.8	1.0	5.0	6.0
K. S. 53 ♂	1.2	4.8	6.0	2.8	8.6	11.4	2.8	5.6	8.4
T. K. 39 ♂	3.6	3.0	6.6	1.2	9.6	10.8	1.2	8.4	9.6
N. E. 20 ♀	1.2	6.4	6.6	1.6	6.8	8.4	0.8	5.2	6.0
S. Y. 32 ♀	0.6	4.8	5.4	2.0	6.4	8.4	0.6	7.8	8.4
B. S. 25 ♀	1.3	5.7	7.0	4.7	11.5	16.2	2.0	10.6	12.6
H. A. ♀	2.4	2.4	4.8	2.4	13.5	15.9	0.4	7.4	7.8
I. M. 26 ♀	1.6	3.8	5.4	0.8	5.8	6.6	0.4	9.6	10.0
Average	1.69	4.09	5.78	1.97	8.36	10.33	1.20	7.36	8.56

F=Free B<sub>1</sub>  
E=B<sub>1</sub> in ester form  
T=Total B<sub>1</sub>

Table 3. Blood B<sub>1</sub> Content of Ordinary B<sub>1</sub> Administration Group ( $\gamma\%$ )  
(period: 1 month)

	Before administration			15 days after starting treatment			24 hours aft. termination of administration		
	F	E	T	F	E	T	F	E	T
M. M. 29 ♂	1.0	9.2	10.2	2.0	7.0	9.0	0.8	9.4	10.2
K. K. 34 ♂	1.2	3.6	4.8	1.2	8.8	10.0	1.4	5.0	6.4
H. M. 36 ♂	1.6	4.4	6.0	0.8	7.6	8.4	0.4	5.6	6.0
M. S. 38 ♂	1.2	4.2	5.4	1.6	6.2	7.8	1.6	5.8	7.4
M. S. 19 ♂	4.2	7.2	11.4	0.8	7.0	7.8	1.4	6.4	7.8
N. K. 23 ♀	1.1	7.3	8.4	1.2	8.4	9.6	0.7	7.3	8.0
K. Y. 25 ♀	0.6	4.2	4.8	1.6	4.4	6.0	0.6	7.2	7.8
K. A. 30 ♀	0.7	4.8	5.5	2.8	8.0	10.8	0.7	10.1	10.8
S. H. 32 ♀	2.0	1.0	3.0	1.6	5.6	7.2	0.6	7.5	8.1
Average	1.57	5.10	6.61	1.51	7.00	8.51	0.91	7.14	8.06

Table 4. Blood B<sub>1</sub> Content of Control Group ( $\gamma\%$ ) (period: 1 month)

	Before administration			15 days after starting treatment			24 hours aft. termination of administration		
	F	E	T	F	E	T	F	E	T
T. K. 48 ♂	0.8	7.6	8.4	2.0	5.8	7.8	0.6	6.6	7.2
A. S. 50 ♂	1.2	5.4	6.6	0.4	3.2	3.6	2.4	4.4	6.8
U. T. 26 ♂	1.2	5.4	6.6	0.6	4.6	5.2	0.8	4.0	4.8
O. A. 19 ♂	1.0	5.0	6.0	0.5	4.3	4.8	0.6	6.0	6.6
T. K. 50 ♂	0.8	4.0	4.8	0.2	2.8	3.0	0.4	6.2	6.6
U. K. 29 ♀	1.0	5.6	6.6	0.8	4.0	4.8	1.2	7.2	8.4
O. M. 20 ♀	0.7	5.3	6.0	1.0	5.0	6.0	1.2	4.2	5.4
S. S. 23 ♀	0.4	3.8	4.2	0.6	5.4	6.0	0.8	4.0	4.8
M. T. 25 ♀	0.6	4.2	4.8	0.4	2.6	3.0	—	—	—
Average	0.89	5.26	6.15	0.78	4.19	4.91	1.00	5.33	6.33

B<sub>1</sub> and there was little fluctuation in the free form.

In the B<sub>1</sub> group (measured in 9 cases) there is increase in B<sub>1</sub> during and after administration but compared to the TPD group the increase during administration is small (Table 3).

That is, the average B<sub>1</sub> value prior to administration was 6.61  $\gamma$ /dl and became 8.51  $\gamma$ /dl and 8.06  $\gamma$ /dl during and after administration respectively. Examined by the t test, the difference between the values before and during administration is somewhat significant ( $P=0.1-0.05$ ) while there is no significant difference between the pre- and postadministration values ( $P=0.1-0.2$ ). The increase in these cases too was in the ester form and there was little change in the free form.

The results in the group in which B<sub>1</sub> was withheld (measured in 8 cases) are shown in Table 4. The average values before, during and after administration were 6.15  $\gamma$ /dl, 4.91

$\gamma$ /dl and 6.33  $\gamma$ /dl respectively. There was a temporary decrease during administration but the value following termination of administration differs little from the preadministration value and there is little fluctuation in the blood B<sub>1</sub> levels.

### 3. Side Effects

Two male patients in the TPD group complained of anorexia but otherwise there were no side-effects.

### Conclusion

The effect of administering 10 mg. daily of either TPD or Vitamin B<sub>1</sub> over a period of 1 month in pulmonary tuberculosis patients with manifestation of beriberi was observed. It was found that disappearance of the beriberi symptoms and increase in blood B<sub>1</sub> were greater in the TPD administered patients than those given B<sub>1</sub> and when compared with those in which B<sub>1</sub> was completely withheld, the difference was very marked.

## The Place of Trichomycin in the Treatment of Candidiasis

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Since the discovery of penicillin, many antibiotics have played a vital role in combating an extensive range of infectious diseases caused by bacteria, rickettsia and large-size virus. These antibiotics, however, have been found ineffective or inadequate in the treatment of fungous and protozoan infections, and moreover, there have been published many reports that fungous diseases were induced or aggravated by the intensive therapy with these antibiotics.

Trichomycin, discovered in 1952 by Dr. S. Hosoya and his collaborators of Tokyo University, is a new antibiotic derived from *Streptomyces hachijoensis* and has been demonstrated to possess quite a potent antifungal and antiprotozoan activities in vitro and in vivo.

### Physical and Chemical Properties

Trichomycin is a yellow, non-crystalline powder, decomposing at about 150°C. with discoloration. It is a polyene antibiotic composed of carbon, hydrogen, nitrogen and oxygen, and ultraviolet spectrum suggests a conjugated heptaene.

In case made phosphate or citrate buffer solution at about pH 7.0, it has been reported that the antibiotic is considerably stable and that appreciable loss of activity is not revealed for several days.

### In Vitro Activity

It was reported that the minimum inhibitory concentrations of Trichomycin were 0.6 mcg./ml. in *Candida albicans* (Hosoya), 0.01 mcg./ml. in *Cryptococcus neoformans* (Fujino), 2 mcg./ml. in *Trichophyton interdigitale* (Karasaki), 0.312–0.625 mcg./ml. in *Trichomonas vaginalis* (Seiga), 10–50 mcg./ml. in *Entamoeba histoly-*

Table 1. In vitro activity of antifungal agents on *Candida albicans*.

Antifungal agent	Minimum inhibitory concentration, mcg./ml.
<b>Antibiotics</b>	
Chromin	0.36–0.8
Eurocidin	1.5
Aureothricin	15.0
Polymyxin B	100.0
Trichomycin	0.017–0.039
Antipyrliculin A	1.56
Nystatin	3.12–6.25
Amphotericin A	10.0
Amphotericin B	0.62–2.5
<b>Chemical compounds</b>	
Gentian violet	5.0
Methylen blue	50.0
Sodium ethylmercuri-thiosalicylate (Merzonin)	0.078
8-Hydroxyquinoline	62.5

Table 2. In vitro activity of antifungal agents on *Cryptococcus neoformans*.

Antifungal agents	Minimum inhibitory concentration, mcg./ml.
Trichomycin	0.009
Nystatin	1.25
Antipyrliculin A	1.25
Amphotericin A	>10.0
Amphotericin B	2.5
Sodium ethylmercuri-thio-salicylate (Merzonin)	0.078

*tica* (Takada), and 25 mcg./ml. in *Leishmania donovani* (Inoki).

Our comparative studies on the in vitro activity of antifungal agents revealed that Trichomycin was the most active of all 17 antibiotics and 25 chemical compounds tested



Table 3. Effects of therapeutic agents employed in the treatment of candidiasis in Japan.

Drug	Route of administration	Disseminated candidiasis				Pulmonary candidiasis				Gastrointestinal candidiasis				Total	
		No. cases	Effective	No. effect known	No. cases	Effective	No. effect known	No. cases	Effective	No. effect known	No. cases	Effective	No. cases	Effective	No. cases
Trichomycin	oral	6	5	1	0	15	13	2	0	5	4	1	0	26	22
Polymyxin B	intratracheal					2	2	0	0					2	2
Sodium iodide	oral	4	0	4	0	14	10	3	1	3	0	1	2	21	10
Nesoban (p-Amino-phenyl-stibinic acid)	intravenous	2	0	2	0	2	0	2	0	1	0	1	0	7	1
Stibunol (Sodium antimonyl tartrate)	intravenous					1	1	0	0	1	0	1	0		
Gentian violet	intravenous; oral; intraduodenal	2	0	1	1	8	3	3	2	2	2	0	0	12	5
Crystal violet	intravenous					3	3	0	0					3	3
Brilliant green	intratracheal					1	1	0	0					1	1
Acriflavine	intravenous	1	0	1	0	2	0	2	0					3	0
Photosensitizing Dyes	Illuminol					2	2	0	0						
	Platonine No. 91	1	0	1	0	1	1	0	0					5	4
Paraben	intravenous	1	1	0	0										
Vitamin K <sub>3</sub>	oral									3	3	0	0	3	3
	intravenous; intraduodenal	1	0	1	0	1	1	0	0	2	2	0	0	4	3
Anticandida rabbit serum	intramuscular	1	1	0	0	3	2	1	0					4	3
Candida vaccine	subcutaneous					1	0	1	0					1	0

against *Candida* and *Cryptococcus*, as shown in the following tables I and II (in which only the data on selected drugs are listed).

### Toxicity

The LD<sub>50</sub> of Trichomycin in mice was found to be 34,000 u./kg., 4,200 u./kg. and 4,300 u./kg. by subcutaneous, intraperitoneal and intravenous administration, respectively (Ozaki). In our studies, the lethal dosage of Trichomycin was about 4–5 mg./kg. by intraperitoneal injection in mice, but no fatal toxicity was demonstrated following oral administration at a daily dosage of less than 36 mg./kg. for 10 days.

### Animal Experiment

The infection-protecting activity of Trichomycin was tested against septic type of candidiasis induced experimentally in mice. All the control animals untreated died within 4 days after inoculation of *C. albicans*, while the mortality rate of animals treated with intraperitoneal Trichomycin at a single dose of 10 mcg./mouse was only 20 per cent. In the therapeutic experiment in mice starting the treatment after infection due to intravenous inoculation of *C. albicans*, intraperitoneal Trichomycin at 10 mcg./mouse exerted favourable effects; animals treated with Trichomycin showed much less mortality rate, less macroscopic renal changes and less numbers of colonies of *Candida* cultured from the kidney than the control. Moreover, oral Trichomycin therapy at 10–40 mcg./mouse/day for 8–9 days showed considerably favourable effects on experimental candidiasis in mice.

In other animal experiments, Trichomycin was found to be effective in the treatment of pulmonary type of candidiasis in rabbits and

in suppressing the fungous flora of fecal specimens in mice given orally *C. albicans* with Tetracyclines.

### Clinical Effects

There were few reports in Japan concerning deep-seated candidiasis before 1943. The first cases of pulmonary candidiasis and generalized fatal candidiasis were published by Mikamo et al. in 1943 and by Donomae et al. in 1951, respectively. Since then clinical cases of candidiasis have been increasingly reported due to a wide use of antibiotics and attention of physicians to such fungous infections.

In the field of internal medicine, 67 cases of deep-seated candidiasis were published from 1954 to 1957 in Japan according to the statistics prepared by Donomae et al. For the treatment of these cases, various drugs have been applied and the therapeutic results are summarized in the above table.

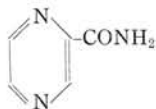
It is apparent from the table III that Trichomycin was administered in many cases and exerted considerably favourable effects. As to side effects by oral administration of Trichomycin, nausea or vomiting was observed in rare cases only when large dose was given for a long period.

From the above results, oral therapy with Trichomycin seems to be worth trying in the treatment of deep-seated candidiasis.

In other fields such as gynecology, urology, dermatology and laryngology, many reports have been published on the therapeutic effects of Trichomycin against fungous and protozoan infections. Above all, in gynecology it has been recognized by Magara, Seiga, Chappaz etc. that Trichomycin vaginal tablets are of choice for the treatment of vaginal candidiasis and trichomoniasis.

## Pyramide in the Limelight

The new tuberculosis drug, PYRAMIDE, marketed by Sankyo Company Ltd. of Japan since January, 1956, is chemically pyrazinamide and it has the following chemical structure:



PYRAMIDE occurs as odorless, white prisms, melting at 188–193°C.

It is only slightly soluble in water (ca. 1%), and sparingly soluble in ethanol, ether, and chloroform. It is stable to heat, even in aqueous solution, its saturated solution withstanding heating at 100°C for 2 hours, without undergoing coloration or decomposition. It is also stable in air.

Although pyrazinamide itself does not have high antibacterial activity against tubercle bacilli, its combined use with isoniazid was found to effect rapid decrease of tubercle bacilli in vivo, a fact revealed by Drs. Schwartz and Moyer of America a few years ago.

In Japan, Prof. Takio Shimamoto of Tokyo Medico-Dental College introduced this drug and published his own clinical results. By now, numerous results of its clinical use have been reported from medical institutions.

The features of pyrazinamide as a tuberculostatic agent are as follows:

- 1) Combined use with isoniazid will give effect far more marked than would be expected from its in vitro antibacterial activity.
- 2) An excellent effect may be expected in serious cases with acquisition of resistance and where other antituberculosis drugs have proved ineffective.
- 3) In the case of original treatment, pyrazinamide can give much more rapid effect than by other mode of treatment, with the body temperature falling to the normal in a short period. Increase in body weight, increased appetite, and improvement in blood sedimentation rate, and other improvement in clinical symptoms in general are remarkable.

The conversion rate of tubercle bacilli in sputum is higher and much more rapid than in the case of other antituberculosis drugs.

4) X-ray observations reveal rapid disappearance or decrease in size of cavity at a high rate.

5) Satisfactory effect can be obtained by oral use and there is no necessity for parenteral treatment. There is no dangerous side effect and any transitory and slight hepatic dysfunctions and articular pains which may occur following the use of Pyramide will pass by discontinuing or reducing the dosage of the drug.

As stated briefly above, the effect of pyrazinamide in original treatment has proved to be excellent and some therapeutic results with pyrazinamide in original treatment will be summarized below:

\* Marked improvement of roentgenograms (M. D. Tsuruhiko Sobami, Tuberculosis Department, Sapporo Medical College)—In 6 cases (4 males and 2 females) under original treatment, daily dosage of 2 g. of pyrazinamide and 300 mg. of isoniazid (initial dose of 150–200 mg., and gradually increased to 300 mg. in 1–3 weeks) were administered for 8–13 weeks and the following results were obtained:

- (1) Marked improvement (1 case) and improvement (2 cases) in general conditions.
- (2) Marked improvement (2 cases) and improvement (2 cases) in chest X-ray observations. No case of worsening.
- (3) In sputum tests, the two cases positive to smear and culture turned negative in about 5 weeks. Other cases were negative from the beginning.
- (4) No changes in hepatic functions or urine.
- (5) No undesirable side effects or accompanying symptoms.

These results indicated that pyrazinamide is highly valuable as a new chemotherapeutic for tuberculosis. (Chiryō Yakuho No. 544).

\* Superior streptomycin-PAS combination therapy. (Prof. Koen Nakanoin Its Internal

Clinic, Kobe Medical College).—Two groups of patients of identical background factors, such as age, sex, degree of disease, and cavity, consisting of 42 cases in each, were treated with a combination of pyrazinamide and isoniazid or of streptomycin and PAS, and their therapeutic effect was compared, results being as follows:

- (1) Improvement of body temperature, appetite, coughing, sputum, blood sedimentation rate, and other clinical symptoms was better in the group treated for 4 months with pyrazinamide than those treated for 4 and 6 months with streptomycin.
- (2) Conversion rate of tubercle bacilli in sputum was also higher in the 4-month-treated pyrazinamide group than in the 4- and 6-months-treated streptomycin group.
- (3) Improvement in X-ray observations, to greater or lesser degree, was found more in the pyrazinamide group than in the

streptomycin group after 4- or 6 months of treatment.

- (4) Closure and reduction of cavity were in higher rate in the pyrazinamide group, good effect having been observed in 69%, including disappearance in 52% and reduction in 17%, while in the streptomycin group after 6 months of treatment, the result was disappearance in 17% and decrease in 39%.
- (5) In general result, the pyrazinamide group showed higher rates of betterment than the streptomycin group.
- (6) Bacterial count and X-ray observations were compared according to the types of disease, between type IV (infiltration) and type VII (mixed). In both the pyrazinamide and streptomycin groups, betterment was obtained in higher rates in Type IV. There was no great difference in betterment rate between types IV and VII in the pyrazinamide group, which was not the case with the streptomycin group,



Fig. 1. ♀ age 27 Before the Treatment



Fig. 2. Inspissation, after 7 month-treatment



Fig. 3. Caviation, after 9 months.

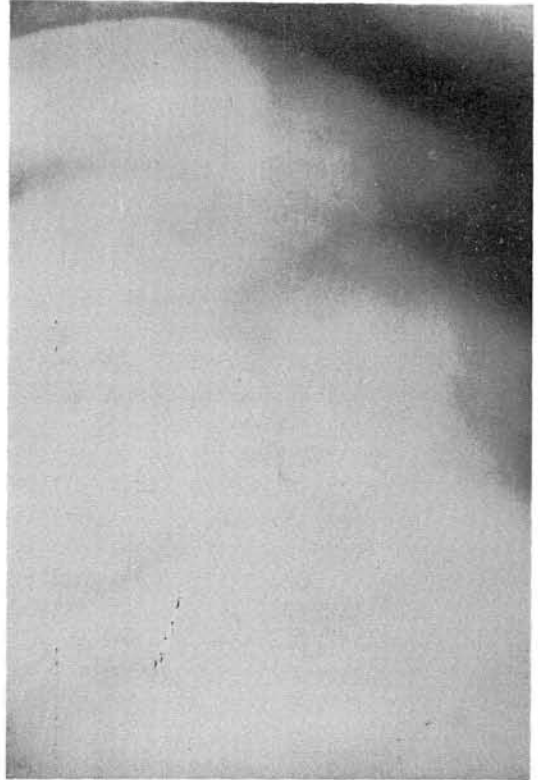


Fig. 4. Inspissation and dispersed after, 12 month-treatment

and this seems to suggest that combined treatment with pyrazinamide and isoniazid would be fairly effective in type VII disease. (Kokyuki Shinryo, April 1957)

\* Effective for new cavity (M. D. Yoshihiko Iizuka, 1st Health Center, Association for the Prevention of Tuberculosis)—Combined therapy with pyrazinamide (2.0g./day, daily) and isoniazid (0.3g./day) was carried out for over 7 months in seven cases, including 5 cases of infiltration type who had not received chemotherapy and 2 cases having a new cavity. After 7–12 months of treatment, there were one case each of total disappearance of focus, only a few scattered, bean-sized foci left, inspissation of cavity and dispersed, leaving only a few, smaller than bean-sized foci, or with a part of the original focus disappearing and the remainder divided into two small foci. In three cases, the diseased focus had

decreased to 30–50% of the original.

As will be seen from the photographs of a case (♀, aged 27, new-cavity type) in which a marked effect was observed in X-ray image, the decrease and dispersion of cavity after 12 months of treatment are clearly visible.

The foregoing reports seem to indicate that combined therapy with pyrazinamide and isoniazid becomes effective rapidly and markedly, and that synergetic effect of the use of pyrazinamide appears over the effect of isoniazid. This seems to be one of the effective combined therapy for infiltration and new-cavity types which are often submitted to chemotherapy. (Naika-no-Ryōiki, August, 1957)

\* One-half is improved after 4 months of administration (M. D. Tokuo Hirai, Internal Clinic, Nagasaki University Medical School)—To 14 cases of pulmonary tuberculosis, as original treatment, daily dose of 40 mg./kg. of pyrazinamide and 4 mg./kg. of isoniazid were

administered for 3-4 months, and general result was 7 cases of betterment, 6 cases of no change, and none of worsening. (One case was discharged by request and no X-ray record to be included in the general result).

- (1) General observations: In the majority of cases, improvement in body temperature, weight, appetite, coughing, sputum, and blood sedimentation rate occurred within 1-2 months of treatment.
- (2) Bacteriological tests: Smear test was negative from the start in 8 cases. In 6 cases of positive smear, 3 remained unchanged but 3 cases had conversion one after 1 month and two after 2 months. In 5 cases showing improvement in culture test, conversion occurred within 1 month in 3 cases and within 2 months in 2 cases.
- (3) X-ray image: Betterment in 6 cases, unchanged in 6 cases, not examined, 1 case, and worsening in 1 case. In 3 cases of betterment, the cavity had closed and it was not observed even in tomography. In one case, the cavity still remained, though smaller in size and peripheral infiltration was much better. In the remaining case, there was no cavity from the beginning and infiltration was better.
- (4) Liver functions: In all the cases, hepatic function was normal before treatment and the majority (13 cases) showed no change.
- (5) Side effects: Articular pain was observed in one case but it was so slight that the patient desired to continue therapy and the pain disappeared on stopping the treatment.
- (6) Conclusion: In 14 cases of untreated pulmonary tuberculosis with normal hepatic functions, daily dosage of 40 mg./kg. of pyrazinamide and 4 mg./kg. of isoniazid were administered for 4 months. Improvement of general conditions and bacteriological test results generally occurred within 2 months, and improvement of X-ray image was found in 6 cases. In general, betterment was found in 7 cases and no change in 6 cases, there being no case of worsening. (Sōgō Shinryo June 1958).

\* A more rapid effect than the combined use of streptomycin, PAS, and isoniazid (M. D. Gihei Kusamitsu, Research Group on Chemotherapy, Association for Prevention of Tuberculosis)—Number of original treatment cases were divided into several groups with the same background factors and each group was submitted to different therapy to compare the result.

- (1) Intermittent streptomycin and daily PAS therapy—Type B (infiltration-caseous type) 74 cases, Ka, -d, type (non-hardening cavity) 52 cases.
- (2) Intermittent streptomycin and daily isoniazid and PAS therapy—Type B 39 cases, Ka -d, type 68 cases.
- (3) Daily isoniazid (0.3 g.) and PAS (2 g.) therapy—Type B 139 cases, Ka -d, type 38 cases.
- (4) Daily isoniazid (0.3 g.) and pyrazinamide (2 g.) therapy—Type B 41 cases, Ka -d, type 49 cases.

In X-ray observations, both in Type B and Ka-d type, the rate of improvement at the end of 3, 6, and 9 months of therapy was the highest in the pyrazinamide-isoniazid therapy group and the rate of improvement at the end of 6 months of therapy in this group was statistically significant.

The presence of tubercle bacilli in the sputum became negative after about 7 months of therapy and there was no difference between these four kinds of therapy, although the period of conversion was much earlier than that observed in earlier treatment with streptomycin and PAS.

Closure of cavity at the end of 3-month-period was slightly higher in the pyrazinamide-isoniazid therapy group, while this group and the combined three-drug therapy showed better results at the end of 6 and 9 months.

The foregoing results have shown that combined use of daily isoniazid, especially that of pyrazinamide and isoniazid, was found to effect early improvement with higher therapeutic effect at the end of 3-6 months of therapy than treatment with intermittent administration of isoniazid, such as by the combined use of three representative drugs, streptomycin, PAS, and isoniazid. (Paper presented at the 33rd General Convention of Tuberculosis Diseases, May, 1958).

## Outlook of 5th International Congress on Diseases of the Chest

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### General events (as of 20th, July.)

Outlook of the Congress will be outlined. It will be, as of 20th July, attended by 472 persons from 48 countries in the world, who include 70 women, and 207 members from Japan. About 700 and 500 persons, amounting to 1200 members in general, are expected to participate respectively from foreign countries and Japan until the opening of the Congress on 7th Sept. The Congress is of course to be principal part of general events, and this is to be summarized later. General events will be said as follows.

As to the Congress, the opening ceremony is to be held at Yomiuri Hall in front of Yurakucho Station, Chiyoda-District, at night of 7th Sept., and they are to be convened at First Life Insurance Hall and council chambers therein for four days from 8th to 11th. Preparations are to be made for round table conference at Tokyo Kaikan, Chiyoda-District.

As to general events, there are scheduled to be held garden party at Kyurinso on 7th Sept. by Mr. Shojiro Ishibashi (Adviser of the Congress), reception on 8th Sept. by Premier Kishi (Honorary President of the Congress), receptions on 9th for foreign participants by respective ministers and ambassadors, Congress banquet on 10th at Tokyo Kaikan, and reception on 11th by Governor Yasui of Tokyo-Metropolis (Adviser of the Congress). In addition, there will be inspections of universities and pharmaceutical factories by applicants. Preparations are being made for fashion shows, tea ceremony, Japanese floral arrangement, hand-molded earthenware, portrait painting, and sights-seeing in Kamakura and Enoshima in behalf of wishful lady accompanists.

### Outlook of the Congress

The themes of the Congress are divided

into 150 individual lectures, five panel discussions, one symposium and 27 fireside conferences. It may be useful that the fireside conference is referred to, because there seems to be few instances of it being utilized in Japan up to now. It aroused much interest in the former Congress in Germany. Now in afternoon of 11th Sept. 27 round tables are to be sat around at Tokyo Kaikan, and selected moderators preside and conduct discussions simultaneously at each table with different special problems as their theme. There is no impromptu interpretation, and there is freedom of use of any language. No restriction is placed for participation in the conference, if they have the right to take part in the Congress. Unexpected enthusiasm may be found in debators who, drinking from bottles of beer placed on table, deliver a fervent speech. Unforgettable peaceful atmosphere was experienced in Köln Congress where they thus exchanged opinion each other on same theme mildly, and shook hands as if they were on intimate terms. Outcome of the conference is said to depend upon rather chairmanship of moderators than enthusiasm of participants. Much value can be accredited to the way in which, taking advantage of these chances, they express their aspiration heartily to persons of the world interested in the same subject and exchange their opinion freely on the spot, than to the way of individual lectures and panel discussions. Only problem is language. The themes of the fireside conference will be said afterwards.

### Used languages in individual speeches and panel discussions

The question always to be taken up in international meetings or congresses is of language. Japanese, English and French are adopted official languages in the Congress. Lecturers have alternative of these three



languages, and accommodations are made for these lectures being interpreted into other two languages and transmitted to auditors by means of earhorns. This may mark great difference from internal congresses, and therefore this brings about indescribable worries to persons concerned.

#### **Character of lecturers, and expectation and wish for their lecture's content**

There are at any rate most Americans among foreign participants. At present there are 196 Americans to come for physicians, and there certainly will be more. There are most American lecturers next to Japanese. They all have a leading position, and are much experienced experts in the field. Some world famous persons will be referred to. Dr. Bailey, professor of surgery in Philadelphia Univ., is an authority on heart-surgery and is in the prime of the forties. We remember much admiration aroused among more than one thousand auditors by Dr. Bailey's long-time special lecture in former Köln Congress, where he, utilizing motion pictures, expressed his opinion upon amazing results he gained from surgical treatment of some hundred patients of angina pectoris produced by myocardial infarction. It is to be greatly expected that Dr. Bailey will apply his whole stock of knowledge in coming Congress. Drs. Ozawa, Kimoto and Sakakibara may be Japanese match for him in the same line. Attention of the world will be especially centered upon original devices concerning operation under direct seeing, cardioscope and alternative cerebral refrigeration anesthesia. We believe securely that much will be thus attributed to operation treatment of inherent and acquired heart diseases, and that of myocardial infarction and angina pectoris causing death to high aged persons.

Recent remarkable increase of the cancer of lung gives a great enigma to the world. Professor Farber of California Univ., authority on internal medicine, especially on respiratory diseases, whose books of the cancer of lung are world-wide, is also known for his much experiences and ideas all over the world. He has visited Japan with his family in July

and improves his impression of this country. Forming interesting contrasts against his study, those of Drs. Kawai, Shinoi and Ishikawa, especially Dr. Ota's pathological study may be cited. As regards Dr. Kawai's tracheal catheter, his diagnosis of cancer by materials obtained by means of brush will surely attract attention. Drs. Nakamura and Katsura are already noted for their surgical treatment of cancer of the esophagus over the world. Dr. Vacearozza in Buenos Aires who is to make a lecture in panel discussion on function of the heart and lung, is heard to be in possession of many achievements. Professor Gordon in Philadelphia, expert in aeronautic medicine, is scheduled to lead panel discussion of aeronautic medicine in next Congress.

Participation of most authoritative specialists is to be found in the following list. Professor emeritus Banyai from U.S.A. is an initiator of the pneumo-abdominal treatment. Participation of Dr. Zorini, successor of Dr. Foranini in Rome, an inventor of the pneumothoracic treatment, and head of the Institute, will lighten dignity of the Congress. Especially the fact that Dr. Hiroshige Shioda, one of the eldest persons in the Japanese medical circle, is to make a speech on the history of development of thoraco-surgery in Japan in spite of his advanced age, will not fail to give great significance to coming Congress. In succession to him, Dr. Tsuzuki, his trusted follower, is arranged to speak on present condition of operation of pulmonary tuberculosis. Special mention must be made of that he, busying himself about the problem of nuclear explosion all around the world, has the eagerness to take up difficult post of head of the section of foreign affairs in the Congress.

A mention must be made of Germany. There are 13 participants coming from that country, more than Japanese ones in Köln Congress. Among them, Professor Knipping, world famous scholar, vice-president of Köln Congress and president of Köln Univ., and Professor Bolt will be said of. Professor Knipping took care of Japanese kindly even while he busied himself in the former Congress,

and Professor Ishida of Keio Univ. and Professor Ebina of Tohoku Univ. is said to have formerly studied under his tuition. He, who visited Japan about thirty years ago, is pro-Japanese. When I called on his schoolroom, he took the trouble to make preparation and experiment on the electrocardiograph with 16 poles initiated by him. There can be found in every modern schoolroom in Japan the apparatus originated by Professor Knipping. It is very interesting whether he will bring the electrocardiograph with 32 poles, as he has told. Considering how Japan stands in this line of researches, we believe surely that he will contribute much. Mr. Fosman who had made demonstration in Dr. Knipping's schoolroom, shortly afterwards gained Nobel prize from his brilliant achievement in photographing blood vessels. We remember that he was then one of lecturers in Dr. Knipping's classroom. Leading visitors from Germany are to include Dr. Rink in connection with coronary circulation and Dr. Dr. Stecken from the Charity in Berlin. Recently Japan has made great progress in researches of function of the heart and lung. Dr. Ishida above-mentioned and Dr. Sasamoto, his follower, both leading personages in this sphere, will carry weight in the next Congress. Dr. Ishida will find it with deep emotion to meet Dr. Knipping on the rostrum.

The remedy for pulmonary tuberculosis is one of the chief themes. Dr. Kumagai is to indicate splendid results chiefly obtained from the Japanized treatment by means of using three kinds of drug at the same time, i.e. streptomycin two days a week, Pas everyday and hydrazide two days a week (everyday in other countries). Dr. Umezawa who invented world famous antibiotics called Kanamycin, and Drs. Yanagisawa and Dōnomae are to show its utility. This is now exported to America. As the problem of antibiotics gains importance, we think that such invention will certainly engage attention of the world. Mr. Kitamoto is to place emphasis upon clinical results from the mass treatment by hydrazide.

Professor Kochwieser of Western Reserve Univ. in U.S.A. experimented in annexing isotope to hydrazide and indicated movement

of hydrazide in living body. Dr. Miyagawa is to report that he has changed such fatty acid as caprinic acid and rodinic acid into colloidal solution by special process and gained noteworthy results from injecting this solution into vein, cavity, fistula and anal fistula. This is one of adjuvants being used together with antibacterial and not yet known in the world. Professor Barach of New York is noted for his study in pulmonary emphysema. Dr. Nukada's new research of Heterozan will attract attention.

Professor Jackson of Philadelphia Univ., son of the founder of bronchoscope and bronchoscopy, is world-wide for his books concerning the apparatus and technique. As import of the apparatus and technique by Dr. Ono, his high disciple, coincided with prevalence of pneumotomy, the manipulation originated by Dr. Ono was the vogue in the clinic of pulmonary tuberculosis. That the teacher and pupil are to apply their whole stock of knowledge to the Congress, will be valuable item worth hearing. Dr. Holigel's lecture is to be added to their addresses. He, founder of broncho-photograph, is regular professor of Illinois Univ. and investigator in the prime of life.

Special mention must be made of Dr. Imamura's study of mycobacterium tuberculosis var. hominis. B.C.G. already known is m. tub. var. bovis, but Dr. Imamura's many years' assiduous efforts have brought about discovery of this bacterium. If it is used vaccination in future, it will be no doubt of superior utility than Calmette gerln bacterium. In Europe and America where pulmonary tuberculosis has turned to be one of past pestilences the nature of prophylactic tubercle bacillus may not arouse as much interest as in past times, but it does not fail to give the useful suggestion for the sake of prophylaxis in another countries where even sign of extermination of the plague has not been shown.

As to electron-microscopic constitution of tubercle bacillus, profound studies will be published by Drs. Terada, Toda and Ebina. The display of electron-microscope of Japanese make in the exhibition held at the

Headquarters of the Red Cross Society together with publication of these researches, will securely show one of present developments in the Japanese medical world at theory and practice. In the above-mentioned exhibition there are to be shown Japanese made electric calculation machine, indispensable apparatus for prodigious statistics and complicated computation, many kinds of superior Roentgen machine, every specimen of Japan made medical apparatus, special medicines, Japanese medical books, and all other pertaining to thoraco-medicine and treatment.

A glance will be given at participants and lecturers from other countries besides Japan, America and Germany. Professor Hedvall of Upsara Univ. in Sweden is a world wide scholar for his so-called primary infection theory of pulmonary tuberculosis, and has many acquaintances among Japanese. Everyone visiting there are said to call on him. He is also an authority on the study of cancer of the lung and an expert in the internal medicine. Dr. Gouch in Wales, Britain, professor of the National Institute, has a great popularity in the pathological field. Investigating thoraco-diseases pathologically from anatomical standpoint, he is expected to make a lecture on the rheumatic pneumonia. Dr. Nakamura is to speak on results obtained from clinical and experimental research of growth process of the chalicosis. Drs. Okinaka and Honma are going to analyze cardio-pulmonary death from view-point of many statistics. Analysis of causes of human death resulting from stoppage of cardio-pulmonary function, pointing the new direction, will provoke interesting repercussion in the internal medical circle of the world.

Further mention will be made of several famous persons. Dr. Faman Viswanathan in India is a specialist in the internal medicine, especially in the tuberculosis. Dr. Canazares of Philippines is a great pro-Japanese, and almost every Japanese physician going there have visited him. Mrs. V. Wyewardene of

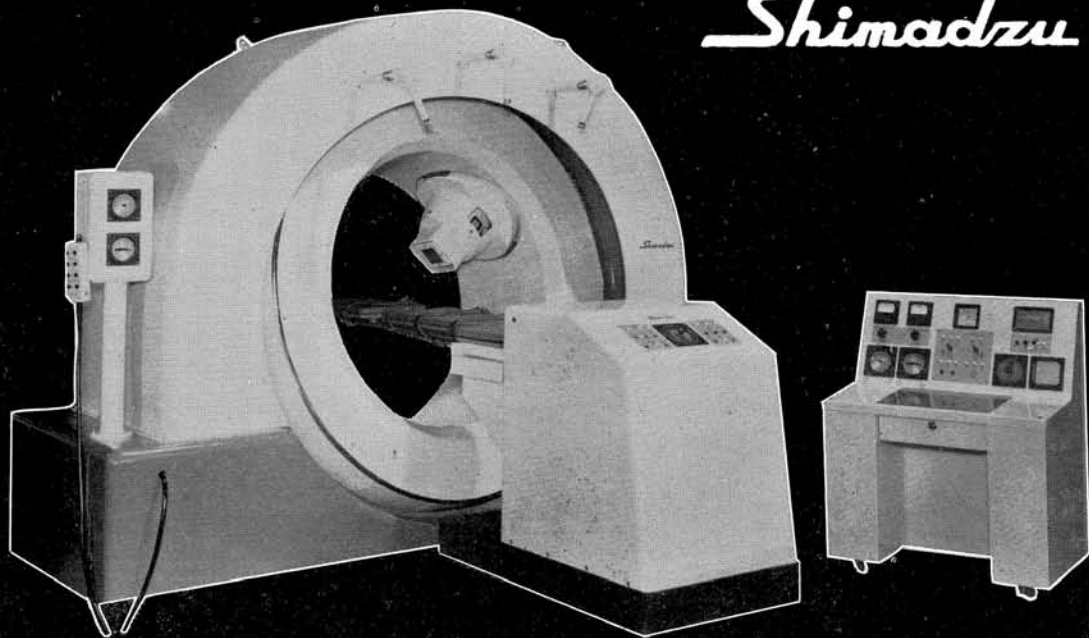
Ceylon is Minister of Foreign Affairs, and Dr. Braga of Malay is Minister of the Health. In addition, there will be many participants from South America, and there are applicants from Hungary, Greece and Iran. There are 11 participants from Formosa, and 5 ones from Korea. But no notice of participation has reached from Soviet Russia and China, but good news is expected in near future.

#### Themes of round table conference

1. Remedy for Pulmonary emphysema
2. Ballistocardiograph
3. Disposition of Infectious Diseases of Lung
4. Chemical and radioactive treatment of Pulmonary tumor
5. Tracheology and Esophagusology
6. Disposition of patients of Coronal Diseases
7. Congestion of the Heart
8. Surgery for Coronal Artery
9. Infectious Diseases of Fungi
10. Chemical Treatment of Tuberculosis
11. Surgical Treatment of Valvulitis
12. Asthma
13. Inoculation of B. C. G. and phylactic internal use
14. Pulmonary Cardiac Failure
15. Steroidal Treatment of Pulmonary Diseases
16. Baby and Child tuberculosis
17. Thoraco-Occupational Diseases
18. Inspection of function of Lung
19. Tuberculosis of the aged
20. Tuberculoma
21. Endurable Tubercle Bacillus
22. Artificial Heart and Lung
23. Remedy for Far Advanced Tuberculosis
24. Far results of Surgical Treatment of Pulmonary Tuberculosis
25. Roentgen Diagnosis and its Radioactive hindrance
26. Virus Infectious Diseases of Respiratory Organs
27. Tubercle Bacillus and Tuberculin

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## Editor's Note

Sadataka TASAKA, M. D.

*Professor of Tokyo University*

We heartily present this Journal to physicians and scholars concerned in the medicine in our Asia. And we have the honor to take advantage of coming Fifth International Congress on the Diseases of Chest to be held in Japan to present the inaugural issue to participants from every countries in the world.

Preparation has been made for publication of the initial number expected in the middle of September. But on the grateful suggestion of Dr. Yoneji Miyagawa that if the inaugural issue of this journal could be presented to the International Congress on Diseases of Chest least likely to be blessed in the Japanese medical world it's significance would be developed greatly, the publication of this issue has been decided rapidly to be advanced.

Consequently it is a matter of sincere regret that a few splendid treatises should be kept for the next issue. But on the other hand we think that the favorable opportunity to present this number to authorities from all countries in the world and make them recognize the existence and the purpose of this journal has more than made up for the regret.

The purpose of the publication of this journal has been already indicated by Drs. Takeo Tamiya, Katsuma Abe and Morizo Ishidate, all of them profound scholars of Japan, in the forewords, but we wish to emphasize that this journal should be made the instrument for persons related to the medicine in Asia to exchange informations each other. We are much self-confident that such enterprise as this may stand unchallenged in the world. But this enterprise of course is beyond all our effort. Accordingly we heartily call for approval and cooperation of physicians in all Asian countries.

This enterprise should have been realized among medical specialists in all Asian coun-

tries consulting with each other. But the chance to consult should not come around, and even though it should happen, it may be after all limited to a part of them.

For early realization of the purpose of this journal we thought it necessary to complete a sample for the first time. And then accepting all varieties of comment from specialists in all Asian countries, and thinking it a short cut to finish the sample gradually to the satisfaction of all concerned, we have embarked upon the publication of this journal with the firm confidence of the necessity of this agency.

The Asian Congress of Health is expected to be held in India November this year. This journal will be issued serially till then. We expect for comment directly from participants of the Congress.

And the General meeting of Asian Federation of Physicians is to be held in April next year. Moreover we consider that it is also a great mission for this journal to connect one international congress with another. And we wish not to make the journal an organ for a specified congress, but to characterize this with a connecting agency of different congresses.

At any rate we have launched out with a great aspiration. We wish for full understanding and enthusiastic cooperation for the purpose of this journal on the part of authorities in Asia.

Finally we express the heartfelt gratitude for Minister R. Hashimoto, Dr. K. Kaneshige, President, the Science Council of Japan, Mr. T. Shimazu, President, Japan Red Cross Society and Dr. T. Takemi, President, Japan Medical Association giving the message for the publication of the initial number of this journal.

We conclude the editor's note with many thanks for professors, in appreciating the purposes of this journal, cooperating with us.





