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Effective Component taken from Fluorescent Bacteria for Rheumatism and Spontaneous Gangrene

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Since the discovery of Penicillin (*Fleming*) and Streptomycin (*Waksman*), many investigators have turned their attention to the research on other antibiotics. There are cases, indeed, who can be completely cured of their infectious diseases by the application of the antibiotics. But at the same time, we must admit there are other infectious diseases which can not be cured or can hardly be cured by the use of such medicines alone. The reasons are: (1) in the latter case, disposition is generally as

important as the pathogens for the onset of their diseases, and (2) the allergic reaction plays an important role both in the prognosis of respective diseases. Rheumatism of the joint may be safely included among these diseases. Accordingly, the use of both the antibiotics and the sulfamid-preparations generally failed to cure the patients of this disease.

Hench and *Kendal* discovered that such hormones as pituitary adrenocorticotrophic hormone (ACTH)

and cortisone act very effectively, though transitorily, upon rheumatism of the joint. In my opinion, however, the relation between ACTH or cortisone and rheumatism is somewhat similar to that between adrenalin and asthma. It seems to me, therefore, that for the best therapy of this disease it is absolutely necessary to search not only for the agents that may act upon the pathogens, e. g., *Streptococcus haemolyticus*, but also for those that may act upon the allergic reactions. The latter agents were almost entirely left unnoticed, so far as the components of the microorganisms are concerned. A series of anti-histaminepreparation that resulted from the researches of the synthetic agents for this purpose, did not come up to our expectations. For the allergic reactions are not so simple as to be explained either with the histaminetheory or with the acetylcholine theory.

As is already stated, however, I discovered, in 1949, a new antiallergic and neurotropic component in the lymph of the cow-pox. This component "Neurotropin" was the first component of micro-organism to be applied to such allergic diseases as asthma, eczema, hemicrania, gastric ulcer and Ménière's syndrom.

A great many Japanese clinicians have already recognized that this medicine surpasses all the anti-histaminepreparations, and they all agree to imagine that this medicine will take the place of these preparations in the near future, as people come to realize what allergic and analogous diseases are, and how Neurotropin acts upon them.

The effect of this medicine upon rheumatism, however, is not of great value when it is applied in smaller dose (10–20 microgram). The effectiveness of this medicine in much larger doses, 1–10 mg, for instance, is still open to research. For we could successfully extract a certain component from the fluorescent bacteria of the cuttle-fish (*sepiola maindroni*) of the Inland Sea, in Japan, in my researches with *Ichiro Kawamura*, on some other agents that might act upon rheumatism. This component, "Florads", had far greater effect upon rheumatism of the joint than Neurotropin had.

This product is non-protein, non-amino acid, and non-lipoid. The chemical analysis is now being continued by my coworker, Prof. *Shiro Akabori* and *Naoichi Sakota* of the Osaka-University.

Anti-Allergic Actions of Florads

According to my coworker, *Yoshitada Takino*,

this product inhibits allergic reactions of guinea-pig. Further experiments were made with both this product and Neurotropin to see which would be more effective in inhibiting the allergic reactions of this animal. Here, Neurotropin turned out to be the better of the two. In his experiments with guinea-pigs, previous injections of this product (10 minutes before re-injection of albumin) could save the lives of 9 out of 10 guinea-pigs from the death by anaphylactic shock. Dyspnoea, however, was generally stronger in these cases than in the cases treated by Neurotropin.

One c. c. of Elorads ampoulé has the effective component of the fluorescent bacteria separated from the water containing 80 mg weight colonies of this bacteria. This dose corresponds to 1.5–2.0 mg of Florads obtained from the methanol fraction of the dried colonies. Later it was found by *Y. Takino* that the complete inhibition of the anaphylaxis of the guinea-pig becomes possible with a shot of the previous injection of over 1 mg. of Florads.

As the action of this component upon anaphylaxis of the guinea-pigs is generally weaker than that of Neurotropin, however, we were carrying on searches for some other agent that may be more effective on rheumatism than Neurotropin. Fortunately, the following story in the *Mainichi*, Dec., 16, 1950, evening edition, started our researches of Florads to the discovery of the real value of this medicine on rheumatism of the joint.

Application to Rheumatism of Joint and Spontaneous Gangrene

A medical practitioner, *Isuzu Kawamura*, was suffering from rheumatism of the joint 5 years ago. One October afternoon, 1950, he went to see the cultural festival of Minakuchi High School (in Shiga Prefecture), where he happened to see the fluorescent bacteria of the cuttle-fish, which had been displayed there by *Yoshio Ishii* and his students of the school.

Having profound knowledge on the vaccine-therapy, he thought of vaccinizing the bacteria, and of applying them to himself to cure his chronic diseases. He tried this, and he was thoroughly cured of his rheumatism within ten days after the application of this vaccine. Then he tried his vaccine on patients suffering from rheumatism of the joint, or spontaneous gangrene on the thigh, with good results.

Learning this fact, we immediately tried on the patients of these diseases our product separated from

the nutrient medium of the fluorescent bacteria. Later we found that this component is contained within the fluorescent bacteria itself, too. Furthermore, we compared this product with Neurotropin. The results showed that the former is far more effective on rheumatism of the joint than is Neurotropin.

This observation of ours agrees with the result of the treatments of *Isuzu Kawamura's*.

One of the outstanding points in this observation of ours is this that Florads, for smaller in quantity than usual (0.1 mg. in general use) sufficed, as in the case of Neurotropin, for the cure of man's rheumatism in its acute or sub-acute state at least, as compared with the quantity necessary for checking the allergic reactions of guinea-pigs (over 1 mg.).

Cases of Rheumatism and Spontaneous

Gangrene treated with Florads

RHEUMATISM CASE 1. A man of 30. In April, 1949, in his Pacific War days in China he felt the first pain in the foot-joint. In those days, he would be obliged to walk about 140 kilometers a day, dragging his sore feet.

This added much to his pain in the joints, and finally he had no joints left in his body that were free from the pain of rheumatism except for the spinal column and the jaw-joints.

Though his pain in these joints were allayed after a year, he was still suffering from lumbago. In 1947, he was healed of the disease without receiving any medical treatment. Soon he felt a severe pain in the hand, and foot-joints again. And one after another, his other joints came to be afflicted with this pain. In 1949, besides this pain, swelling and edema were seen in the knee-, foot-, finger-, and toe-joints, till his lower limbs grew thinner and he could neither stand on his legs nor sit squarely. He received the following treatments.

On March, 12, he received the first injection of Florads (0.1 mg) and felt somewhat better. On the next day, the quantity of urine for the day increased considerably. When he received the 3rd injection, the pain was allayed to a degree and the quantity of urine was larger than usual. The 4th injection (0.2 mg.), relieved him from most of his pain of the day before. He came to be able to move easily his neck, loin, and knees. He could, for the first time in his six years of disease, sit up on his bed for 5 minutes or so without help from others. The swelling of the joint however, remained unchanged. The 5th

Florads-injection (0.5 mg) then, had little effect to be felt on the part of the patients. On March 21, after a 1.1 mg. Florads-injection, the pain was much mitigated. On the next day, when injected the same quantity of this medicine, he could first sit cross-legged. After that, he is in much the same condition. **RHEUMATISM CASE 2.** A woman of 65. In 1944, she suffered from rheumatism of the joint in all the limbs. From 5 years later, she could not stand on her legs. The transplantation of the pituitary gland was tried upon her, but her symptoms in the joint, such as swelling, edema and pain, did not get better. Now she always complained of severe pain in the joint even at the slightest touch of them with the clothes she had on; of course she could not turn herself in the bed without other's help.

Repeated injections of Florads (0.1 mg a day) considerably allayed her pain in the joints and five days later she could turn herself in the bed for herself. The Florads-therapy is now being continued. **RHEUMATISM CASE 3.** A woman of 87. In April, 1949, she had swelling and pain in the hand-joint and the second joints in the fingers of the right hand. These symptoms died away after half a year without his receiving treatment. In April, the next year, these symptoms appeared not only in the same joints, but also in the left hand-joint. The effect of the arterial injection of novocain was transitory. Cutting off the carotid sinus nerves allayed the pain of the joint slightly. Two months later, however, she was as unwell as she had been before.

After three injections of Florads (2.0 mg) the swelling was much reduced in size, and the patient came to be able to use her hand and finger smoothly. **RHEUMATISM CASE 4.** A girl of 18. One January day, 1950, this girl came to be feverish and complained of lumbago when she was home from school after she had played volley ball. This pain increased terribly since March. Then she felt severe pain in the joints of both hands. She was unable to bend her hands. Since August swelling came to be seen and the knee-, foot-, and elbow-joints ached continuously. In January, 1950, she sometimes could not open her mouth wide enough to take in food. Now a move of any one of these joints or a touch of anything with them caused pain in them.

After four injections (0.1 mg a day), she came to be able to open her mouth more widely than before, and the actions mentioned above as probable causes of the pain in these joints now ceased to be

as such. She could now peel oranges with her fingers.

RHEUMATISM CASE 5. A girl of 20. On December 21, 1950, she felt pain in both the knee joints. On the next morning, swelling and edema appeared and the pain was too severe that she could not sleep and was crying day and night. From December 21, 1950 to January 12, 1951, her temperature was 38–38°C.

When she had an subcutaneous injection of Neurotropin (19 microgram a day) on December 29, 1950, she could first sleep well for the night. The symptoms in the joints were as bad as they were before. Two days after an injection of Florads (0.1 mg) on January 16, 1951, there was a remarkable decrease both in swelling and in edema in the joints, together with a fall of temperature. After 10 injections of this medicine rheumatism of the joint was cured completely.

RHEUMATISM CASE 6. A German woman of 56. She was born in the family of rheumatism. Fifteen years ago, she suffered from neuralgia on the left lower limb. Ten years later, she had swelling, edema and pain in the hand-, and foot-joint, but her temperature was normal. Later the left knee-joint, then the right one, were afflicted with severe pain. Now swelling and deformation were seen in the knee-, and hand-, and finger-joints, and she could not use her hand and legs freely. Owing to the pain, she could not stand up or walk without the help of a walking cane, and without much difficulty. After an injection of Florads (1 mg), she came to be able to use her hand with much ease. When she received an injection of Florads (1 mg) and Neurotropin (18 microgram), she could walk as she wished without a cane. Now the therapy is being given her.

GANGRENE CASE 1. A man of 38. He suffered from malaria in January, 1944, when he was 31 years of age. In March that year, he was afflicted with claudicatio intermittens. When 33, he felt spontaneous pain in the fifth toe of the left foot. This symptom disappeared in March, the next year. In December, he felt severer pain in the same toe. He was diagnosed as a spontaneous gangrene case and had this toe amputated. In May, 1950, he was further obliged to have his peripheral half of the left lower limb cut off. In January, 1951, he felt pain in the second toe of the right foot. The toe was dark red. Towards the end of this toe a necrotic wound was seen. This wound in the patients of this disease is rarely to be cured. The pulsation was hardly felt

both in the left artery femoralis and in the right artery pedis, but was felt strongly in the right artery femoralis. Now he complained that he could hardly sleep well because of a severe pain in the toe in question.

An injection of Florads (1 mg.) allayed this pain. After the second injection (1 mg.), the toe become warmer and turned clear red except for the first joint of it.

GANGRENE CASE 2. A woman of 78. She came from the family of asthma. Since several years ago, she was suffering from spontaneous gangrene, and complaining of a severe pain on the toes in winters. These toes were violet red and showed in parts the symptoms of necrosis. Furthermore, since January of this year, she had lumbago and pain in the calf of the left leg. She sometimes cried, complaining of these pains. With an injection of Florads, she was freed from lumbago, but the pain in the calf and the foot-joints were not allayed yet. Since the seventh injection, she came to be able to stand on her legs. Further applications of Florads (0.1 mg) plus Neurotropin (6 microgram) calmed down these pains. Not only that, her spontaneous gangrene came to be felt very slightly and the violet red of the toes became redder still. Finally, the necrotic wounds were almost completely cured.

Discussion

To be sure, various hypotheses about the aetiology of rheumatism have been put forward, but some of them have been good enough to explain the clinical symptom complex and the mechanism of the onset of this disease.

As is already mentioned, disposition and allergic reactions play important roles for the onset and progress of this disease. In this respect, rheumatism of the joint is pretty different from general infectious diseases. This is another reason why rheumatism in general, can hardly be cured with causal treatment alone and why this disease is apt to relapse. This also constitutes the reason of why the pathogens of this disease have not yet been decided completely.

Rheumatism of the joint has thus far been attributed to the microbes such as *Streptococcus haemolyticus* and virus. Rheumatism of the heart, on the other hand, is believed by some, to be caused by *Bacillus tuberculosis (Masugi)*, or by *Bacillus leprae (Suzue)*. Exclusive of *Streptococcus haemolyticus*, however, pathogens are not yet agreed upon as sure causes of this disease. In my opinion, however, the question

of whether tuberculosis and leprosy may change the innate disposition into such dispositions as is to be easily afflicted with rheumatism and of whether they strengthen the innate disposition for this disease requires further examination before this problem is to be settled. This may be presumed when you think about the relation of tuberculosis with the onset of urticaria. According to my investigations, urticaria sets on occasionally in the course of tuberculosis. For tuberculosis may form an acquired disposition which is easily subject to urticaria or strengthen the disposition that is innately favorable for this disease.

It is evident that the antigen of urticaria is not related to pulmonary tuberculosis itself. From this fact, it is to be deduced that the question of whether the rheumatic changes in the hearts of the tuberculosis and leprosy cases are to be attributed to pathogens of these diseases requires further investigation.

The disposition of rheumatism which I mentioned above, has already been supposed as probable by many investigators. In order to clarify this disposition, it is absolutely necessary to examine the heredities of mankind. Here I want to call your attention to the fact that the investigations of the heredity should not be directed to rheumatism alone, but to all the allergic and analogous diseases, especially essential hypertension, including apoplexy. For rheumatism is another disease of mesenchymal tissue and in this respect it may be regarded as one of the allergic diseases. And such mesenchymal tissues as capillaries, blood vessels, collagenous tissue are often hypersensitive in the persons of the family of essential hypertension. These persons are subject to allergic diseases. Most of the rheumatism cases who came to our institute, though they were not so many in number, had the heredity of allergic and analogous diseases, especially of the hypertension. The importance of the examination of heredities and investigating the families of essential hypertension will be understood easily by the following fact.

Rheumatism of the joint is far more easily caused experimentally by antigen-antibody reaction in rabbits than in dogs, cats, guinea-pigs and rats. For the capillaries, the blood vessels and collagenous tissue of these animals are vastly different as regards the reactions of these tissues against chemical and physical stimulations as well as the innervations of arteriola. And so far as the reactions and the innervation of the arteriola in these animals are concerned,

rabbits are very similar to the persons from the family of essential hypertension in that these tissues of both of them are hypersensitive.

The question, however, of whether polyarthritis which may be caused in rats by the administration of desoxycorticosterone acetate (*Selye* and his co-worker) be identified with polyarthritis in human beings and with the above said experimental arthritis in rabbits, requires further investigations. This problem shall be described in another article.

On the other hand, *Hench* discovered that rheumatism of the joint takes a favorable turn, when the illness is accompanied by pregnancy, jaundice, operation and so on. These good effects, in the mind of this clinician, came from some biochemical change which he thought would follow these causes. This presumption led to the use of the so-called compound E or cortisone produced by *Kendall* for the cure of rheumatism of the joint.

Similar symptoms, however, were seen not only in rheumatism of the joint, but also in other allergic diseases. *Racémier* found that, when hemicrania had disappeared in some patients, gout set in, while, when the former had appeared, the latter disappeared. Similar relations are seen between any two of the allergic diseases, asthma and gout, gout and urticaria (*Lichtwitz*) asthma and urticaria or eczema (*Takino*), gastric ulcer and asthma (*Takino*), *Ménière's* symptom complex and asthma (*Takino*) and jaundice and asthma (*Nathan Gorin*). If the common biochemical change which is enough to explain the above mentioned facts with are not found among these relations mentioned in the foregoing paragraph, we should examine some other mechanism in search of the favorable influences of these causes upon allergic diseases. Such mechanism remained undiscovered for a long time till I found, in my systematic investigation of the autonomic nervous system of human bodies, the relation between the onset or the cure of allergic and analogous diseases and the movement of the tension in the parasympathicus, together with the important role played by the unspecific stimulation working as the regulator of the autonomic nervous system in the persons suffering from allergic and analogous diseases and in the persons with the abnormality of this nervous system.

Pregnancy, jaundice, operation, other allergic and analogous diseases and various other causes that may act as unspecific stimulation in the course of allergic diseases, may have mostly favorable influences upon

the allergic diseases the patients are now suffering from. The manners and intensities of these influences are quite different from those in ordinary persons.

According to my investigations, the effects caused by these unspecific stimulations are different according as the kind of allergic diseases, the sort and degree of the stimulations and the organs and tissues on which the stimulations are given.

Needless to say, unfavorable effects also may be seen in the afflicted organs, when either the stimulations themselves or the organs and tissues to which they are given are unsuitable for the diseases. This reason shall be described minutely in my monograph which is to come later.

A warning is here given to the method of hitherto investigators in this field who have overlooked the important role played in the afflicted organ or tissue by unspecific stimulation given to some organ or tissue of human bodies through the change of the autonomic nervous system, especially that of the parasympathicus thus caused in the former.

Finally, I shall state here briefly the action of *Florads*. This medicine dilates arteries in pathologico-physiological and pathological condition. This has already been proved by us with spontaneous gangrene cases. It has been made sure through the observation that this medicine may in effect get rid of the disturbances in the local blood circulation of the afflicted part. This was verified in the cases of rheumatism of the joint, too. For the afflicted part is occasionally heated after the injection of *Florads*.

Furthermore, *Florads* calms local pains of these diseases effectively. In my examinations of some cases of rheumatism of the joint, the application of *Florads* in combination with Neurotropin often proved to be more effective than they might when applied individually. The question, however, of whether *Florads* has other actions requires further research.

Conclusion

We discovered the effective component of the fluorescent bacteria. According to our investigations, this component or *Florads* has anti-allergic and neurotropic action and acts effectively upon rheumatism of the joint and spontaneous gangrene without causing any bad effect. Here I stated my presumption and opinion about the mechanism of the onset and the cure of rheumatism of the joint.

The detailed explanations for a number of facts were omitted here. They shall be given in my monograph which is to appear soon later.

I had sent this article directly to Dr. *Austin Smith* on 24th May, 1951, entitled as "Discovery of Effective Component of Fluorescent Bacteria for Rheumatism and Spontaneous Gangrene." Then it was submitted by him to Dr. *French K. Hansel* in accordance with my request, for its publication in America.

However, it missed the chance of publication there and was sent back to me on 7th March, 1952.

The publication here was delayed, and during the delay, our investigations in this field have made a further progress. And I think I may, with some reason, publish this article, as a milestone to the present investigation, before I introduce to you the records of my recent investigations.

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寒冷に対する反応性肢端温度の變化に関する研究

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I 緒 言

生體の一部特に手指、足趾、耳朶等を寒冷に晒すと、その皮膚温度は一度下降した後反応性上昇を示す事が1930年 Lewis によつて始めて記載された。

人の指を冷水に浸すと、その皮膚温度は始め急激に下降した後上昇、下降を反復する。又指を冷水から出すとその温度は急激に上昇して對稱指の温度より高くなる。Lewis は冷水中の上昇を初期反應 (initial reaction)、離水後の上昇を後効果 (after effect) と名づけ、之等の反應を寒冷刺激により遊離したヒスタミン様物質が知覺神經末端を刺激しておこす軸索反射であると考えた。その後 Grant & Bland が之を追試し、この寒冷反應には動靜脈吻合枝が重要な役割をなす事を指摘した。我が國に於ても久野、高橋、飯田、奥田等により生理學的方面から種々の實驗が行われているが、未だ臨床的方面からの詳細な研究は見られない。そこで著者はこの問題を臨床的方面から取上げて、先ず A) 健常者に於ける寒冷反應を觀察し、又左右の差、気温、入浴による變化、血流阻止及び自律神經に作用する藥物による影響を見、更に B) 血管神經症、レーノー氏病、ビュルゲル氏病等の肢端疾患に應用し、診斷的價値を有するや否や、又 C) 諸種神經疾患々々で中樞神經系の一部に器質的障礙ある場合を選択し、この寒冷反應の發現様式を檢討してその發現機序を解明せんと企圖した。

II 實驗方法並被檢者

1) 實驗方法

肢端温度の測定には銅とコンスタンタンの熱電對を用い、4ミリボルトの電壓計を使用した。圖に示す如く、熱電對の一端を水温 0° の水を充した魔法壺の中に入れ、他端を手に於ては拇指と示指、足に於ては第一趾と第二趾との末端の兩指趾面にはさみ、絆創膏で軽く固定する。豫め一定温度に調節した水槽に末端指骨關節迄浸し

電壓計の振れを1分毎に読み之を記載した。冷水に浸す前の肢端温度については大凡一定する迄 (3~5分) 測定し、水から上げた後も後効果が出終る迄測定した。寒冷反應の出現には環境気温の影響があるとされているから検査はなるべく氣候温暖の時期に、冬期はなるべく室温 15°C 以上の暖かな部屋で行い、浸水前の肢温を 20°C 以上に保つようにした。Lewis の成績に於ても、又著者の健常者に於ける觀察に於ても全て反応性上昇は 20 分以内に出ているから、浸水時間はだむね 20 分間とした。

2) 被 檢 者

a) 健常者：循環器系統の疾患のない健康醫局員、看護婦及びその家族31例につき指尖に於て水温 4°C、更にその中 25 例に於て水温 8°C、12°C、15 例に於て足趾で 4°C の水温で實驗を行つた。

b) 肢端疾患々々者：i) 發作的に肢端蒼白となり激痛を伴う如き血管攣縮を示すレーノー氏病患者 8 例を第 I 群、ii) 肢端厥冷、異常感覺等の自覺症狀を訴え、他覺的にも發赤、チアノーゼ、時としては蒼白等の症狀を認め、自律神經機能検査が陽性に出るもの、即ち自律神經不安定状態を示す血管神經症と稱すべき患者 16 例を第 II 群、iii) 肢端に厥冷、疼痛等の自覺症狀を訴えるが、他覺的症狀は認められず、又自律神經の機能検査も行い得なかつた診斷不確實なるものを第 III 群、iv) 血管に器質的障礙のある 4 例の患者を第 IV 群とする。以上 4 群の患者につき、症狀が足にのみある 4 例 (I 群 2 例、III 群 2 例) では足趾に於て、その他の患者では手指に於て 4°C の水で實驗を行つた。

c) 神經疾患々々者：脊髄性のものは脊髄炎 5、筋萎縮性側索硬化症 3、脊髄壓迫症、蜘蛛膜炎、脊髄空洞症、脊髄癆、脊髄梅毒、急性脊髄前角炎、脊髄出血各々 1、計 15 例で、その中知覺脫失及び完全麻痺あるもの 4、知覺鈍麻及び不完全麻痺あるもの 7、運動障害のみあるもの 4 でいずれも兩側性である。腦性のものは腦出血 7、腦栓塞 3、腦軟化 2、腦梅毒、一過性腦性麻痺、進行性麻痺各々 1、計 15 例で、その中知覺脫失並びに完全麻痺あるもの 2、完全麻痺あるもの 1、知覺鈍麻及び不完全麻痺あるもの 9、知覺鈍麻のみあるもの 1、不完全麻痺のみあるもの 1 で知覺、運動共に障害のないもの 1 である。足のみに症狀ある 5 例 (脊髄性 4 例、腦性 1 例) では足趾に於て、その他では手指に於て水温 4°C の水で實驗を行つた。尙偏癱患者に於ては麻痺側、健側兩側に於て