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Abstracts of "Tuberculosis Research"

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Studies on the Antituberculous Compounds. XXVII.

Synthesis of 7, 8-Dihydropyrdo [2, 3-d] pyridazin-5 (6 H)-one

Shichiro KAKIMOTO and Shuichi TONOOKA

The cyclization of ethyl 2-bromomethylnicotinate with hydrazine hydrate gave a mixture of 7, 8-dihydropyrdo [2, 3-d] pyridazin-5 (6 H)-one and its structural isomer. The former was also obtained by reduction of pyrdo [2, 3-d] pyridazin-5 (6 H)-on-thiol with amalgamated aluminum. The latter could be converted to the former under mild basic conditions.

The Immunological Relationship of the Rabbit Appendix to the Intestinal Organisms (E. coli)

Eiji HAMADA

For the purpose of studying the role of the rabbit appendix against the intestinal organisms, E. coli were isolated from healthy rabbits and used as antigens for immunization. Soluble antigens were obtained from the isolated E. coli by extraction with heated water and used in the following serological and skin tests.

1) The Middlebrook-Dubos hemagglutinin test and skin test were carried out in healthy nontreated rabbits from neonatals to adults.

The M-D antibodies failed to be detected until 5 weeks after birth, whereas those increased gradually and reached to 40 at the age of 12 weeks.

The skin reaction was of immediate type at 4-6 weeks after birth, but after 8 weeks it changed to be of delayed type. The histological observations of the test sites were similar to those of the tuberculin skin test.

2) Newborn rabbits were sensitized with single injection by the following various routes:

1 subcutaneous, 2 intrathymic, 3 intra-appendicular and 4 intra-appendicular after neonatal thymectomy. During 5 to 10 weeks after antigen administration, a considerable suppression could be observed in both skin reactivity and antibody formation in the 2nd and the 4th groups. On the other hand the highest hemagglutinin titer and skin reactivity were observed in the 3rd group.

3) Adult rabbits were also inoculated with living E. coli or killed S. typhi by the same routes described above.

a) The hemagglutinin titer increased markedly following single intra-appendicular injection of living E. coli, whereas intrathymic administration depressed the antibody formation.

Two weeks after inoculation the skin reaction showed its peak at 6 hours after antigen injection, but 6 weeks after the inoculation the peak was shown at 24 hours.

b) Both groups of intrathymic and intra-appendicular injection of *S. typhi* showed a lower agglutinin titer than the other groups did.

Histologically plasma cells and the germinal centers could not be found in the thymus injected directly with the vaccine.

From these findings the rabbit appendix seems to be a peripheral lymphoid tissue playing a very important role in protection against the invasion of the intestinal organisms.

Immunopathological Studies on Antibody Formation

VIII. Effects of the thymectomy and bursectomy of the chicken on the delayed hypersensitivity responses

Akio TAKAHASHI

It is the purpose of this report to present the effect of the removal of the thymus and/or the bursa of Fabricius on the delayed hypersensitivity response and antibody producing capacity. Chickens were surgically thymectomized and/or bursectomized immediately after hatching.

- 1) These operations had no effect on body weight until 10 weeks of age, but at 24 weeks the thymectomized, bursectomized and thymo-bursectomized animals showed 17, 12 and 16 per cent weighing less than the unoperated ones, respectively.
- 2) Tuberculin was intradermally injected into the wattle of the chickens sensitized with H 37 Rv, the histological examination of the injection sites showed a close resemblance to the classical tuberculin reactions in the guinea-pig.
- 3) Four weeks after sensitization one hundred per cent of unoperated animals responded to tuberculin, whereas 90 per cent of the thymectomized, 33 per cent of the bursectomized and 89 per cent of the thymo-bursectomized animals. The thymectomy performed until 10 days after hatching suppressed significantly the tuberculin reactivity.
- 4) The production of the Middlebrook-Dubos hemagglutinin was observed to be markedly reduced in the following descending order as the thymo-bursectomized, bursectomized and thymectomized animals. The anti-BGG antibody titers were very low in the bursectomized and thymo-bursectomized animals.
- 5) Histologically, 5 weeks after tuberculous infection there was no distinct difference of the intensity of tuberculous lesion in the operated and unoperated animals. The spleen of the thymectomized and thymo-bursectomized animals showed 25 per cent less in weight than those of the unoperated ones.
- 6) The findings described above suggest as follows: a) Principally the thymus-dependent tissue is basic to cellular antibody formation, while the bursa-dependent tissue is basic to humoral antibody formation. b) Under a particular condition, however, both the thymus and the bursa might play a role in humoral and cellular antibody formation.

Mechanism of Development of Delayed-type Hypersensitivity Reaction

I. Skin stimulating activity of culture supernatants of antigen-treated cells

Harue OKUYAMA and Kazuo MORIKAWA

Peritoneal macrophages of tuberculous or normal rabbits were treated with tuberculo-protein in vitro for one hour, and then incubated without the antigen for 24 hours. On the other hand, lymphocytes from the popliteal lymph nodes of these animals were incubated with the antigen for 24 hours. Supernatants from these cultures were injected into the skin of normal rabbits and examined for the presence of skin stimulating activity.

Intradermal injection of all these supernatants caused erythematous reactions which reached to the maximum at 6-24 hours. Of these materials examined it was the supernatant from tuberculous macrophage culture that showed the largest and the most intensive erythematous reaction. The skin stimulating activity was not diminished by heating at 56°C for 30 minutes.

In these supernatants tuberculo-protein remained to possess the activity as a tuberculin test antigen, since the supernatants showed a typical delayed-type skin reaction at the injected site of tuberculous rabbits.

Histologically, the supernatant of tuberculous lymphocyte culture was shown to produce a cellular response of mononuclears rather than polymorphonuclears.

Sur la distribution des variants à l'éthambutole ou bien à la capréomycine dans des souches sauvages de *Mycobacterium tuberculosis*.

Hitoshi IGARASHI

Afin d'établir bactériologiquement le critère de résistance des bacilles tuberculeux vis-à-vis de l'éthambutole et de la capréomycine, nous avons fait, selon la méthode de Canetti, une analyse en ce qui concerne les teneurs des souches de bacilles tuberculeux en variants résistants à ces drogues.

- 1) En cas de l'éthambutole, la teneur en variants résistants est très haute à la concentration de 1. 25 µg/ml, mais elle baisse brusquement aux concentrations au delà de 2. 5 µg/ml.
- 2) En cas de la capréomycine, les taux de variants montrent des valeurs comparativement hautes aux concentrations de 12. 5 µg/ml et de 25 µg/ml. De plus, même à la concentration de 50 µg/ml, le développement des variants résistants s'observe, bien que leurs taux ne soient pas très hauts.
- 3) A l'appui des résultats ainsi obtenus, nous pensons que le critère de résistance est de 5 µg/ml pour l'éthambutole et de 50 µg/ml pour la capréomycine.

Studies on the Functional Limitation of the Lung
in Patients with Pulmonary Tuberculosis

— Mechanism Producing Chronic Hypercapnia in Pulmonary Insufficiency —

Takashi OHSUGI

Arterial blood gas analysis and various lung function tests were performed in 800 patients admitted to the 2nd Hokkaido National Sanatorium during the past two years.

- 1) A considerable number of patients in the Sanatorium revealed restrictive respiratory insufficiency.
- 2) Reduction in vital capacity or FEV_{1.0}/predicted V. C. was found to be closely correlated with the risk of hypercapnia. But such correlation was not found in case of FEV_{1.0}%.
- 3) Most of the patients with far advanced tuberculosis generally exhibited hypoxemia, but not hypercapnia in ordinary condition.

Hypercapnia was observed only when pulmonary tuberculosis was in activation or when infections other than tuberculosis were combined, namely when severe obstructive respiratory insufficiency was combined. By contrast, in the thoracoplasty group, hypoxemia and hypercapnia were found coexisted even when a slight obstruction was found.

- 4) Out of 63 patients with hypercapnia, 20 had undergone thoracoplasty, while the remainder 43 had not been operated on. Most patients of the former group presented minimal tuberculosis and the latter far advanced tuberculosis. Remarkable reduction in vital capacity was observed in the thoracoplasty group. Severe obstruction was seen in half of the non-operated group.
- 5) Following voluntary hyperventilation, P_a c_o2 decreased in all patients with hypercapnia. In all the patients in whom initial P_a c_o2 exceeded 50 mm Hg, P_a c_o2 increased significantly following inhalation of 100 % O₂. On the basis of these findings, the author considers that hypercapnia occurs possibly as an adaptation to increase in O₂ cost of breathing. Increase in P_a c_o2 was not always observed in patients with hypoxemia in whom P_a c_o2 was below 50 mm Hg, when they were subjected to inhalation of 100 % O₂.
- 6) O₂ cost of increased ventilation was measured in 28 tuberculous patients. In functionally normal subjects, it was 2.2 ml/liter of ventilation. On the other hand, in patients with hypercapnia, it was 10.1 ml/liter of ventilation. Therefore, it was suggested that increase in O₂ cost of breathing might be an important factor for the production of chronic hypercapnia in patients with pulmonary tuberculosis.
- 7) The author considered that severe restrictive respiratory insufficiency in the thoracoplasty group, while restrictive and severe obstructive respiratory insufficiency in the non-operated group with far advanced tuberculosis were the initial factors for increase of O₂ cost of breathing.

A Study of the Virulence of Tubercle-Bacillus Strains Isolated from Patients with Pulmonary Tuberculosis with Special Reference to Strains from Minimally Sputum-positive Patients.

Saburo KUREMATSU

Strains of tubercle bacilli isolated from minimally sputum-positive tuberculous patients, strains with varying drug-resistance, drug-sensitive strains, strains from patients who had exhibited a particular clinical course and other bacteriologically interesting strains were studied of their virulence in guinea pigs. The study led to the following conclusions :

- 1) Strains from minimally sputum-positives were all found of low virulence against guinea pigs, while some of them were rather of high virulence against mice.
- 2) No correlation was noted between the virulence of strains from minimally sputum-positives and the clinical symptoms of the latter after the isolation of the strains, especially their sputum findings.
- 3) Two INH-resistant strains were isolated which were all of high virulence against both guinea pigs and mice. One of them showed a complete resistance against 5 μ g of INH and over.
- 4) Of three sensitive strains isolated from patients who had received treatments of long duration with streptomycine, PAS and INH, two were highly virulent against both guinea pigs and mice, while the last one was of low and moderate virulence against guinea pigs and mice respectively.
- 5) Of all the strains isolated in the course of the present study, a Niacin-negative, apparently human-type strain isolated from a patient who had died from intestinal tuberculosis showed the highest virulence against both guinea pigs and mice. Its virulence was comparable to that of th human-type tubercle bacillus of the Nakano strain (a highly virulent laboratory strain).
- 6) A strain was isolated which showed bacteriological characteristics of atypical mycobacteria. It was of very low virulence against both guinea pigs and mice.
- 7) In guinea pigs, a good concordance was found between the two different methods for virulence testing, splenic cell-suspension method and subcutaneous injection method (gross findings and spleen indices). However, results from guinea pig experiments for virulence testing did not always run parallel with those from mouse experiments for the same purpose (measurements of the bacillary growth in the lungs, relative mortality rates, changes of the body weight).