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## Abstracts of "Tuberculosis Research"

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### Antituberculous Compounds, XXVI. Sulphur Derivatives of Pyrido-pyridazine.

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New sulphur compounds of pyrido pyridazine, pyrido [2, 3-d] pyridazin-5-(6 H)-on-8(7 H)-thione, pyrido [2, 3-d] pyridazin-8 (7 H)-on-5 (6 H)-thione, pyrido [3, 4-d] pyridazin-4 (3 H)-on-1 (2 H)-thione and pyrido [3, 4-d] pyridazin-1 (2 H)-on-4 (3 H)-thione were prepared and their antibacterial activities in vitro were examined. Effective compounds were not found.

### Tuberculosis and Clubbed Finger

—Some observations on pulmonary tuberculosis patients with  
clubbed finger—

M. MATSUMURA, H. TAKASE, T. HIRATA,  
T. MATSUBARA, A. KUZE and K. KONDO

Four hundreds and thirty-seven patients admitted in the 2 nd Hokkaido National Sanatorium were examined to obtain the clinical aspects of clubbed finger on July 31, 1966.

Clinical diagnosis of clubbed finger was made onyl when the "profile sign" by Lovibond (1938), which is the obtuse angle laterally between the nail and the skin over the distal phalange, indicated the angle of over 160 degrees.

- 1) The incidence of clubbed finger was found in 24 per cent (96 patients) of 400 patients with pulmonary tuberculosis, and in 13.5 per cent (5 patients) of 35 patients with thoraco-lumbar caries.
- 2) No significant sex and age difference was noted in these incidences except for a slight increase in older ages.
- 3) In clubbed finger, the terminal phalange was apparantly swollen with respect to the middle or proximal phalange. However, the most significant feature was the profile sign of over 160 degrees and the curved nail.
- 4) The plain roentgenogram revealed a small amount of new bone spinate formation at the distal end of the digits.
- 5) No linear correlation was noticed between the degree of finger clubbing on the one hand and the duration of clinical course, the routine chest x-ray findings, lung functions and electrocardiograms on the other hand.
- 6) Only one case of hypertrophic pulmonary osteoarthropathy was found in this series.

## Comparison of Pathogenicity of *Mycobacterium Avium* and Battey Bacilli for Mice.

Ken-ichi YAMAMOTO, Jun ARIMA, Hiroaki FUSE,  
Setsuro NAKAMOTO and Yoshio TAKAHASHI

In order to differentiate *mycobacterium avium* from Batty bacilli, comparison was made of their pathogenicity.

Four strains of *M. avium* and eleven strain of Batty bacilli were employed. Ten-day old bacilli of each strain harvested on Dubos medium were infected intravenously into mice. The animals were sacrificed at a given time after infection and comparison was made of their lung indexes, viable units of bacteria recovered from the lungs, histological findings on the lungs, liver, spleen and kidney, and the virulence evaluated by means of spleen cell suspension culture. Survival time was also observed as long as for 93 days. Then, survivors were autopsied and gross findings on the lungs and the lung indexes were recorded.

All the four strains of *M. avium* and only four strains out of Battey bacillus strains were found to be fairly pathogenic for mice.

Then, these four strains of each bacillary group were inoculated intravenously into mice in a dose of one-hundredth the amount of bacilli used in the previous experiment. The animals were sacrificed immediately, 4, 8 and 12 weeks after infection and the number of bacilli recovered from the lungs and liver were calculated.

While no distinct difference was found in the viable units recovered from the lungs between *M. avium* and Battey bacilli, a significant difference was observed in the viable units from the liver between the two.

The results indicated that a small amount inoculation of *M. avium* and Betty bacilli into mice and calculation of the viable units from the liver is a useful method for differentiating *M. avium* from Battey bacilli.

## Etude comparative sur les méthodes d'évaluation de l'immunité antituberculeuse.

par Ryuji MARUYA

Afin d'étudier les méthodes d'évaluation de la résistance acquise contre la tuberculose, nous avons entrepris une série d'expériences, en utilisant, comme animaux, des cobayes et des souris, et comme antigènes BCG et des bacilles tuberculeux morts enrobés dans de l'émulsion détergent-huile. Les sujets comparés étaient ceux qui sont en emploi dans les méthodes conventionnelles : changements macroscopiques des viscères, nombre de bacilles contenus dans les organes, temps de survivance, poids du corps, et poids relatif des poumons vis-à-vis du poids du corps. Nous avons aussi examiné, comme méthodes nouvelles, la culture *in vitro* des suspensions cellulaires de rates de cobayes immunisés et la densité des poumons des souris infectés. En voici les résultats :

1) La méthode d'inoculation souscutanée au cobaye serait une méthode moins convenable pour estimer l'effet immunisant, parce qu'elle demande une assez longue période de temps pour qu'on puisse s'assurer du résultat. Pourtant elle serait encore une méthode très importante, parce qu'elle reflète bien sensiblement l'effet immunisant.

## Comparison of the Reactivity of $\gamma$ M and $\gamma$ G Antibodies in Passive Hemagglutination and Farr's Test.

Tohru OHARA and Takuro KIMURA

- 1) On a weight basis,  $\gamma$ M antibody is 50-350 times more efficient than  $\gamma$ G antibody at agglutinating red cells sensitized with immunizing antigen.
- 2) On the contrary, the former is about 100 times less effective than the latter in antigen-binding capacity.
- 3) The sequential synthesis of  $\gamma$ M and  $\gamma$ G antibody thus far reported was discussed from the data described above.

### Immunopathological Studies on Antibody Formation

#### V. Morphological and Ontogenetical Observations of the Rabbit Appendix

Eiji HAMADA

Morphological and ontogenetical observations were made of the appendices in adult rabbits as well as in new born rabbits aged between 0 day and 14 days by the use of light and electron microscopy. In adult rabbits, the appendiceal lymph follicle could be divided morphologically into four parts: (1) "subepithelial zone" mainly composing of reticulum cells and macrophages which contain many phagocytic granules of enterobacteria in the cytoplasm. Plasma cells can be seen beneath the epithelial lining cells. (2) "marginal zone" in which small and medium-sized lymphocytes are seen compacted in the network of reticulum cells. Mitosis takes place frequently in this zone. (3) "central zone" comprising of free reticulum cells which include electron-dense phagocytic granules and of lymphocytes containing frequently similar granules indistinguishable from azurophilic granules. And, (4) each follicle have been connected with through the part termed "junction" connecting each follicle, which seemingly corresponds to the prolongation of lamina propria of the appendiceal villi. Plasma cells surrounding blood vessels are abundant in this part.

Cytological observations of the maturation process of the new born rabbit appendices indicated that the aggregation of reticular cells and lymphoid cells in the submucosa might precede the so-called domed elevation of the appendiceal epithel, and no lymphocyte might transform from the appendiceal epithelial cells which have been firmly separated from the primary lymph follicle by the basal membrane and epithelial lining cells until 4 days after birth. Morphological observations suggested that the origin of the lymphocytes which first appeared in the primary lymph follicle of the new born rabbit appendix was not of epithelial nature. No germinal center was observed in the appendiceal follicle in the present study.

### Immunopathological Studies on Antibody Formation

#### V. *In vitro* antibody production of lymph node cells of rabbits

Harue OKUYAMA, Eiji HAMADA and Kazuo MORIKAWA

Lymphoid cell suspensions were prepared from regional lymph nodes of rabbits to which primary or

secondary injections of crystalline ovalbumin were made into the foot pads, and passed through a glass wool column. The lymphoid cells thus obtained were seeded onto Petri dishes in which cover slips were inserted, and cultured for 7 days in a humidified incubator supplied with a constant gas flow of 5 per cent CO<sub>2</sub> in air. The cells which had adhered on the cover slips were examined morphologically by means of Giemsa and the methylgreen pyronin stainings. Antibody producing cells were detected by use of the immunofluorescent technique. Antibody titers were measured by the tanned cell hemagglutination technique.

In case of the lymphoid cells of primary response, the appearance of fluorescent, antibody containing cells started only from their 5 days' incubation, whereas it was already apparent on the second day of incubation in case of the lymphoid cells of secondary response, with gradual accentuation thereafter. Morphologically the antibody producing cells were round and medium or large in size, having basophilic cytoplasm with or without poor cytoplasmic processes. Antibodies were detected in the culture medium simultaneously with the appearance of the antibody producing cells on the cover slips. These findings suggest that the antibody producing cells might be derived from the small lymphocytes.

## BDB Antibodies in Sera of Patients with Pulmonary Tuberculosis

Akio TAKAHASHI and Kaoru KAWACHI

The presence of BDB (Bis-diazotized benzidine) hemagglutinating antibodies to tuberculin protein was verified in sera of 111 patients with tuberculosis, and the possible relationship between the clinical status of the patients and the BDB antibody titers was discussed.

- 1) Chest X-ray findings showed no conceivable relationship between disease types and antibody titers, which the latter was found to be closely related to the extents of lesions.
- 2) Bacteriologically, BDB antibody titers were considerably higher in sputum-positive patients than in sputum-negative.
- 3) Further studies remain to be made, especially in tuberculin-negative healthy persons, in order for the BDB test to be evaluated as a reliable clinical test.
- 2) La méthode de culture *in vitro* des cellules de rates de cobayes a du mérite nous démontre l'effet immunisant avec exactitude et dans une période de temps relativement courte.
- 3) Pour toutes les méthodes étudiées avec des souris, l'effet immunisant ne s'est manifesté nettement que chez les souris inoculées avec des doses d'antigènes plus grandes que celles employées pour les cobayes. Ce qui montrerait que la souris est moins sensible pour la tuberculose que le cobaye.
- 4) La méthode de la densité des poumons des souris ne s'est pas montrée nécessairement meilleure que les autres.
- 5) Comme méthode d'évaluation chez la souris, il serait recommandable d'avoir recours aux critères suivants : temps de survivance, nombre de bacilles contenus dans les poumons, et accessoirement poids relatif des poumons vis-à-vis du poids du corps ou bien poids du corps.

## Complications Detected in Recently Autopsied Cases of Pulmonary Tuberculosis

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Pulmonary tuberculosis cases autopsied in Japan between 1958 and 1963, totaling 3,662, and 80 cases autopsied in The 2nd Hokkaido National Sanatorium between 1955 and 1967 were examined in regard to their combinations.

- 1) Heart : atrophy and ventricular hypertrophy and dilatation, particularly in the right ventricle were predominant.
- 2) Liver : congestion, atrophy and fatty degeneration were remarkable.
- 3) Kidney and spleen : congestion and atrophy were frequent.
- 4) Tuberculous complications : tuberculosis in the liver, 3.7%; kidney, 5.8%; spleen, 3.6%. Meningitis, 3.5%; intestinal tuberculosis, 2.4%; peritonitis, 0.8%; tuberculosis in the sexual organ, 1.6% and pancreatitis, 0.1%.
- 5) Non-tuberculous complications : right ventricular hypertrophy, the so-called cor pulmonare was most frequent. Arteriosclerosis, 12.6%; liver-cirrhosis, 4.0%; nephrosclerosis, 3.4%; cancer of the lung, 4.4%; ulcer of the stomach and duodenum, 5.4%; silicosis, 2.6%; diabetes mellitus, 1.6%. Cerebral weakness and cerebral haemorrhage were found only in a few cases.
- 6) The features similar to the preceding items were found in the autopsied cases in The 2nd Hokkaido National Sanatorium
- 7) Of all the autopsied cases, 70% was over 40 years of age and 32% over 60 years.