ABSTRACTS

ANTITUBERCULOUS ACTIVITY OF CAPREOMYCIN AND CROSS RESISTANCE AMONG KANAMYCIN, CAPREOMYCIN, AND VIOMYCIN

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Experimental studies on capreomycin, a new antibiotics, were made.

The minimum inhibitory concentration of capreomycin against *Mycobacterium tuberculosis* H37Rv strain was approximately 1 to 2 mcg. per ml. in liquid media and Kirchner's agar, but 10 to 20 mcg. per ml. in egg medium. The tuberculostatic activity was considerably reduced in proportion as the pH of medium was changed to acid, the inoculum size was strengthened, and/or the serum concentration in medium was increased.

No cross resistance existed between capreomycin and other antituberculous drugs excluding kanamycin, and viomycin (neomycin did not be studied). Among kanamycin, capreomycin, and viomycin, one way or reciprocal cross resistance was observed. High degree resistant strain to kanamycin was relatively resistant to capreomycin, but sensitive to viomycin. Low degree as same as high degree resistant strains to capreomycin were resistant to both kanamycin and viomycin. Low degree resistant strain to viomycin was sensitive to kanamycin but resistant in some extent to capreomycin, while the high degree resistant strain was resistant to both kanamycin and capreomycin.

Some increases of tuberculostatic activity *in vitro* were shown when capreomycin was combined with isoniazid, p-aminosalicylate, kanamycin, or ethionamide. No antagonistic effect was demonstrated between capreomycin and the other drugs.

Although tuberculocidal activity of capreomycin was evidently observed, it seemed to be less potent than kanamycin.

Therapeutic effect of capreomycin against experimental tuberculosis in mice was studied. The mean survival times were prolonged by the treatment of capreomycin, both in single use and in combined use with cycloserine. The effects of capreomycin for the mouse tuberculosis were compared to kanamycin.

In summary: According to the antituberculous activity, capreomycin will be placed in second class along with streptomycin, kanamycin, viomycin, ethionamide, and ethambutol. In the clinical use, careful thought should be given for the cross resistance among kanamycin, capreomycin, and viomycin.

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EXPERIMENTAL AND CLINICAL STUDIES ON THE ADJUVANT CHEMOTHERAPY OF LUNG CANCER

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Experimental and clinical studies were made on the prevention of vascular dissemination of cancer by the "shower" of cancer cells during surgical operation for lung cancer.

In an experimental study using Ehrlich ascites tumor cells and DDD-female mice, the effect of Mitomycin-C was examined.

The results are summarized as follows.

1) The drug showed more carcinostatic effect when it was injected immediately after intravasation of cancer cells, than when it was injected 24 hours or more after the intravasation.

2) This carcinostatic agent showed a more marked carcinostatic effect *in vivo* than *in vitro*.

3) With low concentrations fo carcinostatic agent, the socalled "adverse effect" was seen in some cases.

4) Carcinostatic effects depend on the concentration of drugs and not on the duration of reaction.

On the basis of these results, we decided on a schedule of adjuvant chemotherapy for lung cancer surgery, including intravenous injection of large doses of drugs during operation.

We treated 48 cases on this schedule; the results of the clinical study are summarized as follows

1) In selecting the drugs, one must consider the sensitivity of individual cells to each drug. The succinic dehydrogenase inhibition method (Kondo) was investigated, and it was found that the sensitivity of cancer cells tended to depend somewhat on the histologic type.

Sensitivity tests for each cancer cell will be most important in the future.

2) No severe side effect was seen in the patients in this series.

3) The prognosis for these patients proved to be better than for patients in the control group in terms of one-year survival rates.

THE EFFECT OF INH ON TUBERCULOUS PULMONARY LESION AND THE MECHANISM OF ITS ACTION

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It has already been made clear clinically and empirically that compared with SM and other antituberculosis drugs INH accelerates remarkably the absorption and cicatrization of tuberculous lesions. In general this is attributed to the excellent antituberculous effect of INH, to the fact that it is comparatively free from secondary effects, and to the fact that with its advent it has become possible to carry out a truly effective long-term chemotherapy.

Teramatsu and others took note of the particular accelerating effect of INH on the absorption and cicatrization of tuberculous lesions, and inferred that INH acts on tubercle bacilli in such a way that the decrease of bacillar lipid takes place.

The findings of Teramatsu et al that formed the basis for this inference, however, are not wholly reliable and seem to require reconsideration in various respects. The purpose of this study is to supplement and further verify these findings.

In Chapter I, for the purpose of confirming anew the accelerating effect of INH on the absorption and cicatrization of tuberculous pulmonary lesions, mainly lesions obtained from resected lungs of cases treated for the first time singly with INH and SM were studied and compared pathohistologically.

Teramatsu uses as his index for measuring the stabilization of the lesion and the state of absorption and cicatrization the degree of formation of his so-called outer stratified tissue in the capsule of lesion, but we use as our index the so-called inner fibrous layer of Yamazaki which corresponds roughly with the metachromasia positive layer of Teramatsu's outer stratified tissue. This is because it has been made clear by Yamazaki that the inner fibrous layer is better as an index for studies of this kind.

In lesions of cases treated for the first time singly with INH, the formation of the inner fibrous layer was poor in many lesions. The proliferation of epithelioid cells was remarkable, and granular tissue accompanied by abundant capillary vessels was observed here and there to invade the caseous area. That is, the indication of the absorption and cicatrization of the lesion was clearly observed. On the other hand, in lesions of cases treated for the first time singly with SM, the formation of the inner fibrous layer was remarkable in most lesions, and there was a strong indication of the stabilization of the lesions.

In Chapter II, for the purpose of confirming these findings by animal experiment,

lesions treated with SM or INH and lesions made with bacilli treated beforehand with INH were studied and compared.

Compared with the control group, in lesions treated after infection with SM the the perifocal inflammation was remarkable inhibited, the lesion was considerably localized, and collagen fibre layer covering the caseous necrotized part was observed.

On the other hand, in lesions treated with INH and in lesions made using bacilli treated beforehand with INH, a proliferation of epithelioid cells was observed. Necrotized lesions were small in number, and the capsula was not formed in most lesions.

Considering that such effects of INH are a result of the decrease of bacillar lipid caused by the action of INH on tubercle bacilli, tuberculoid lesion were made using tubercle bacilli which were extracted lipid with ether.

In the lesion thus obtained, no necrosis or capsulation of lesion was observed. The proliferation of epithelioid cells was remarkable. In fact findings suggesting epithelioid cell tubercle were obtained.

Tuberculoid lesions producted with tubercle bacilli extracted lipid are very much like lesions treated in various ways with INH, which seems to suggest strongly that INH causes the decrease of lipid of bacilli.

In Chapter III, the lipid volume of tubercle bacilli treated with INH or SM was calculated by applying Folch's method. In bacilli treated with INH the lipid volume had decreased.

In Chapter IV these results were summarized and the mechanism of the action of INH was considered.

The conclusion obtained is as following. Like SM, INH acts on the tubercle bacilli in the lesion and causes their number to decrease, but at the same time it checks the synthesis of the lipid of the individual bacilli, and consequently the formation of the capsula, in particular, the inner fibrous layer. The lipid derived from the tubercle bacilli in the lesion is made to decrease more remarkably than in the case of SM. As a result the formation of necrosis is inhibited and the absorption or cicatrization of the lesion is facilitated.

PATHO-ANATOMICAL STUDIES OF THE LUNG CANCER AS RELATED TO THE RADIOLOGICAL FINDINGS

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The auther studied the relationship between patho-anatomical structure and radiological findings in one hundred cases of primary carcinoma of the lung, and should like to conclude as follows:

1) Radiologically, primary lung cancer can be classified in 3 major groups as follows: a) nodular type, b) infiltrative type, c) secondary changes. The nodular type is most frequently found of three types.

2) Nodular shadows are frequently accompanied by linear shadow, radiated shadow or triangular shadow.

3) Accompanying shadows are suggestive on site and extension of original lesions of lung cancer.

4) Retrospective observations of X-ray films show that many cases of lung cancer arise peripherally and appear as the infiltrative type in the earliest stage.

5) The rate of growth of the lung cancer was estimated roentgenologically by the method of Collins and others. The volume doubling time ranged from 2 months to 6 months.