Résumé

ON THE ANTIBACTERIAL ACTIVITY OF PYRONE DERIVATIVES IN VITRO

Studies on the Chemotherapeutic Agents. I
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In order to investigate the relationship between chemical structure and antibacterial activity, 30 pyrone-derivatives, dehydroacetic acid type and 3-acyl-4-hydroxy coumarin type compounds, were examined. Serial dilutions of each compounds were prepared with the media, and the minimal concentration of growth inhibition of bacteria was estimated. The bacterial strains used were Staph. aureus 209 P, Bac. subtilis, E. coli, Sh. flexn. 2a, Myc. tbc. H 37 Rv and 6 Candida strains. The media used were KIRCHNER’s 10% serum media for Myc. tbc., SABOURAUD bouillon against Candida and nutrient broth for other bacteria.

The results showed that the pyron derivatives had the antibacterial effect against Gram positive bacteria but not against Gram negatives. In order to get the powerful activity, the compounds must have “tricarbonyl methane” type. As a rule the antibacterial power of 4-hydroxy coumarin type was higher than that of triacetic acid lactone type. Pyrone derivatives having the 3-position acyl group showed various grades of antibacterial activity according to the structure of the acyl group. Among the compounds possessing various structure at the terminal end of the acyl group, the compounds possessing methyl group had the highest antibacterial power, the second was ethoxycarbonyl group and the third carboxyl group. The α-Imino and acid amide group was not found any activity.

Toxicity of Ethyl-4-hydroxy-α-oxo-3-coumarin-decanoate and 3-n-Decanoyl-4-hydroxy coumarin, both of them had the high antibacterial power, were examined by mice abdominal injection. The result showed that the former could not kill the mice in 1,013 mg/kg, and the latter could kill in 300 mg/kg at 2 hours after injection.

ON THE ANTIBACTERIAL ACTIVITY OF NITROFURAN DERIVATIVES IN VITRO. II

Studies on the Chemotherapeutic Agents. II
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In order to discover the chemotherapeutic agents having excellent antibacterial action, and to investigate the relationship between antibacterial activity and chemical structure, the antibacterial effect of new 9 Furan and 50 Nitrofuran derivatives was investigated in vitro. Serial dilution of each compound was made with the media, and the minimal concentration of growth inhibition of bacteria was estimated. The bacterial strains used were Staph. aureus 209 P, E. coli B, S. tiphi H 901, Sh. flex. 2a, Pseud. aeruginosa, Vibrio cholerae-INABA and Myc. tbc. H 37 Rv. The media used were KIRCHNER’s serum medium against Myc. tbc., and nutrient broth for other bacteria.

The results showed that:
1) Furan derivatives are not effective against all strains at the concentration of 1 : 10,000.
2) Nitrofuran derivatives having a 5-position nitro radical have various grades of antibacterial power against all strains without Pseudomonas aeruginosa according to the character of the 2-position side chain.
3) Comparison between 2-(5-Nitro)-furyl acrolein and 2-(5-nitro) furfurylidene showes that the former is more effective than the latter in general.
4) In β-(5-nitro-2-furyl) acrolein derivatives, comparison between α-methyl, α-ethyl and α-bromo radical shows that α-methyl type is the highest bacteriostatic effect against Myc. tbc., and α-bromo typeis that against other strains.
5) Many compounds in nitrofuran derivatives show the excellent antibacterial activity in vitro. Especially β-(5-nitro-furyl)-α-methyl acrolein semicarbazone inhibits the growth of Myc. tbc. at 1 : 1,280,000 dilution as well as streptomycin does. And β-(5-nitro-2-furyl)-α-bromoacrolein semicarbazone, 2-(5-nitro)-furyl acrylidene picolinoyl hydrazone and 1-[2-(5-nitro)-furyl acrylidene]-2-(6-amino-3-pyridinoyl)-hydrazone inhibit the growth of St. aureus or V. cholerae at 1 : 1,280,000.
STUDIES ON CANCER CHEMOTHERAPY (1ST REPORT)

Studies on the anti-neoplastic action of MH (Haematoporphyrin-Hg) upon Ehrlich-carcinoma

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We studied the anti-tumor effect of MH upon Ehrlich solid tumor. The mechanisms were discussed especially about its activity on liver-catalase.

BACTERIOLOGICAL STUDIES ON TUBERCLE BACILLI IN THE SPECIMENS, RESECTED SURGICALLY FROM PULMONARY TUBERCULOSIS. REPORT I

Mainly in Regard with Staining and Culture

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Bacteriologic investigations were carried out on 284 surgical lesions removed by segmental, subsegmental or partial resections from 204 patients with pulmonary tuberculosis, mainly localized in a segment or smaller area. The following conclusions were obtained.

1) Microscopical acid-fast bacilli and culturable bacilli were found in 172 specimens (60.5%) and 79 specimens (28%) respectively. There were much more demonstrable bacilli in cavities than in any other kind of specimens. Bacilli visible in acid-fast staining, but not culturable, remained in 115 lesions (40%), and there was no difference in the appearance of these bacilli between cavities and encapsulated foci.

2) The larger the resected lesions, the higher was the percentage of acid-fast bacilli found, but there was no correlation between the size of lesions and rate of positive culture.

3) The maximum effective duration of preoperative chemotherapy was to be between 6 and 12 months. The microscopically acid-fast-positive but not culturable bacilli were found in high percentage in the specimens resected during this period.

4) The longer the preoperative negative period in sputum-culture, the lower the rate of bacilli demonstrable in the resected specimens.

5) There was no relationship between the number of acid-fast bacilli in the specimen and the rate of positive culture.

6) Guinea pig inoculation was more favorable method than culture for demonstration of viable bacilli.

7) It could be said that several methods of pretreating the specimen before culture had no influence in the result.

8) Simple washing of the specimen by albumin solution did not influence the result.

9) Cultures of 210 specimens were observed in both Ogawa's egg media and fluid media, and demonstrable microorganisms grew macroscopically in just 11 specimens in fluid media, not in solid media. It is assumed that these bacilli in 10 out of 11 specimens were able to begin active growth only in the fluid culture.

To summarize, it can be suggested that there were dormant tubercle bacilli different from normal bacilli in vitro, which were modified into a kind of life cycle in the tuberculosis lesions under specific circumstances.

BACTERIOLOGICAL STUDIES ON TUBERCLE BACILLI IN THE SPECIMENS, RESECTED SURGICALLY FROM PULMONARY TUBERCULOSIS. REPORT II

Studies on Virulence of Bacilli, which were Culturable by Fluid Media, but not Culturable by Solid Media

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It was reported in the previous article that there were tubercle bacilli, in few specimens, resected from pulmonary tuberculosis surgically, which were unable to grow in Ogawa's egg media, but which could begin formation of colonies in the same media after culture in the fluid media for a period of 10, 30 or 60 days.

This report deals with experimental studies on the
A QUANTITATIVE ANALYSIS OF THE DRUG RESISTANCE OF MYCOBACTERIUM TUBERCULOSIS IN SPUTUM. REPORT VI

Confidence Limits of the Methods of Testing Drug Resistance

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The number of viable units of *Mycobacterium tuberculosis* occurring in sputum was estimated on various sputa by the method described by us (the enumeration of viable *Mycobacterium tuberculosis* by egg medium slant and whirled loop inoculation, *Kekkaku*, in press, 1958-1957), and standard deviations in the estimations were estimated and expressed as percentage standard deviations. From these estimates, a possible maximal value of the percentage standard deviation was determined as 32% at 95% confidence rate.

Substituting this value in a given case, the following postulations have been presented, assuming that the estimation will be made under the same conditions and the number of colonies of a given estimate is not less than 10.

The mean value of viable units in sputum ($\bar{x}$) that should be obtained by more accurate experiments using many tubes would be between the following limits.

- If $x$ is an estimate obtained by only one tube, at 70% confidence rate, $(\bar{x} \pm 0.32\bar{x})$
- at 95% confidence rate, $(\bar{x} \pm 0.64\bar{x})$
- If $x$ is an average of two tubes, at 70% confidence rate, $(\bar{x} \pm 0.23\bar{x})$
- at 95% confidence rate, $(\bar{x} \pm 0.46\bar{x})$
- If $x$ is an average of three tubes, at 70% confidence rate, $(\bar{x} \pm 0.19\bar{x})$
- at 95% confidence rate, $(\bar{x} \pm 0.37\bar{x})$

See also table.

(Predicted in Vol. 6 No. 1)

THE EFFECT OF HYDRONSAN FOR SEVERE PULMONARY TUBERCULOSIS

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Twenty-two patients of severe pulmonary tuberculosis were given hydronsan. The medicine was given during six months, and the daily doses were from 2g to 5g. The resistance to antibiotics of *Mycobacterium tuberculosis* in sputum, the chest-radiograph, the progress of clinical symptom were observed. And as above mentioned, thirteen patients were given isoniazid. Hydronsan was manufactured by Chugai Seiyaku Co., Ltd, and sodium isonicotinylhydrazide gluculonate.

1) The maximum doses was two and a quarter times as much for hydronsan as for isoniazid.

2) On the appearance of resistance to antibiotics, the effect of antibiotics in the group of patients treated with hydronsan was equal to that in the group with isoniazid.

3) On the progress of clinical symptom and on the effect of the chemotherapy so far, the number of improved patients in the group of treated with hydronsan was greater than that in the group with isoniazid.

4) The blood concentration of drug was from 2 to 2.5 times as much in 3g of hydronsan as in 1 g isoniazid.

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