Résumé

STUDIES ON THE MODE OF ACTION OF ANTIBIOTICS

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For the purpose of studying the mode of action of antibiotics in the body, the following experiments were performed.

1) The rate of absorption of antibiotics to erythrocytes were examined *in vitro*.

Streptomycin (SM) is hardly and penicillin (PC) is slightly absorbed to erythrocytes. On the contrary, chlortetracycline (AM) and chloramphenicol (CM) are highly absorbed to erythrocytes. The rate of absorption of erythromycin (EM), oxytetracycline (TM), tetracycline (TC) and carbomycin (MM) are moderate.

2) The rate of protein binding of antibiotics were estimated by dialysis method.

EM, TC, TM and SM are slightly, PC and CM are moderately, AM and novobiocin are highly bound to serum protein and also to human albumin.

3) The differences of the distributions of these antibiotics in the blood are clearly explained with these patterns such as absorption to erythrocytes or binding to serum protein.

4) Reversibility of the inactivation of TC due to protein binding was demonstrated by diluting the serum.

5) Antimicrobial inactivations of antibiotics in the tissue were examined *in vitro*.

TM, PC and CM are slightly or moderately inactivated by the liver emulsion of rabbits. MM is highly inactivated by the various tissue emulsions, f. e. brain, lung, liver, spleen and kidney. SM, AM, TC and EM are little inactivated by any of these tissue emulsion.

In spite of the existence of inactivating facility of the normal liver emulsion, the inactivation of CM by carbon tetrachloride injured liver emulsion was not demonstrated. This finding explains the interesting fact that active CM is excreted in higher concentration in the bile when the liver is injured by carbon tetrachloride in the dog.

In general, the absorption to erythrocytes and binding to serum protein are considered to play the role of depot or vehicle of various substances such as pharmaca, toxins and microorganisms. In antibiotic therapy the meaning of blood level is very important and the above mentioned data of absorption to erythrocytes and binding to serum protein explain the differences of distribution in the blood of various antibiotics. And furthermore, the differences of the rate of penetration of the drugs into the inflammatory area are also explained with these data. Inactivating processes by some tissues show one of the fates of antibiotics in the body.

A STUDY ON CHEMOTHERAPY FOR PULMONARY SUPPURATION, WITH SPECIAL REFERENCE TO DRUG RESISTANT CASES AND THEIR HISTO-PATHOLOGICAL FINDINGS

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It can not be denied that the efficacy of antibiotics for pulmonary suppuration has recently diminished and become null in many cases. This results from the increase of drug resistant germs and from the histologic alterations produced by chronicity of the disease.

From this point of view, the author examined, in a series of 32 cases of pulmonary suppuration, the resistance of microbes with the sputum samples prior to surgery, and attempted to investigate the relation between the degree of drug resistance and the histologic changes of pulmonary lesion resected. The results are to be described under.

1) Lung specimens from 32 resection cases were grouped histopathologically into five forms which were further examined for the relationship with the degree of drug resistance. Strongly resistant cases were discovered at 73.3% of the present series and mostly belonged to the abscess-cavity form. Slightly resistant cases were found at 71.4% and the majority of them were included in the pneumonitis form. Non-resistant cases belonged most frequently to the cleaned cavity and next frequently to the pneumonitis form.

2) The tendency was observed that the larger the size of cavity, the stronger was the degree of resistance.

3) The mixed lesions were detected at 66% of the strongly drug resistant cases, and the preponderantly productive lesions were in 57% of the slightly resistant cases while in 83% of the non re-

sistant cases. In other words, the stronger the degree of resistance, the intenser was the pyofibrosis.

4) As for the germs within lesion, typical microbial form was observed in 20 cases (62%); the germs were most frequently distributed in the cavity walls and decreased with approaching to the lower layer, and no bacilli were found in the deep layer.

5) The stronger the drug resistance, the denser was the microbial distribution in various parts of the lesion. The variety of microbes was many. *Spirocheata* was found very sparingly. *Staphylococcus* was found even in the relative periphery and assumed to play the leading rôle in the emergence of drug resistance.

BACTERIOLOGICAL STUDIES ON 779 CASES OF SUPPURATIVE DISEASES

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Reports of bacteriological studies on 779 cases of suppurative diseases, which were examined in the laboratory of Tokyo University Hospital during 1956, are reviewed. About 460 bacteriologically positive cases of them, percentage of causative organisms are stated.

Furthermore, in comparison with HOSOYA's data in the period during which only sulfa-drugs were available, remarkable changes are observed in bacterial flora. Conspicuous decrease of *Streptococci* is noted and, on the other hand, relative increase of *Staphylococci* and Gram negative bacilli are recognized.

As to sensitivity test, many antibiotics resistant *Staphylococci* are observed and especially the ones resistant to penicillin and sulfa-drugs are noted to be remarkably increased. *Streptococci* are sensitive to each antibiotics, but *Pseudomonas aeruginosa* is resistant to almost all of antibiotics. Many strains of *Escherichia coli* are sensitsve to chlortetracycline, oxytetracycline and chloramphenicol.

EFFECT OF MITOMYCIN C UPON EXPERIMENTAL TUMORS

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Effect ot mitomycin C, which is the same substance as mitomycin X, upon various experimental tumors was studied. Hybrid rats weighing about 100g and dd mice weighing about 20g were used in the experiments.

A) Effect on ascites tumors : 50~500 mcg of mitomycin C was daily injected into the abdominal cavity during 3~38 days starting from 48 hours after the intraperitoneal transplantation of the tumor.

Striking effect was recognized in the cases of diploid, tetraploid Hirosaki sarcoma and Ascites hepatoma 130, where daily administration of 50~100 mcg/kg was sufficient to prolong the survival days of the animals.

Marked effect was recognized in the cases of Ehrlich carcinoma, where daily administration of 200 mcg/kg was sufficient.

Moderate effect was recognized in the cases of Yoshida sarcoma and mouse lymphatic leukaemia S. N. 36, where daily administration of 500 mcg/kg was required. Slight or no effect was recognized in the cases of Takeda sarcoma, ascites hepatoma 7974 and Usubuchi sarcoma.

B) Effect on solid tumors : 200~500 mcg/kg of mitomycin C was daily injected into the abdominal cavity during 7~15 days starting from 3~10 days after the subcutaneous transplantation of diploid or tetraploid Hirosaki sarcoma. The growth of the solid tumor was inhibited completely in the cases of earlier treatment, while in the cases of later treatment recidivation was recognized in some instances.

Sulfisoxazoleと抗結核剤との試験管内併用効果 (続報)

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前報で, bacterial population の一部の菌の発育を阻止する濃度の SM, INAH, PAS と sulfisoxazole (SZ) との併用効果について報告したので, 本報では, bacterial population の大部分の菌の発育を阻止する濃度の抗結核剤と SZ との併用効果について実験した。

SM 20 mcg または INAH 1 mcg と SZ 0, 1, 5, 10 mcg とを併用した際の耐性集落数は, SZ の有無によつて, 有意の差を示さなかつた。しかし, SZ を併用した培地では, 耐性集落の大きさが小さくなるので, 結局 SZ 併用により耐性菌総数が減少すると考えられる。従つて, 恒量継代法によつてみられる, SZ の SM または INAH 耐性遅延の機作の1つは, 発育遅延による耐性菌絶対数の減少によるものと想像される。一方, PAS 10 mcg または tibione 20 mcg と SZ との併用では, SZ 併用によつて却つて耐性集落数の有意の増加がみられた。すなわち, PAS と SZ または tibione と SZ との間には拮抗作用があると考えられる。

SM と SZ 併用または INAH と SZ 併用は, SM 耐性または INAH 耐性の *in vivo* 出現をも遅延させることが想像され得る。一方, PAS と SZ の併用または tibione と SZ の併用では, PAS 耐性または tibione 耐性の *in vivo* 出現を遅延させることは期待できそうにない。

INAH-Sulfathiazole 併用療法による INAH 耐性出現の遅延

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INAH-Sulfathiazole (ST) 併用によつて, INAH 耐性の出現を遅延し得るかどうかを観察するために次の臨床実験を行なつた。1953～1955 年に大府荘入院中の陳旧空洞を有し, 常時排菌を示す重症肺結核患者で過去に INAH 投与を受けなかつた例, 81 例を対象とし, 第 I 群 INAH 0.2 g ST 2.0 g 併用毎日, 11 例, 第 II 群 INAH 単独 0.2～0.3 g 毎日, 63 例, 第 III 群 ST 単独 2.0 g 毎日, 7 例の3群に分けて治療を行ない, 3カ月後に INAH 耐性検査を行なつた結果を集計した。第 I 群では, 3カ月後に排菌のなかつた3例を除外して, 8例中1例だけが INAH 1 mcg 耐性を示したが, 第 II 群では 63 例中 35 例が INAH 1 mcg 耐性を示した。この差は χ^2-test により, 6% の包険率で有意である ($\chi_0^2=3.50$, $p=0.06$)。従つて, INHA-Sulfathiazole 併用療法により, INAH 耐性出現が臨床的にも遅延することは確からしく思われる。なお, INAH-Sulfathiazole 併用療法は 3～7 カ月間行なつたが, 特に副作用を示すことはなかつた。