Résumé

結核の化学療法 第1報
Thiosemicarbazone 類及び関連化合物の試験管内抗菌力

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Thiosemicarbazone 27 種類, Aldehyde 2種類, Ketone 2種類, Semicarbazone 4種類, Guanylhydrazone 4種類, Nitromethane 誘導体3種類, の人型結核菌 $H_{37}Rv$, ブドー菌 209 P 及び大腸菌に対する試験管内抗菌力試験を行い, 次の結果を得た。

Thiosemicarbazone 類の結核菌に対する抗菌力は Benzaldehyde 誘導体, Acetophenone 誘導体, Cinnamaldehyde 誘導体, Benzalacetone 誘導体の順に低下する傾向が認められ Vinylog の方が一般に抗菌力が低かつた。

p-Acylamino 基を有する Thiosemicarbazone の抗菌力の対数と Acyl 基の炭素類との間には略々直線的な関係が成立し, 炭素数が小さい場合には α, β 不飽和 Acyl 基の着いた化合物が対応する化合物よりも抗菌力が高く, p-Crotonylamino-benzaldehyde Thiosemicarbazone が供試化合物中最大の抗菌力を示した。

α, β 不飽和 Carbonyl 化合物の Thiosemicarbazone の結核菌に対する抗菌力は α 位に Br を導入することにより低下するが他の菌に対しては逆に上昇した。

α, β 不飽和 Aldehyde 及び Ketone 自体も結核菌に対して可成りの抗菌力を有し, α 位に Br を導入すると抗菌力は上昇した。

Semicarbazone, Guanylhydrazone, Nitromethane 誘導体中には結核菌に対する高い抗菌力を示すものはなかつたが, 他の菌に対しては Br を有する Guanylhydrazone が可成りの抗菌力を示した。

DRUG SENSITIVITY OF *SHIGELLAE* ISOLATED FROM PATIENTS IN 1953 AND THE COMBINED ACTION OF UREA WITH SULFATHIAZOLE TO *SHIGELLAE*

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The authors determined the *in vitro* sensitivity of *Shigellae* isolated from patients of Kyoto University Hospital in 1953 to chlortetracycline (aureomycin), chloramphenicol, oxytetracycline (terramycin), streptomycin, and sulfathiazole by means of tube dilution method, and studied on the combined action between sulfathiazole and urea to *Shigellae, in vitro*. The results were summarized as follows :

On the sensitivity of *Shigellae* to antibiotics, of 49 strains, each strain to chlortetracycline and chloramphenicol and 3 strains to streptomycin were about 8 times resistant than the standard strain. Of 45 strains, 21 were sensitive to sulfathiazole, and most of these were identified with *Sh. sonnei*.

A simple method for determining whether sensitive or resistant to sulfathiazole was studied. The method, determining by growth or no growth on the BTB-lactose-agar plate containing sulfathiazole 100 mg/dl, showed the good correlation with the results in the synthetic medium. The potentiating effect was found between sulfathiazole and urea to the bacteriostatic rate by means of the tube dilution method. This effect was marked when 2.5 or 5% of urea was added. To the resistant strain, also, this effect was found, but the sensitivity of these resistant strains was not less than 10 mg/dl in the synthetic medium employing casamino acid. Although the potentiating effect was found between sulfathiazole and urea, the repression of the development of sulfathiazole-resistance by urea was not observed.

STUDIES ON THE GROWTH MECHANISM OF *CANDIDA ALBICANS*, I

HIDEO OIKI
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1. Oral administration of *Candida albicans* had no unfavorable effect on the health of experimental volunteers. *Candida albicans* was detected in the feces soon after the administration but quickly decreased in number thereafter.

2. Following the administration of chloramphenicol (chloromycetin), *C. albicans* increased rapidly as the population of *E. coli* decreased among the intestinal flora.

3. The proliferation of *C. albicans* within the intestinal tract was accelerated not only by the oral administration of chloramphenicol but also by the administration of sulfathiazole.

4. *C. albicans* and *E. coli* does not impair the growth of each other in any appreciable degree.

5. The culture filtrate of *E. coli* seems to have no harmful effect on the growth of *C. albicans*.

6. *Candida albicans* cannot grow in the pure glucose solution.

7. The minimum concentration of simple peptone solution capable of sustaining growth of *C. albicans* with an inoculum of 0.0001 mg was found to be 1.0 mg/cc.

8. When 2.5 mg/cc of glucose was added to the peptone solution, the growth of *C. albicans* was seen even when the peptone was reduced to $\frac{1}{10}$ of the original concentration.

9. Growth of *C. albicans* was detected even at such low glucose concentration as 1.0 mcg/cc, and the cell yield increased with the elevation of glucose concentration. With 2.5 mg/cc of glucose, a cell yield 10 times that of the control with no glucose was obtained by 40 hours culture.

10. When a small inoculum of *C. albicans* and *E. coli* was cultured together, there was no sign of growth of *C. albicans* after 48 hours.

11. When a larger inoculum of *C. albicans* was cultured with *E. coli*, the growth of *C. albicans* was not observed even after 48 hours in 1.0 mcg/cc of glucose, however, in excess amount of glucose (20 mg/cc), the growth of *C. albicans* was 15 times as greater as compared with 1.0 mcg/cc of glucose. This seems to indicate that *C. albicans* had utilized the surplus g lucose with *E. coli* had failed to break down.

From the foregoing experimental results, the explosive proliferation of *C. albicans* within the intestinal tract following the oral administration of antibiotics may be considered to be due to the utilization by *C. albicans* of the small amount of glucose accumulating in the intestines in consequence of the decrease in the population of *E. coli* which otherwise would have used up the glucose.

STUDIES ON THE GROWTH MECHANISM OF *CANDIDA ALBICANS*, II

HIDEO OIKI

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1. The growth of *Candida albicans* was not influenced by pH changes within the limits of physiological variation occurable within the intestinal canal.

2. The metabolic products (in the culture filtrate) of *B. coli* was found to inhibit the growth of *Candida albicans* to some extent.

3. The growth of *Candida albicans* was somewhat promoted by chloramphenicol, chlortetracycline and oxytetracycline, but not by other antibiotics and sulfathiazole.

4. The growth mechanism of *Candida albicans* within the intestinal canal during the administration of antibiotics may therefore be presumed as follows;— (a) The antibiotics inhibit the growth of *B. coli*. (b) Consequently, the metabolic product of *B. coli* which tend to inhibit the growth of *Candida albicans* decreases and nitrogenic and energy source (glucose) which otherwise would have been utilized by *B. coli* accumulate within the intestinal canal. (c) Devoid of the inhibitory substance produced by *B. coli*, *Candida albicans* proliferate explosively by utilizing the surplus nitrogenic and energy producing sources left over by *B. coli*.

THE MECHANISM OF ACTION OF HOMOSULFAMINE (MARFANIL)

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Action of homosulfamine (aminomethylphenylsulfornamide-HCl) on isolated enzyme systems was tested.

Flavoproteins, *l*-amino acid oxidase and DPN-linked cytochrome C reductase were extracted from washed cells of *Mycobacterium tuberculosis* var. *avium* according to USAMI, *et al.* (Symp. on Enzyme Chem. (Japan), 8 : 82, 1953) and MAHLER, *et al.* (J. Biol. Chem., 199 : 585, 1952), and action of homosulfamine (aminomethylphenylsulfonamide-HCl) on *l*-amino acid oxidase and the diaphorase activity was tested in systems using neotetrazolium chloride (NTC) as the hydrogen acceptor. Homosulfamine inhibited significantly the action of *l*-amino acid oxidase and the diaphorase activity. However, hydrogen transfer from reduced diphosphopyridine nucleotide (reduced DPN) to flavoprotein occurred in the presence of homosulfamine, when the amount of decrease of reduced DPN in the presence of flavoprotein was measured in the presence or absence of homosulfamine by photoelectric spectrophotometer at wave length 340 mμ. It is, therefore, believed that homosulfamine does not inhibit the hydrogen transfer from reduced DPN to flavoprotein but a process of reoxidation of reduced flavoprotein, and this is the mechanism of inhibition of reduction of NTC in the system consisting of reduced DPN, flavoprotein, and NTC. It is, therefore, suggested that homosulfamine inhibits function of an unknown factor between flavoprotein and cytochrome systems which would catalyze the oxidation of reduced flavoprotein.

ON THE ANTITUBERCULOUS ACTION OF HOMOSULFAMINE (MARFANIL)

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The antituberculous action of homosulfamine (Marfanil, aminomethylphenylsulfoneamide-HCl) on the Jucho strain of *Mycobacterium tuberculosis* var. *avium* (*M. avium*) was tested and the following results were obtained.

The oxygen uptake measured by conventional WARBURG method and the reduction of neotetrazolium chloride and picric acid by living whole cells of *M. avium* were inhibited by homosulfamine. It was, therefore, suggested that respiratory enzymes, that is, dehydrogenase–flavoprotein-(-factor X) of the cells were inhibited by homosulfamine, because these dyes were recognized as hydrogen aceptors from flavoprotein.

The oxygen uptake and the reduction of the dyes by the living cells were inhibited by the drug at higher concentrations than encountered in the *in vitro* assay. However, the amount of cells used in the experiments was great. Thus, effect of the amount of cells on the reduction of the dyes was tested, and it was observed that the smaller the amount of cells the larger the rate of inhibition. It was, therefore, suggested that *in vitro* inhibition of growth, whi ch was observed in experimeents using small inoculations, might be produced by the inhibition of respiratory enzymes.

It was suggested that lower susceptibility of the strain against the drug might be produced by lower diffusibility of the cell membrane against the drug.

In the experiments, in which *M. avium* was used as the test strain, it was also observed that *p*-aminobenzoic acid showed no antagonistic action against homosulfamine.

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ブドウ球菌感染症に対するエリスロマイシン

WALLACE E. HERRELL, *et al*.. Erythromycin for infections due to Micrococcus pyogenes. J. A. M. A. Vol. 152, No. 17

PC, AM, TM, SM, 等の抗生物質に抵抗性であるブドウ球菌感染症に対してエリスロマイシン投与による治療を行つた。今迄ブドウ球菌のエリスロマイシン抵抗性Qものは殆んど発見されていない。54 例の各種ブドウ球菌感染症の中，敗血症 8 例に対しては，6 例に著効を認めたが 2 例は治療中に急速にエリスロマイシン抵抗性となり患者は心内膜炎で死亡した。エリスロマイシンの耐性獲得は試験管内では緩徐であると云われているが，この 2 例では耐性獲得が甚だ早く SM. 耐性獲得によく似ている。骨及び軟部組織の感染症に於ては 17 例中 8 例に満足すべき結果を得ている。この中の失敗例の原因はエリスロマイシンに対する抵抗性の発展によるものもあるし，他の原因によるものもある。Staphylococcic ileocolitis 14 例に於てはすべて満足すべき結果であつた。腸管中にブドウ球菌を証明したが臨床症状のない 5 例にエリスロマイシンを用いたが，何れも菌を取り除くことに成功した。その他脳膜炎，咽頭炎，扁桃腺炎，尿路感染等種々のブドウ球菌感染症に対してエリスロマイシンは効果があつた。以上エリスロマイシンの投与によつて重篤な中毒症状を呈したものはなかつた。

（慶大外科　関根抄）

抗生物質の治療中に合併するブドウ球菌性腸炎及びそれに対するエリスロマイシンの効果について

DEARING, W. H. & HEILMAN, F. R.: Micrococcic (Staphylococcic) enteritis as a complication of antibiotic therapy. Its response to Erythromycin. Proc. Staff. Meet. Mayo Clin. 28 : 121–134, 1953.

AM（オーレオマイシン），TM（テラマイシン）の何れかで治療を受けている患者 44 人について，手術時に腸内より細菌を培養し，下痢をしている患者からは，糞便或は腸分泌物より細菌培養を試みブドウ球菌と大腸菌との比率を見，之と起つて来た臨床症状とを較べて次の如き結果を得ている。抗生物質を全然受けていない患者でも腸内より培養すると少数のブドウ球菌を稀に証明する。AM, TM の治療を受けている患者で，腸内より少数のブドウ球菌及び多数の正常腸内細菌を証明する場合には，臨床的に特別な症状は起つて来ない。正常の腸内細菌に比しブドウ球菌を多数に証明した時には，下痢その他の胃腸症状及び全身反応を惹起し中にはショック状態となつて死亡した者もある。この死亡者は解剖によつて何れも偽膜性腸炎(Pseudomembranous enteritis)を証明している。以上の症状の発現のあつた患者に AM, TM の投与を中止し Erythromycin を投与すると，その症状の軽快或は消失を来たしブドウ球菌は陰性となつている。

即ち，AM や TM の様な抗生物質の普及につれ，入院患者に之等に抵抗性のブドウ球菌が増加し，腸内細菌叢が之等抗生物質によつてその正常発育を阻止せられた場合に，抵抗性ブドウ菌が腸管内に侵入増殖しこの毒素によつて種々の胃腸障害及び全身反応を惹起して来る。之等患者の咽頭及び上気道に抵抗性ブドウ球菌を証明することは，此処からブドウ球菌が腸管内に侵入して増殖することを暗示している。このブドウ球菌性腸炎と偽膜性腸炎との間に必然的関係があるか否かは不明である。ブドウ球菌性腸炎の症状を要約すると，下痢は主要な訴えであるが必発するものではなく，種々の程度があつて大量の緑色がかつた糞便を伴うものである。全身倦怠感，発熱，食慾不振，吐気，嘔吐，腹部膨満感，その他全身状態の如何によつては，ショック状態を発現するものもある。

若し AM, TM の投与を受けている患者で，下痢その他の胃腸障害及び全身反応を来たした時には，腸の分泌物及び糞便より細菌培養を行ない，ブドウ球菌を証明した時には AM, TM の投与の中止，エリスロマイシンの投与，対症療法等適宜の処置を講ずべきである。

（慶大外科　関根抄）