

ABSTRACTS

1. FUNDAMENTAL STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS

PART 60. TUBERCULO-BACTERIOSTATIC EXPERIMENTS WITH 2,2'- DIHYDROXYAZOBENZENE AND HYDROXYBENZYLIDENE-2- AMINOPHENOL DERIVATIVES

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Received for publication, April 2, 1956.

A total of 26 derivatives of 2,2'-dihydroxyazobenzene and hydroxybenzylidene-2-aminophenol were tested for their tuberculo-bacteriostatic activity in Kirchner's medium containing 10 % rabbit's serum (pH 6.8).

The data obtained may be summarized as follows :

- 1) 2- (5'-bromo-salicylidene) aminophenol (No. 683) and 2-(3', 5'-dichlorosalicylidene) aminophenol (No. 688), both exhibited growth-inhibitory activity up to a dilution of 1:512,000, while o-aminophenol was proved to be effective up to a dilution of 1:1,280,000.
- 2) 2- (2'-hydroxy-3', 5'-dibromophenylazo) -4-chlorothymol (No. 672) was growth-inhibitory up to a dilution of 1:128,000.
- 3) All the remaining compounds were found to be far less active.

2. FUNDAMENTAL STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS

PART 63. EXPERIMENTS ON REPEATED EXPOSURE OF TUBERCLE BACILLI TO VARIOUS ANTIBACTERIAL SUBSTANCES *in Vitro*

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Received for Publication, April 10, 1956.

From the chemotherapeutic point of view, it was thought to be of interest to carry out a systematic study on the relation between the kinds of the antibacterial substances and the appearance of drug-resistant strains of tubercle bacilli.

A human strain of *Myco. tuberculosis*, "Kawakami", which had never come into contact with any of the 12 antibacterial substances included in the present investigation, was used as the parent organism. The serial dilution method, using 10 % serum-Kirchner's medium, was employed for all of the exposure and titration experiments.

The results obtained may be summarized as follows :

- 1) There occurred no appreciable decreased in sensitivity of tubercle bacilli to any of

the following substances even after ten successively performed exposure experiments: o-aminophenol (Minimum growth-inhibitory concentration = 1 : 640,000~1,280,000), 3-aminophenoxazone-(2) (=1 : 1,280,000~2,560,000), 3-diazophenoxazone-(2) (=1 : 640,000 ~ 1,280,000), 3-acethylaminophenoxazone-(2) (=1 : 1,280,000~2,560,000), 3-chloroacethylamino-phenoxazone-(2) (=1 : 320,000~640,000), 3-(N, N-diethyl- β -alanyl-amino)-phenoxazone-(2) (=1 : 320,000~640,000), 3-(p-acethylaminobenzylidne-amino)-phenoxazone-(2) (=1 : 40,000~80,000), amethyst violet (=1 : 1,280,000~2,560,000), 8-hydroxyquinoline (=1 : 640,000~1,280,000).

- 2) The repeated exposure of tubercle bacilli to acriflavine resulted in a gradual development of resistance, although the tendency for resistant strains to appear was less with the drug, than with dihydrostreptomycin (DHSM) and isonicotinic acid hydrazide (INAH). Whereas the parent strain was, for example, inhibited by 3 micrograms of acriflavine per ml, the variant, which was obtained after the tenth generation, grew even in 25 micrograms acriflavine per ml.

Thus, the following three resistant strains were isolated:

- a) Acriflavine-resistant strain,
- b) DHSM-resistant strain,
- c) INAH-resistant strain.

And it was demonstrated on one hand that these three resistant strains could be successively subcultured in ordinary 10 % serum-Kirchner's medium without any change in their degree of resistance, and on the other hand that between these three strains there existed no cross resistance.

- 3) Experiments, in which the sensitivity of each of these three resistant strains was tested against o-aminophenol, 3-aminophenoxazone-(2), amethyst violet, and 8-hydroxyquinoline, have shown that these four substances were all strongly active in causing the tuberculo-bacteriostasis in 10 % serum-Kirchner's medium.

3. IMMUNOLOGICAL STUDIES IN TUBERCULOSIS

PART 4. EXPERIMENTAL STUDIES ON THE INFLUENCE OF ANTIGEN-INJECTION AND IRRADIATION UPON THE PRODUCTION OF ANTIBODIES

AND THE DEFENCE-ACTION OF LIVING BODIES

NO. 2. INFLUENCES OF TYPHOID VACCINE INJECTION AND X-RAY IRRADIATION UPON THE SERUM PROTEIN AND HEMOGRAM

II. INFLUENCES OF TYPHOID VACCINE INJECTION

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Received for publication, Mar. 10, 1956.

The influence of typhoid vaccine injection upon the serum protein and hemograms of rabbits was observed.

The results obtained were as follows:

- 1) The total protein content of the serum was not observed to increase after the

immunization.

- 2) The albumin content was observed to decrease after the immunization and the α -globulin content did not show any appreciable change.
- 3) The β -globulin content was observed to increase in the early stage of the immunization and to return to the normal level in the late stage, when the γ -globulin content was observed to increase.
- 4) Rise of the agglutinin titer of the serum was observed to run parallel with increase of the β -globulin content in the early stage of immunization and to reach a maximum when the γ -globulin content began to increase in the late stage.
- 5) In contrast, the decrease of lymphocytes following each injection of typhoid vaccine, there occurred marked temporary increase of leucocytes owing especially to the remarkable increase of meteosinophilic leucocytes.

4. IMMUNOLOGICAL STUDIES IN TUBERCULOSIS

PART 6. EXPERIMENTAL STUDIES ON THE MECHANISM OF DESENSITIZATION NO. 1. INFLUENCE OF DESENSITIZATION OF RABBITS WITH OLD TUBERCULIN UPON THEIR IMMUNE REACTIONS AND RESISTANCE AGAINST TUBERCULOSIS

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Received for publication, Aug. 29, 1955.

The following three groups of rabbits, A, B and C were subjected to the experiment to investigate the influence of desensitization with old tuberculin (OT) upon their immune reactions and resistance against tuberculosis.

Group A : Infected with human type tubercle bacilli "H₃₇ Rv".

Group B : Inoculated with paraffin oil heat-killed "H₃₇ Rv".

Group C : Control.

Groups A and B were each divided into two subgroups, one subgroup receiving daily injection of OT for a certain period and the other receiving no injection. The schedule of the experiment is briefly shown in the following table.

Group	Treatment	Number of rabbits	Weeks after inoculation			
			4	20	24	44
A	1.0 mg of "H ₃₇ Rv"	2	← daily desensitization with OT (total: 6.7ml) → a			
		2	not receiving desensitization a			
B	10 mg of paraffin oil heat-killed "H ₃₇ Rv"	2	← receiving desensitization (total : 9.5 ml) → *			
		2	not receiving desensitization * a			
C	Control	2	* a			

a : autopsied

* : infected with 1.0 mg of "H₃₇ Rv"

At intervals throughout the course of the experiment, tuberculin allergy, phagocytic power of leucocytes against heat-killed "H₃₇ Rv" strain and growth inhibitory power of the serum against "H₃₇ Rv" strain as shown by the slide cell culture method were tested, and at the same time titration of hemagglutinin, agglutinin (*Inoue*) and pretipitin (*Kochi*) was carried out. Further, electrophoretical observation of serum protein was occasionally performed.

At the end of the experiment, all the animals were killed, and pathological examination of visceral organs and quantitative culture of tubercle bacilli in the viscera were carried out.

The results obtained were as follows:

- 1) Daily injection of OT (desensitization) for 16 weeks or so in group A and B, produced rises of the antibody titer, promotion of phagocytic power of leucocytes and growth inhibitory power of the serum, and increase of γ -globulin content accompanied with fall of tuberculin skin sensitivity.
- 2) The antibody titer, the growth inhibitory power of the serum and the γ -globulin content affected by the challenge infection of human tubercle bacilli "H₃₇ Rv" in group B were found to return to normality completely in the desensitized group and less completely in the undesensitized one.
- 3) The animals desensitized with OT showed less extensive tuberculous lesions in visceral organs than the undesensitized animals. Further, the results of quantitative culture of the bacilli in visceral organs ran parallel with the extent of the lesions.

5. IMMUNOLOGICAL STUDIES IN TUBERCULOSIS

PART 6. EXPERIMENTAL STUDIES ON THE MECHANISM OF DESENSITIZATION

NO. 2. INFLUENCE OF DESENSITIZATION OF RABBITS WITH O-AMINO-PHENOL AZO-TUBERCULIN UPON THEIR IMMUNE REACTIONS AND RESISTANCE AGAINST TUBERCULOSIS

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The following three groups of rabbits, A, B and C were subjected to the experiment to investigate the influence of desensitization with o-aminophenol azo-tuberculin (AT) upon immune reactions and resistance against tuberculosis.

Group A : Infected with human type tubercle bacilli "H₃₇ Rv".

Group B : Inoculated with paraffin oil heat-killed "H₃₇ Rv".

Group C : Control.

Groups A and B were each divided into two subgroups, one subgroup receiving daily injection of AT for a certain period and the other receiving no injection.

The schedule of experiment is briefly shown in the following table.

Group	Treatment	Number of rabbits	Weeks after inoculation			
			4	20	24	44
A	1.0 mg of "H ₃₇ Rv"	2	← daily desensitization with AT (total : 61.6 r) → a			
		1	not receiving desensitization a			
B	10 mg of paraffin oil heat-killed "H ₃₇ Rv"	3	← receiving desensitization (total : 84 r) → * a			
		3	not receiving desensitization * a			
C	Control	2				

a : autopsied

* : infected with 1.0 mg of "H₃₇ Rv"

At intervals throughout the course of the experiment, tuberculin allergy, phagocytic power of leucocytes against heat-killed "H₃₇ Rv" strain and the growth inhibitory power of the serum against "H₃₇ Rv" strain as shown by the slide cell culture method were observed, and at the same time titration of hemagglutinin and agglutinin (*Inoue*) was carried out. In addition, electrophoretical observation of serum protein was occasionally performed.

At the end of the experiment, all the animals were killed, and pathological examination of the visceral organs and quantitative culture of tubercle bacilli in the viscera were carried out.

The results obtained were as follows :

- 1) Daily injection of AT (desensitization) for 16 weeks or so in groups A and B, produced rise of the antibody titer, promotion of phagocytic power of leucocytes and growth inhibitory power of the serum, and increase of γ -globulin content accompanied with fall of tuberculin skin sensitivity.
- 2) The antibody titer, the growth inhibitory power of the serum, the phagocytic power of leucocytes and the γ -globulin content affected by the challenge infection of human type tubercle bacilli "H₃₇ Rv" in group B were found to return to normality completely in the desensitized group and less completely in the undesensitized one.
- 3) The animals desensitized with AT showed less extensive tuberculous lesions in the visceral organs than the undesensitized animals.

6. STUDIES ON THE RESISTANCE OF MICROORGANISMS TO VARIOUS CHEMICALS

PART 3. ON THE EFFECT OF SIMULTANEOUS EXPOSURE TO TWO CHEMICALS

NO. 3. EXPERIMENT WITH ISONICOTINIC ACID HYDRAZIDE-RESISTANT HUMAN TYPE TUBERCLE BACILLI "H₂" STRAIN

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By successive cultivation of isonicotinic acid hydrazide- (INAH-) resistant human type tubercle bacilli "H₂" strain (50 γ /ml) in samples of Kirchner's medium respectively containing INAH, INAH plus streptomycin (SM), INAH plus p-aminosalicylic acid (PAS) and INAH plus o-aminophenol (OM), the tuberculostatic power of the above-mentioned drugs singly or in combination, as well as their liability of inducing drug-resistance of the bacilli was estimated.

The measurement of the drug-resistance was carried out quantitatively with samples of Ogawa's 1% KH₂PO₄ egg yolk medium containing each of the antituberculous agents in various concentrations.

The results obtained were as follows :

- 1) Rise of INAH-resistance of the bacilli was observed by successive culture on the medium containing INAH alone.
- 2) SM combined with INAH was observed to have some effect of inhibiting the rise of the INAH-resistance, and to produce conspicuous degree of SM-resistance in the bacilli.
- 3) Addition of PAS, as well as addition of OM to INAH was proved to be effective for inhibiting the rise of INAH-resistance while there was some increase of bacilli having low INAH-resistance (0.1 and 1.0 γ /ml).
- 4) Addition of INAH to SM and to PAS was proved to be ineffective for inhibiting the development of SM-resistance (100 γ /ml in the 5th stage), and the PAS-resistance (1.0 γ /ml in the 5th stage) respectively.
- 5) Development of OM-resistance of the bacilli was not observed by successive culture on the medium containing OM, singly or combined with INAH.
- 6) OM and PAS were demonstrated to have greater additive effect than SM of augmenting the tuberculostatic power of INAH.

7. STUDIES ON THE RESISTANCE OF MICROORGANISMS TO VARIOUS CHEMICALS

PART 4. STUDIES ON THE VIRULENCE OF DRUG-RESISTANT TUBERCLE BACILLI FOR THE GUINEA PIG

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Received for publication, Mar. 16, 1956.

Human type tubercle bacilli "H₂" resistant to streptomycin (SM) and same bacilli resistant to isonicotinic acid hydrazide (INAH) used in the present experiment were obtained by successive cultivation of the bacilli in a series of samples of Kirchner's medium containing SM or INAH as the case may be.

The following three groups of 6 guinea pigs each were subjected to the experiment in which virulence of SM- and INAH-resistant "H₂" was examined.

- 1) Guinea pigs infected with SM-resistant "H₂".
- 2) Guinea pigs infected with INAH-resistant "H₂".

3) Guinea pigs infected with the parent drug-sensitive "H₂" as control.

Each group was divided equally into two subgroups, one subgroup being sacrificed 4 weeks after infection and the other subgroup 7 weeks after infection. In each case histo-pathological examination of the visceral organs and quantitative cultivation of the tubercle bacilli in the viscera were immediately carried out.

It was revealed that the parent "H₂" strain was the most virulent and the SM-resistant "H₂" and the INAH-resistant strain came next in that order.

8. STUDIES ON THE RESISTANCE OF MICROORGANISMS TO VARIOUS CHEMICALS

PART 5. STUDIES ON THE SENSITIVITY OF STREPTOMYCIN-, p-AMINOSALICYLIC ACID- AND ISONICOTINIC ACID HYDRAZIDE-RESISTANT TUBERCLE BACILLI TO VARIOUS ANTITUBERCULOSIS AGENTS

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Using samples of Ogawa's 1% KH₂PO₄ egg yolk medium containing various concentration of p-aminosalicylic acid (PAS), streptomycin (SM), viomycin (VM), tibione (TbI), o-aminophenol (OM) or sodium isonicotinic acid hydrazide methanesulfonate (IHMS), the drug-sensitivity of SM-, PAS-, or INAH-resistant human type tubercle bacilli "H₂" and of tubercle bacilli isolated from sputa of 34 tuberculosis patients was examined.

The sensitivity of the parent human type tubercle bacilli "H₂" and "H₃₇ Rv" to the above-mentioned drugs was examined in the same way.

The results obtained were as follows :

PAS- and SM-resistant tubercle bacilli were sensitive to all the other chemicals, but of the 7 strains of INAH-resistant tubercle bacilli 5 were proved to be resistant to IHMS, though to different degrees, and two were found sensitive to IHMS.

9. STUDIES ON CULTURE OF TUBERCLE BACILLI

PART 2. STUDIES ON THE INFLUENCE OF VARIOUS SUBSTANCES UPON THE GROWTH OF TUBERCLE BACILLI

NO. 2. THE INFLUENCE OF TUBERCULIN AND VARIOUS CONSTITUENTS OF TUBERCLE BACILLI UPON THE GROWTH OF TUBERCLE BACILLI

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Received for publication, Jan. 15, 1953.

A series of examination was carried out concerning the influence of various substances upon the growth of human type tubercle bacilli "H₂". In a previous paper, it was reported that the growth of bacilli on Masuda's medium was observed to be more luxuriant in the presence of old tuberculin (OT) prepared from glycerin-bouillon or Sauton-culture and various amino acids than in their absence. In the present paper are described studies on some constituents of old tuberculin having the power of promoting the growth of tubercle bacilli.

The experiments consisted of three parts.

- I) Samples of OT were prepared from one- to seven-week culture fluid, and their activity on the skin were determined. Each of them was added to Masuda's medium, the growth of tubercle bacilli planted was observed and it was demonstrated that the growth-promoting effect of individual samples varied in parallel with their potency of eliciting skin reaction.
- II) In order to separate the growth-promoting constituents of OT, kaolin, charcoal, human O type blood cells were used as absorbents. It was revealed that the growth-promoting factors in OT were absorbed sufficiently well by kaolin but not by the others.
- III) The protein-, polysaccharide- and phosphatide-fraction of tubercle bacilli were tested in the same way as OT. The protein-fraction was proved to promote the growth of the bacilli most strongly. When o-aminophenol azo-tuberculin, o-aminophenol azo-tuberculoprotein or citrate-tuberculin was used in place of the protein-fraction no promotion of the growth of the bacilli was observed.

10. HISTOLOGICAL STUDIES ON TUBERCULIN ALLERGY

PART 2. HISTOLOGICAL STUDIES ON THE SKIN REACTIONS CAUSED BY INTRADERMAL INJECTION OF FRACTIONS OBTAINED FROM TUBERCLE BACILLI

NO. 1. STUDIES ON SKIN REACTION CAUSED BY THE PROTEIN-FRACTION

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Received for publication, Mar. 1, 1956.

The following three groups of rabbits were given skin test with the protein-fraction from human type tubercle bacilli "Aoyama B" (P-"H"), azo-P-"H", protein-fraction from BCG (P-"B") and azo-P-"B".

Rabbits of group A : Infected with human type tubercle bacilli "H₃₇ Rv".

Rabbits of group B : Infected with BCG.

Rabbits of group C : Controls, receiving no treatment.

These four reagents were simultaneously injected on the back of each rabbit of the

three groups at spots 5 cm apart, and the affected parts of the skin were cut out at various intervals, and a comparative study of histological changes was carried out.

The results obtained were as follows :

- 1) Regardless of the difference in kind of the reagents used, cellular infiltrations at the site of skin reaction of rabbits of group A began with predominant appearance of polymorphnuclear leucocytes, which was followed by increase of mononuclear cells, and then by granular inflammation.
- 2) The rabbits of group B showed less degree of the early polymorphnuclear response than those of group A, whichever of the reagents was used.
- 3) In the control rabbits, the cellular reactions caused by the four reagents differed from the corresponding reactions of rabbits of group A in the following two respects;
 - a) feebler response of polymorphnuclears, and
 - b) feebler response and quicker disappearance of mononuclears.
- 4) Whichever reagent was used pyroninophilic cell infiltration was observed to be feeble to the same degree in the rabbits of group A and B.

11. HISTOLOGICAL STUDIES ON TUBERCULIN ALLERGY

PART 2. HISTOLOGICAL STUDIES ON THE SKIN REACTIONS CAUSED BY INTRADERMAL INJECTION OF FRACTIONS OBTAINED FROM TUBERCLE BACILLI NO. 2. STUDIES ON SKIN REACTION CAUSED BY THE POLYSACCHARIDE- AND PHOSPHATIDE-FRACTION

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Received for publication, Mar. 1, 1956.

The following two groups of rabbits were given skin test with the polysaccharide- and phosphatide-fraction from human type tubercle bacilli "Aoyama B".

Rabbits of group A : Infected with human type tubercle bacilli "H₃₇ Rv"

Rabbits of group B : Controls, receiving no treatment

These two reagents were simultaneously injected on the back of each rabbit of the two groups at spots 5 cm apart, and the affected parts of the skin were cut out at various intervals, and comparative study of histological changes was carried out.

The results obtained were as follows :

- 1) Generally speaking, the cellular response caused by polysaccharide was quite feeble in both groups A and B, but more intense histological response was found in the rabbits of group A than group B. In the rabbits of group B only the general cellular response toward foreign bodies was found to be elicited, and in the rabbits of group A polymorphnuclear leucocyte infiltration in the early stage was found to be more marked and mononuclear cell infiltration in the subsequent stage was observed to disappear quickly.

- 2) The histological lesion caused by phosphatide was observed to be localized at the site of injection. Infiltration of polymorphnuclear cells occurred in the early stage and then followed by necrosis. Transformation of mononuclear cells into epitheloid cells was detected 5 to 7 days after injection, then a few giant cells were found 2 to 3 weeks later. The histological response caused by phosphatide injection was found to be more intense in the rabbits of group A than in the rabbits of group B.

12. HISTOLOGICAL STUDIES ON TUBERCULIN ALLERGY.

PART 2. HISTOLOGICAL STUDIES ON THE SKIN REACTIONS CAUSED BY INTRADERMAL INJECTION OF FRACTIONS OBTAINED FROM TUBERCLE BACILLI

NO. 3. STUDIES ON SKIN REACTION CAUSED BY THE ACETON SOLUBLE FAT- AND WAX-FRACTION

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Received for publication, April 9, 1956.

The following two groups of rabbits were given skin test with the aceton soluble fat-fraction and wax-fraction from human type tubercle bacilli "Aoyama B".

Rabbits of group A : Infected with human type tubercle bacilli "H₃₇ Rv".

Rabbits of group B : Controls, Receiving no treatment.

These two fractions were simultaneously injected on the back of each rabbit of the two groups at spots 5 cm apart, and the affected parts of the skin were cut out at various intervals, and histological examination was carried out.

The results obtained were as follows :

- 1) Intense polymorphnuclear leucocyte infiltration accompanied by the formation of small necrobiotic foci was found in the earlier stage of the response caused by aceton soluble fat-fraction and then followed by mononuclear cell infiltration, and transformation of mononuclear cells into epitheloid cells was observed in the surrounding of small necrobiotic foci.
- 2) Tendency of localization of histological response was noted at the site of purified wax-fraction injection, and polymorphnuclear leucocyte infiltrated in the earlier stage changed into abscess. Emergence of mononuclear cells and of Langhans type giant cells mixed with foreign-body giant cells was detected 7 and 14 days later respectively.
- 3) These changes were clearly observed to be more marked in group A than group B, but no essential difference was found in the histological response.

13. STUDIES ON BLOOD VESSEL PERMEABILITY AT THE SITE OF TUBERCULIN REACTION

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Received for publication, April 9, 1956.

The following three groups of rabbits were used in the present studies of the permeability of the blood vessels at the site of skin reaction produced by old tuberculin, o-aminophenol azo-tuberculin "Human" and o-aminophenol azo-tuberculin "BCG" individually. The permeability was examined by injecting into the ear vein physiological saline containing 1% trypan blue.

Rabbits of group A : Controls, receiving no treatment.

Rabbits of group B : Inoculated with human type tubercle bacilli "H₃₇Rv".

Rabbits of group C : Inoculated with BCG.

The results obtained were as follows :

- 1) In group A, the blood vessel permeability at the site of tuberculin reaction was found to be feeble, regardless of the types of tuberculin used. The sites receiving different types of tuberculin differed very little from one another, as well as from the site receiving physiological saline, as to the permeability of the blood vessel.
- 2) In group B, the permeability of the blood vessel at the site of injection was found to have distinctly increased regardless of the types of tuberculin used. The increase was especially conspicuous 24 to 48 hours after the injection, and remarkable difference was observed between the values at the site receiving physiological saline.
- 3) Less degree of permeability was found in group C than group B. In group C the blood vessel permeability caused by the injection of o-aminophenol azo-tuberculin "Human" was less in degree than that of o-aminophenol azo-tuberculin "BCG" throughout the whole period of experiment.

14. CLINICAL STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS

PART 23. ORAL ADMINISTRATION OF O-AMINOPHENOL
IN PULMONARY TUBERCULOSIS

NO. 1. RESULTS OF TREATMENT FOR 6 MONTHS

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Received for publication, April 25, 1956.

Patients of pulmonary tuberculosis, 153 in number, were treated with oral administration of o-aminophenol alone for six months. The daily dose of the drug was 0.5-3.0 gm.

The results obtained were as follows :

- 1) The use of o-aminophenol was definitely effective in the treatment of pulmonary tuberculosis, but its effect was dilatary.
- 2) The toxic effect of o-aminophenol was so slight that it could be neglected.
- 3) Development of resistant thercle bacilli against o-aminophenol was not seen.

15. ELECTROPHORETIC PROPERTIES AND ULTRAVIOLET-AND INFRARED-ABSORPTION SPECTRA OF PURIFIED STREPTOLYSIN S AND YEAST RIBONUCLEIC ACID

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Received for publication, April 14, 1956.

In view of the fact that no definite conclusion has yet been reached as to the chemical nature of streptolysin S, it was felt that some other kind of analytical investigation was necessary for final resolution of the problem. For approaching the matter, purified streptolysin S (I-N-F-Streptolysin fraction) and yeast ribonucleic acid were compared as to their behavior in electrophoresis, and their ultraviolet and infrared spectra.

It was found that 1) the electrophoregrams of purified streptolysin S and sodium yeast ribonucleate are identical, that 2) the infrared spectrum of purified streptolysin S is quite similar to that of the sodium ribonucleate, and that 3) the same type of ultraviolet absorption curve of sodium ribonucleate is also shown by the purified streptolysin S samples.