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ADMINISTRATION OF SM PLUS PAS AND SM PLUS O-AMINOPHENOL (OM)

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Mice infected intravenously with human type tubercle bacilli "H₂" were divided into 5 groups and treated with SM, PAS, OM, SM plus PAS and SM plus OM, respectively.

The results obtained are summarized as follows :

1) The number of tubercle bacilli in the viscera was found by quantitative culture to be less in the animals treated with SM plus PAS and SM plus OM than in those treated with any one of them.

2) Appearance of the drug-resistant bacilli was far less in the animals treated with SM plus PAS and SM plus OM than in those treated with SM, PAS or OM alone.

3) No difference was observed in the curative effect between SM plus PAS and SM plus OM.

2. FUNDAMENTAL STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS

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No. 2. PREVENTION OF EXPERIMENTAL TUBERCULOSIS

WITH INAH AND ITS DERIVATIVES

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Normal guinea pigs and guinea pigs inoculated with BCG 6 weeks previously were infected with human type tubercle bacilli "H₂". The infected animals were given INAH (3 mg/kg body weight/day) or INHG-Na (8.2mg/kg body weight/day) for 4 weeks starting on the 8th day after the infection.

The results obtained were as follows :

- 1) Development of tuberculin skin allergy and production of the antibody responsible for Middlebrook-Dubos reaction were slightly inhibited by the administration of the drugs.
- 2) BCG-inoculation and drug-administration were observed to act cooperatively in inhibiting the development of tuberculosis by challenge infection.
- 3) Daily administration of 3mg INAH showed almost the same curative effect as daily administration of 8 mg INHG-Na.

3. IMMUNOLOGICAL STUDIES IN TUBERCULOSIS

PART 19. IMMUNOLOGICAL PROPERTIES OF EXTRACTS OF
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No. 4. ON THE EXTRACT OF BCG

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Water extracts of BCG and human type tubercle bacilli, abbreviated to BCG-P and HTB-P respectively, were compared about their antigenicity.

The results obtained are summarized as follows :

- 1) In ability of producing the antibodies responsible for Middlebrook-Dubos reaction and precipitin reaction, BCG-P and red cells sensitized with BCG-P were as potent as HTB-P and red cells sensitized with HTB-P respectively, and the sensitized red cells were superior to the extracts themselves.
- 2) No antigenic specificity was observed between BCG-P and HTB-P.

4. IMMUNOLOGICAL STUDIES IN TUBERCULOSIS

PART 20. ON THE PASSIVE TRANSFER OF TUBERCULOUS
IMMUNITY AND TUBERCULIN ALLERGY

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The peritoneal exudate cells of tuberculin positive guinea pigs immunized with heat-killed human type tubercle bacilli suspended in paraffin oil were injected subcutaneously or intraperitoneally into normal healthy guinea pigs. The animals

thus treated were tested for development of tuberculin skin allergy and appearance of the antibody responsible for Middlebrook-Dubos reaction, and then challenged with human type tubercle bacilli "H37Rv" in order to examine the defensive power acquired.

The results obtained were as follows :

1) After the injection of the cells, development of tuberculin allergy and appearance of the antibody were observed.

2) The phagocytic activities of leucocytes against heat-killed tubercle bacilli and their power of inhibiting the growth of tubercle bacilli in slide cell culture were observed also to increase after the injection of the cells.

3) Histological examination showed that the passive transfer was effective in protecting the animals from the challenge infection, and the number of the bacilli in the viscera of the challenged animals ran parallel to the histological findings.

5. STUDIES ON THE RESISTANCE OF MICROORGANISMS TO VARIOUS CHEMICALS

PART 13. ON THE EFFECT OF SIMULTANEOUS EXPOSURE OF BACILLI TO INAH OR ITS DERIVATIVES WITH PYRAZINAMIDE

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The change of bacteriostatic action of INAH, IHMS, INHG-Na and IPN on human type tubercle bacilli "H₂" in Kirchner medium containing 10% bovine serum caused by addition of PZA was studied at pH 7.0 and 6.0. Next, the influence of the simultaneous use of PZA with each one of the four drugs on the development of drug-resistant bacilli was observed by six successive cultures at pH 7.0.

The results obtained are summarized as follows :

1) The bacteriostatic power of each drug showed no difference at pH 7.0 and 6.0.

2) By addition of PZA, the bacteriostatic power of the four drugs was observed to increase to the same extent at pH 7.0 and 6.0.

3) Throughout the six successive cultures of the bacilli, simultaneous use of PZA with the drugs was observed to be effective bacteriostatically but ineffective for inhibiting the development of drug-resistance.

6. STUDIES ON THE INFLUENCE OF CULTURE FILTRATE OF ACID-FAST BACILLI ON THE GROWTH OF VARIOUS BACILLI

PART 2. GROWTH-PROMOTING SUBSTANCE IN CULTURE FILTRATE OF ACID-FAST BACILLI FOR VARIOUS BACILLI

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A series of experiments was carried out for the purpose of clarifying the growth-promoting substance in culture filtrate of human type tubercle bacilli "Aoyama B" using *B. coli*, *B. typhi abdominalis*, *Sh. dysenteriae* and *Staphylococcus "Terashima"*.

The results are summarized as follows :

- 1) The growth-promoting activity ran parallel to the specific skin-reacting activity of the culture filtrate.
- 2) The growth-promoting substance was adsorbed by kaolin but not by animal charcoal or human erythrocytes.
- 3) Marked growth-promoting activity was observed in the protein fraction of the culture filtrate, but little in o-aminophenol azo-protein prepared from the culture filtrate.
- 4) A pepton medium containing the culture filtrate lost its skin-reacting activity by the culturing of *Staphylococcus* in it.
- 5) The growth-promoting activity was observed in the protein fraction but not in the phosphatide fraction of tubercle bacilli.

7. HISTOLOGICAL STUDIES ON TUBERCULIN ALLERGY

PART 7. STUDIES ON INTRACUTANEOUS REACTION PRODUCED BY FRACTIONS OF OLD TUBERCULIN

No. 1. ON RABBITS SENSITIZED WITH HUMAN TUBERCLE BACILLI

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Skin tests were carried out with OT "human", o-aminophenol azo-tuberculin "human" (OA-Azo-T "human"), protein and polysaccharide fractions from OT

"human" (PF "human" and CF "human") and with OT "BCG", OA-Azo-T "BCG", PF "BCG" and CF "BCG" on rabbits sensitized with heat-killed human tubercle bacilli suspended in paraffin oil.

The parts of the skin receiving the injection were removed at stated intervals of time and examined for histological and histochemical changes.

The results are summarized as follows :

- 1) All the preparations caused skin reaction of the delayed type.
- 2) The reaction caused by OT "human" was of the same degree as that caused by OT "BCG".
- 3) The skin reaction caused by OA-Azo-T "human" and OA-Azo-T "BCG" was of the typical delayed type, and the reaction caused by the latter was slightly less intense than that caused by the former.
- 4) The relation in skin-reaction-causing activity between PF "human" and PF "BCG" was almost equal to that between OA-Azo-T "human" and OA-Azo-T "BCG".
- 5) The skin reaction caused by CF "human" was considerably more intense than that caused by CF "BCG", and the reaction caused by CF "human" and CF "BCG" was less intense than that caused by PF "human" and PF "BCG" respectively.
- 6) No striking difference was observed between the histochemical changes caused by the corresponding preparations from human tubercle bacilli and from BCG.

8. SOME EXPERIMENTS CONCERNING THE DETOXICATING EFFECTS OF D-GLUCURONOLACTONE AND SODIUM D-GLUCURONATE UPON o-AMINOPHENOL

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Experiments were carried out in man for the purpose of examining the detoxicating effects of D-glucuronolactone (I) and sodium D-glucuronate (II) upon o-aminophenol (III).

1) Oral administration of (III) brought about increased urinary excretion of conjugated sulfuric acid (A) and o-glucuronide glucuronic acid (B). When, in addition to (III), either (I) or (II) was given, excretion of (B) increased still further, but that of (A) remained the same as when (III) alone was given.

2) Formation of methemoglobin by (III) was suppressed, though slightly, by (I) as well as by (II).

9. STUDIES ON INFLUENCE OF VARIOUS SUBSTANCES
ON THE STREPTOLYSIN-S SUSCEPTIBILITY OF
ERYTHROCYTES, WITH SPECIAL REFERENCE
TO CONSTITUENTS OF TANNIC ACID
AND PROTEIN REAGENTS

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Following the observation, previously reported, that erythrocytes of certain species of mammals, when treated with tannic acid, were rendered insusceptible to streptolysin S, a wide variety of substances, chosen with special consideration on the chemical constitution and protein-precipitating action of tannic acid, were tested for their influence upon the susceptibility of erythrocytes to the toxin. The substances studied were (1) 14 compounds belonging to the series of phenols and phenolic acids, including gallic acid and phloroglucin; (2) 12 sugars; (3) 8 heavy metal salts; (4) 4 agents reactive to protein; and (5) 19 miscellaneous compounds, including anticholinesterases, surface-active agents, hemoglobin-affecting agents, cytotoxic drugs and so on.

Washed red cells of guinea pig were treated with an agent under study at room temperatures for 20 minutes, after which time the cells were washed, suspended in saline to 1%, and assayed for their streptolysin-S susceptibility by means of hemolysis test.

The results of hemolysis experiments are as follows:

1. The individual constituents of tannic acid and their allied compounds were all shown to be quite ineffective to reduce the susceptibility of red cells to streptolysin S.
2. All the metal salts failed to affect the toxin susceptibility of the cells.
3. Of the protein reagents studied, formalin was found to cause marked loss of the toxin susceptibility of the cells, while all others showed no effect. The effect of formalin, however, was shown to differ from that of tannic acid in the following points; (a) rabbit erythrocytes, upon which tannic acid was ineffective, were readily affected by formalin, and (b) gelatin, which was able to restore the lost susceptibility of tanned erythrocytes, failed to exert a similar restorative action upon the formalinized cells.
4. None of the miscellaneous compounds tested exhibited any appreciable effect on the toxin susceptibility of red cells.

VISCERO-CUTANEO-VASCULAR REFLEX AND ITS CLINICAL SIGNIFICANCES

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1. When abnormal stimuli from a viscera are projected to the respective paries through the spinal cord, the results are various visceroparietal reflexes.

The viscerocutaneous (vascular) reflex is described here as a reflex to cause the neural vasomotor disturbance in the subcutaneous arterioles.

2. The subcutaneous arteriole represents a typical end-artery, and its irrigation area is only 0.5 to 1.0 mm. in diameter on the skin surface. Owing to the reflexive vasomotor disturbance, there appear the exudative and bionecrotic wedge-shaped changes definitely demarcated from the surroundings.

3. The above mentioned histological changes are accompanied by the changes in the electrophysiological nature.

In general, the electrophysiological nature of the skin is illustrated by the equivalent circuit of the resistance paralleling with the capacity. Experimentally values were determined relating to the factors in the equivalent circuit of the normal skin (the horny, intracutaneous, and subcutaneous layers, respectively).

Likewise, the equivalent circuit of the cutaneous reflex points were determined. The values differs with the degrees of the exudative changes, and are characteristic compared with the equivalent circuit in the normal skin.

4. Firstly, the resistance is decreased in about to 10^{-2} 10^{-3} order due to the exudative changes. Secondly, the capacity is increased in about 10^{+2} to 10^{+3} order.

5. Generally speaking, the capacity of the skin consists of an electrostatic capacity (C_0) mainly in the horny layer and a diffusion capacity (C_s) mainly in the stratum germinativum. As our reflex is based on the exudative changes beginning around the subcutaneous arterioles, there appears initially a strong change in the diffusion capacity.

6. Our cutaneous reflex points reveal the changes both in the resistance and capacity. The change of the C is quantitatively described by the phase angle ϕ . In other words, ϕ gives the degree of the exudative change. Among the Japanese, ϕ of the normal skin is about $7-9^\circ$, but ϕ of the cutaneous reflex points is steeper than the former and sometimes bigger than 45° .

7. We invented an electrodermatograph to record the changes of the characteristic ϕ in the cutaneous reflex points. Although the cutaneous reflex points can be pointed out by this machine, it is very difficult by other methods to do so. Firstly, there has been no adequate machine for it, and secondly, the cutaneous reflex points are 0.5 mm. in diameter and so small that they have been neglected. For these two reasons, our cutaneous reflex points have not been noticed or

described.

8. Our cutaneous reflex points are given the bases on the subcutaneous arterioles, but are not correlative with the sweat or sebaceous glands. There has been only the psychogalvanic reflex for the electrophysiological record of the cutaneous reflexes. It is based on the reflexive sweating, and is applied to record the increase of the electrical conduction in the sweat-moistened skin due to change of the resistance. The capacity, however, is neglected here.

9. In the psychogalvanic reflex, there is no change present in the deep layer of the skin (accordingly capacity, especially the diffusion capacity is neglected), and the skin is moistened by the sweat (i.e. the reflex is recorded as an area).

On the contrary, in the cutaneo-vascular reflex, where capacity is of significance, the changes in the deep layer of the epidermis are followed, and the exudative changes are 0.5 mm. in diameter on the skin surface (i.e. the reflex is described as a point).

These two reflexes are different in the bases, electrophysiological nature, and histological pictures from each other.

10. Like the psychogalvanic reflex, the cutaneo-vascular reflex is of clinical use. The establishment of a cutaneous reflex point means the existence of a causative visceral disease.

11. The stimulus from the visceral disease is projected to the corresponding dermatome through the spinal segment of the visceral sensation. In our reflex, it is projected to the subcutaneous arterioles within the respective dermatomes. Particularly, it centers the site where the three branches of the centrifugal spinal nerves appear from the deep layer to the superficial one of the paries. Thus, there are anatomical localizations present in the cutaneous reflex points.

12. It is interesting to determine the localizations of the reflex points in all visceral diseases, such as Boas' point in the gastric diseases. These cutaneous reflex points can be objectively disclosed by our electrodermatograph which differs from the subjective ones used for the examination of the tender points.

13. In this report, the viscerocutaneous reflex points are explained in the diseases of the heart and liver. In the heart diseases, the localization of the reflex points is differentiated corresponding to the diseases in the right or/and left ventricles and/or auricles, ascending and descending aorta, and pericardium.

In the liver diseases, the reflex points are localized differently according to the intrahepatic diseases and the extrahepatic complications.

The higher the incidence of the respective reflex points, the higher is the rate of diagnostic accuracy.

The map of distribution of the cutaneous reflex points is named "Electrodermatogram", which can be applied to make some adequate diagnosis.

14. The heart diseases are accurately diagnosed by the electrocardiography. However, there are a great number of patients with complaints of definitely cardiac symptoms with negative electrocardiograms. How should we deal and warn these cases? Comparing the two, our "Electrodermatogram" shows much higher incidence

and positivity of diagnosis thus it appears more useful. The electrocardiogram and the electrodermatogram reveal their own diagnostic characteristics.

15. The liver diseases are diagnosed by the liver function tests. The changes in the liver function tests mean that the disturbance has already taken place in the major part of the liver tissues. Even in the moderate case of hepatic damage, the compensation is accomplished by the remained liver tissues, and shows no changes in the liver function tests. How should we treat and advise these patients?

Our hepato-cutaneous reflex points are higher in the diagnostic accuracy and appear earlier than any of the present liver function tests. The usefulness of the reflex points are practically explained in the results of the following experiments.

The incidence of the serum hepatitis was lowered by 1/5 to 1/25 through the screening of cases of the hepatic damage (including latent hepatitis) among donors by the cutaneous reflex point method. This result has never been obtained through screening by the present liver function tests.

16. It takes only 60 seconds to find out the hepato-cutaneous reflex points by our electrodermatograph, and it is easy to examine 600 donors per day. The test is simple beyond imagination compared with the established liver function tests. The diagnostic reliability was already described.

The simpleness and accuracy of the diagnostic method are the absolute conditions for its use in mass survey.

17. The visceral sensation is projected to the corresponding dermatomes with the spinal segmentations.

Our cutaneo-vascular reflex or the psychogalvanic reflex, both are sympathetic, and hence the distributions of these reflexes must be reviewed through the sympathetic dermatomes.

The dermatomes in the text books are chiefly of spinal nerves. The dermatomes in the trunk are mostly in accord with the sympathetic ones, but those in the upper and in the lower extremities are quite different from each other.

The dermatomes in the lower extremities were already determined by Richter, but those in the upper extremities have not been established yet because of the anatomical complexity. By our indirect method, the dermatomes were determined and illustrated.

18. Similar to the viscerocutaneous reflex, the stimulus to the skin is projected to the viscera as the cutaneo-visceral reflex. The therapeutic effect can be expected by giving the stimulus to the skin and projecting the reflex to the viscera. The cutaneous reflex points are of use to select the injection site of the nerve blocking drug. In other words, the cutaneous reflex points can be the diagnostic points, and at the same time the therapeutic ones.

19. The conception of "the Keiketsu" in the oriental medicine emphasizes the idea that the viscerocutaneous or cutaneo-visceral reflex takes place in a point on the skin surface. In this meaning, our reflex points should be used for the comment on "the Keiketsu".

As most of the items of the oriental medicine were discovered through ex-

periences, there are scientific explanations lacking. In this sense, the oriental medicine will be systematized scientifically by our reflex points.