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Observations on the Mechanism of Chloride Retention in Pneumonia.

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In 4 experiments upon 3 dogs, following the intratracheal or intrapneumonic injection of Type I pneumococcus, there was a large increase in the excretion of chloride on the first day. Thereafter, the output was much lower than in control experiments. This finding resembles those reported by von Moraczewski[1] and by Terray[2] in regard to the increased excretion of chloride during the febrile period in malaria.

It is possible that there is a similar large excretion of chloride on the first day of pneumonia in man. This would account for the low concentration of chloride in the blood and for at least part of the marked retention usually observed. Other factors, such as the accumulation of chloride in the consolidated lung tissue and the retention of water, also play a part and account for the post-critical excretion of chloride that has so frequently been observed.

If the conditions in pneumonia should resemble those observed in these experiments, as much as 8 gm., or more, of sodium chloride might be lost on the first day of the disease. It is not surprising, therefore, that analyses of tissues of patients dead from pneumonia have failed to disclose where the retained chloride was deposited.

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On the Mechanism of Chemotherapeutic Action. I. Formation of the Parasitotropic Agent from Arsenicals.

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In a prior paper[1] a method was described by which single phases

[1] von Moraczewski, W., *Virchow's Archiv.*, 1899, clv, 11.

[2] Terray, P., *Z. f. klin. Medizin*, 1894, xxvi, 346.

[1] Reiner and Köveskuti, *Deutsche med. Wochschr.*, 1927, liii, 1988; *Orv. Hetilap.*, 1928.

of chemotherapeutic action could be studied separately*. These phases are possibly due to interactions between (1) agent and parasite, (2) agent and host, and (3) host and parasite.

Working[1] with Bayer 205, weak solutions (0.5% and 0.05%) were allowed to act upon trypanosomes (*Tr. equiperdum*); then the parasites washed several times with a saline-broth mixture and rats infected with them. Control rats were infected with trypanosomes which had been treated similarly with saline-broth mixture only. If a small number of untreated trypanosomes were injected together with 10 times as many treated trypanosomes into one rat, and the small amount of untreated trypanosomes only into another, in all experiments both animals died at the same time and much earlier than rats which were infected with the large amount of treated trypanosomes only. This proved that Bayer 205, once bound, could not act upon other trypanosomes. Thus with Bayer 205, a direct action of the chemotherapeutic agent upon the parasites was demonstrated; only a decrease of virulence results. Similar experiments with arsenicals are described in the present paper.

It was to be expected that in this type of experiment, arsenicals would behave similarly to Bayer 205. Such was not the case. If an emulsion of trypanosomes was brought in contact with neoarsphenamine dissolved in nutrient broth in a dilution of 1/5000, or with sodium atoxylate, and allowed to stand for 20 minutes, then centrifuged and washed, the trypanosomes remained almost as virulent as the controls. Time of action and dilution of the chemotherapeutic agent were chosen far below the limits which produce a damaging effect as shown by the change in motility.

These experiments show that the arsenicals investigated either were not bound to the parasite, or, if bound were not active as chemotherapeutic agents. However, since activity is usually seen when these compounds are injected into infected animals, it seemed probable that an interaction occurs between the chemotherapeutic agent and the host, resulting possibly in the production of a new

* Even *in vitro* experiments like those of Castelli[2] and Gonder[3] do not allow any conclusions to be drawn as to the interaction between chemotherapeutic agent and host and are thus not absolutely conclusive as to the direct action either. Objection to some of the conclusions very recently arrived at by G. A. Cooper[4] may also be based on failure to separate the action of the parasite on the host from the action of the arsenical on the host.

[2] Castelli, *Z. Chemotherapie*, 1913, i, 122, 321.

[3] Gonder, *Z. Immunitäts.*, 1912, xv, 257.

[4] Cooper, G. A., paper read before the Pharmacological Society at Chicago meeting, March, 1930.

active compound. The findings of Swift and Ellis[5] and Stühmer[6] indicated that such compounds might be present in the blood of a non-infected, healthy animal, treated with neoarsphenamine. Corresponding experiments were conducted in 3 stages: (1) treatment of a normal animal with the arsenic compound; (2) treatment of the trypanosomes with the serum of an animal treated with the chemotherapeutic agent; (3) infection experiments, in the manner described above, with trypanosomes treated with the plasma or serum from rats and rabbits, both arsenic treated and untreated.

In Stage 2 no *in-vitro* parasitocidal action could be detected but in Stage 3, trypanosomes treated with neoarsphenamine-plasma or serum showed, in accordance with the experiments of Swift and Ellis[5], a distinct protection as compared to infections with the same number of trypanosomes treated similarly with normal plasma or serum. If more trypanosomes were injected (about 1,000,000) the animals infected with treated trypanosomes lived 1 or 2 days longer than the controls. If the number of trypanosomes injected did not exceed 100,000 the controls died, whereas the animals infected with treated trypanosomes usually survived.

Whereas, in the case of Bayer 205 the chemotherapeutic action is due to 2 factors, namely direct action of the chemotherapeutic agent on the parasite and protective action of the host (reticuloendothelial system), in the case of arsenic compounds an interaction between the host and the chemotherapeutic agent must also be assumed, since, *compared with the arsenic content, a very active parasitotropic agent is present in the serum or plasma of animals treated with neoarsphenamine. This agent acts by the same mechanism as Bayer 205.* The active compound is probably a loose combination of serum protein (globulin) and neoarsphenamine, for it is also formed *in vitro* by mixing neoarsphenamine, with serum or plasma.† Atoxyl and tryparsamide are, however, as little active with serum as either substance in broth. Results, analogous in principle to those obtained with neoarsphenamine, were also found with bismuth thiosulphate.

We have said nothing as to the forces which may be concerned in binding the active chemotherapeutic agent to the parasite, nor those concerned in the decrease of virulence which results. We have not proposed a precise chemical mechanism for the reaction by which the chemotherapeutic agent is formed. Possibly the sulf-

[5] Swift and Ellis, *J. Exp. Med.*, 1913, xviii, 435.

[6] Stühmer, *Münch. med. Wochschr.*, 1914, decxlv, 1101, and 2338.

† It is obvious that Castelli and Gonder were investigating this combination.

hydryl mechanism is involved in one or all of these reactions.[7] Further study of various chemotherapeutic agents and heavy metal compounds is in progress.

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Mechanism of Chemotherapeutic Action. II. Rôle of Reticulo-endothelial System in Formation of a Parasitotropic Agent from Arsenicals.

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Recently many investigators[1-10] have attempted to study the rôle of the host in chemotherapeutic action by investigating the influence of blockade of the reticulo-endothelial system. They found that different chemotherapeutic agents were less effective with blocked, or blocked and splenectomised animals than with normals. From prior experiments[11] it appears that even as active an agent against trypanosomes as Bayer 205 needs the host's normal protective mechanism for the destruction of the parasites. Thus it was to be expected that blockade would influence unfavorably the course of an infection whether or not a chemotherapeutic agent was also applied. Confirming this view, Kikuth and Regendanz's experiments indicate that treated and non-treated infections are influenced similarly by the blockade. On the other hand, it is known[12] that arsenicals, especially the less diffusible, trivalent compounds

[7] Voegtlin, Dyer and Leonard, *U. S. Public Health Rep.*, 1923, xxxviii, 1882; *J. Pharmacol. Exp. Therap.*, 1925, xxv, 297.

[1] Kritschewsky, I. L., and Meersohn, J. S., *Z. Immunitäts.*, 1926, xlvii, 407.

[2] Kritschewsky, I. L., *Z. Immunitäts.*, 1927, liii, 506; *Centr. Bakt. Parasitenk. Orig.*, 1927, civ, 214; *Z. Immunitäts.*, 1928, lix, 1.

[3] Kritschewsky, I. L., Baskin, M. M., and Lebedjeva, M. N., *Centr. Bakt. Parasitenk. Orig.*, 1930.

[4] Kolpikow, N. W., *Z. Immunitäts.*, 1926, xlviii, 182.

[5] Jungeblut, Cl. W., *Z. Hyg. Infektionskrankh.*, 1927, cvii, 357.

[6] Jungeblut, Cl. W., and McGinn, Barbara R., *J. Exp. Med.*, 1930, li, 5.

[7] Feldt and Schott, *Z. Hyg. Infektionskrankh.*, 1927, cvii, 453.

[8] Jancso, N. v., *Z. ges. exp. Med.*, 1926, lxi, 63; 1929, lxv, 98.

[9] Schlossberger, H., *Centr. Bakt. Parasitenk. Orig.*, 1929, cx, 210.

[10] Kikuth and Regendanz, *Z. Immunitäts.*, 1929, lxi, 422.

[11] Reiner and Köveskuti, J., *Deut. Med. Wochschr.*, 1927, liii, 1988.

[12] Voegtlin, C., and Thompson, J. W., *J. Pharmacol. Exp. Therap.*, 1922, xx, 85.