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Bacillary Dysentery.

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(Conclusion.)

A fundamental improvement in our therapeutic armamentarium has arrived with the sulfonamides. All sulfonamides are more or less active against *Enterobacteriaceae,* although the example of their failure in typhoid fever shows that experimental results do not always parallel effectiveness in man. As in the whole field of chemotherapy with sulfonamides, a great number of publications have appeared which cannot all be reviewed here. Only the most essential points can be mentioned. There are two main points of view for evaluation of therapeutic activity. The first is action upon the invasive agent. In this respect, a definite graduation of effectiveness can be observed in the case of *Shigellae.* The sequence of increasing activity is sulfanilamide, sulfapyridine, and sulfathiazole. Similar to sulfathiazole is the action of sulfadiazine, its congener sulfamerazine and also sulfapyrazine (114). The second point is toleration, and the superior properties of sulfadiazine in this respect give this compound a great advantage (115).

Starting from the idea that in the case of enteric infection the enemy is located in the lumen of the intestine, sulfonamides which appear in high concentration in the lower intestinal tract have been recommended (116) in the hope of avoiding potentially dangerous concentrations of sulfonamides in the tissues. There is, however, reason to doubt whether experimental data obtained on normal intestines hold true for the conditions in the inflamed and ulcerated bowels of dysentery patients (117) (118). Moreover, sulfonamide compounds which are slowly absorbed have often a relatively low antibacterial activity. Besides it is to be remembered that everything we know about the pathology of dysentery points to the microorganisms within the intestinal wall as the enemy we have to combat (119). Practical experience confirms these considerations.

It was found necessary to employ relatively large doses of compounds that are slowly absorbed. When properly used, compounds like sulfaguanidine and succinyl sulfathiazole are effective. On the whole, however, clinical observers (see for instance [114] and [128]) are returning to the more easily absorbed compounds—part-

icularly since in sulfadiazine a drug has been found that combines high antibacterial activity with generally excellent toleration. Thus, the present situation can be summarized by a recent utterance from the Office of the Surgeon General of the U.S. Army to the effect that "sulfadiazine is the drug of choice" (121).

Sulfamerazine is another promising compound; but no large scale experience of its use has been reported in the literature.

The SONNE bacillus appears to be somewhat more resistant to the action of sulfonamides than are the other species of *Shigella* (122) (123).

In addition to their usefulness in the treatment of acute and, with some restrictions, also of chronic cases, sulfonamides constitute one of our most valuable agents for the prophylaxis of bacillary dysentery (124). It is generally agreed that the drug greatly reduces the average time during which convalescents carry bacteria. It has, however, to be stressed that relapses do occur, particularly in SONNE infection, but also with other species; and that repeated stool examinations over several weeks are necessary to insure that the intestines have definitely been cleared of all remaining dysentery bacilli.

Effective sulfonamide treatment has greatly reduced the danger of chronicity of infection. What this means needs no elaboration for anyone who has observed the untold misery of chronic ulcerative colitis.

It is also possible to eliminate the bacteria from a high percentage of healthy carriers by sulfonamide treatment for several days, and it has been shown that effective prophylaxis is possible by sulfonamide treatment of a whole population; as, for instance, the healthy inmates of institutions during the time of an outbreak (125) (126).

Nothing will be gained by prolonged sulfonamide treatment and little by overdosage, but definite harm can be done in this respect both by transgressing the limits of toxic effect and by causing sensitization to the drug. Thus common sense and consideration of biological limits will always have to be employed. If that is done, an enormous amount of good can be done and is being done by sulfonamides.

What could have been predicted from theoretical reasons and from experimental results (127) (128) is happening now: Sulfonamide resistent strains of *Shigellae* are being encountered with increasing frequency. The transition from sulfonamide susceptible to resistant strains during protracted endemics has been repeatedly reported (120) (129) (130). One observer had no difficulty to pick up 100 sulfonamide resistant strains from carriers (120).

The allied forces all over the world were fortunate indeed that this did not happen to any large extent during the war years. However, the U.S. fleet anchored in Tokyo Bay experienced a large outbreak of sulfonamide-fast dysentery caused by FLEXNER type III which resulted in a number of protracted cases (129). Thus, the practical problems of dysentery will require continuous effort. And particularly the prevention of dysentery by sanitary and, if at all possible, by immunologic methods remains an urgent task.

Penicillin has little effect on gram-negative bacteria, even though it is not true that it is entirely ineffective (131). Thus, it does not seem to be a very hopeful instrument of therapy in dysentery. Recent experimental work has shown that another antibiotic agent is effective against gram-negative bacteria, and among these the *Shigellae*. This drug is streptomycin (132). No clinical results have yet been reported with this compound.

A considerable amount of work on an experimental scale has been done both in animals and in human beings during the war years with the goal of developing a prophylactic vaccine. It has been shown that agglutinating and protective antibodies appear in circulation of both animals and man (48) (49) (100) (101) (102) (133) (146). Methods have been proposed to increase antigenicity and decrease the toxicity of antigens (134 to 137), (147). However, no information has been published whether these vaccines are of actual prophylactic value. In contrast to the vaccines for the prophylaxis of enteric fever where correlation between protective value and circulating antibody has been reasonably assured, the appearance of circulating antibody is not per se evidence of protection against clinical dysentery, because dysenteric infection is an essentially localized affection of the intestinal wall; and circulating antibody must not necessarily be effective under such conditions, nor does circulating antibody necessarily parallel local resistance. Thus only experience in actual exposure of vaccinated human beings can give the necessary evidence, and such evidence has not yet been published.

Bacteriophages versus *Shigellae* are of a rather confusing complexity in their relations to different strains as an extensive recent investigation has shown anew (138). Unfortunately, no effort was made to integrate this investigation with modern data on serological specificity. It is obvious that this is of more than theoretical importance because the possibilities of employing bacteriophage for therapeutic or prophylactic purposes has by no means been exhausted. At the present time, regardless of enthusiastic reports (139) and not unfavorable experimental results (140 to 142), the therapeutic and prophylactic effectivity of anti-dysenteric bac-

teriophages as available now is open to grave doubt. The only well controlled investigation of the therapeutic effect of bacteriophage in dysentery was made with a German preparation salvaged after Rommel's disaster. The result was by no means complimentary for the makers of this material (143).

It is hoped that this short résumé will show that there has been indeed considerable progress achieved in the field of dysenteric infections. New methods for the isolation and exact and speedy identification of the offending organisms have been obtained. Several new types and species of *Shigella* have been found and the known ones have been better defined. The antigen that dominates the immunological response of the body has been recognized as a complex molecule whose specificity is determined by polysaccharides. The reinvestigation of the antigenic composition of the most important species—the FLEXNER bacillus—has opened a vista for effective epidemiological and preventive work. And in the sulfonamides, particularly in sulfadiazine, a powerful weapon has been acquired for therapeusis and prevention.

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(Restrictions of space do not allow extensive citation of the literature. However, the author will be glad to answer inquiries concerning literature on special aspects of the subject.)

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Addendum: for a more extensive, recent review see: *Weil, A. J.*: J. Immunol. 55: 363 (1947).

Zusammenfassung.

Die während des Krieges geleistete experimentelle Arbeit, am Menschen sowohl wie an Labor.-Tieren, um zu einer brauchbaren Schutzimpfung gegen baz. Dysenterie zu gelangen, stellt eine beachtenswerte Leistung dar. Gezeigt wurde, daß sowohl beim Labor.-Tier, wie beim Menschen agglutinierende und schützende Antikörper im Blut auftreten (48, 49, 100, 101, 102, 133, 146). Methoden werden beschrieben, welche erlauben, die Wirksamkeit der Antikörper zu erhöhen, unter gleichzeitiger Herabsetzung ihrer Toxizität (134—37, 147). Über den praktischen Wert solcher Impfstoffe liegen allerdings noch keine Mitteilungen vor. — Im Gegensatz zu den Verhältnissen bei Typhus abdominalis, wo eine feste Beziehung zwischen Schutzwirkung und zirkulierenden Antikörpern erwiesen ist, bedeutet der Nachweis von im Blut zirkulierenden Antikörpern keine Gewähr für effektive Schutzwirkung bei klinischer Dysenterie, weil diese Krankheit eine lokale Affektion der Darmwand darstellt, wobei die Möglichkeit besteht, daß die Antikörper des Blutes unwirksam bleiben, m. a. W., es fehlt die feste Beziehung der Antikörper des Blutes zu der lokalen Geweberesistenz. Nur praktische Resultate der Geimpften bei Infektionsmöglichkeit sind beweisend, und solche Beobachtungen sind noch nicht publiziert.

Zwischen Bacteriophag und den verschiedenen Shigella-Stämmen bestehen sehr komplexe Beziehungen, wie aus rezenten For-

schungsergebnissen aufs neue hervorgeht. Leider wurde versäumt, diese Ergebnisse in Einklang zu bringen mit denjenigen der modernen serologischen Spezifitätslehre. Dies aber wäre von ebenso großer praktischer, wie theoretischer Bedeutung, da die therapeutischen und prophylaktischen Möglichkeiten des Bakteriophagen durchaus nicht ausgeschöpft sind. Trotz einiger optimistischer Berichte (139) und nicht ungünstiger Versuchsresultate (140—124) muß beim heutigen Stand unseres Wissens die therapeutische und prophylaktische Wirksamkeit des Bakteriophagen noch als durchaus zweifelhaft betrachtet werden. Die mit einem deutschen, aus der Armee Rommels stammenden Phagenpräparat angestellten, wohlkontrollierten Versuche ergaben jedenfalls kein ermutigendes Resultat (143).

Die vorstehende Übersicht zeigt, wie wir hoffen, daß auf dem Gebiet der bazillären Ruhrinfektionen bedeutende Fortschritte gemacht worden sind. Es wurden neue Methoden zu rascher Isolierung und exakter Bestimmung der pathogenen Arten ausgearbeitet. Mehrere neue Shigella-Typen und -Arten wurden gefunden, und die schon bekannten wurden besser definiert.

Das Antigen, welches die Immunitätsreaktionen des Körpers beherrscht, wurde erkannt als hochmolekularer Komplex, dessen Spezifität bestimmt wird durch seinen Polysacharidbestandteil. Erneute Analyse der antigenen Komposition der wichtigsten Species, i.e. des Flexner-Bacillus, hat die Aussicht eröffnet für erfolgreiche epidemiologische und präventive Arbeit. In den Sulfonamiden endlich, besonders im Sulfadiazine ist uns ein neues und wirksames Mittel für Therapie und Prophylaxe zuteil geworden.

Résumé.

Au cours de la dernière guerre d'importants travaux expérimentaux, tant sur les animaux de laboratoire que sur l'homme ont réalisé des progrès remarquables dans l'obtention d'une vaccination antidysentérique de valeur pratique. Dans le sang de l'homme ainsi que dans celui des animaux de laboratoire des anticorps agglutinants et protecteurs ont été démontrés (48, 49, 100, 101, 102, 133, 146). Des méthodes ont été trouvées, qui permettent d'augmenter l'activité de ces anticorps, en diminuant en même temps leur toxicité (134-37, 147). Il est vrai qu'au moment présent la confirmation en pratique de l'activité de ces nouveaux vaccins n'a pas encore été publiée. — Tandis qu'au cas de la fièvre typhoïde il y a une corrélation constante entre l'action protectrice et les anticorps circulants dans le sang, la présence dans le sang de tels anticorps

chez des malades atteints de dysenterie bacillaire est loin de garantir une activité protectrice. La dysenterie étant une affection localisée de la paroi intestinale, les anticorps circulants dans le sang peuvent rester sans effet, ce qui veut dire qu'il n'y a aucune liaison constante entre les anticorps du sang et la résistance locale des tissus atteints. Ce ne seront que les expériences pratiques de protection des vaccinés en milieu contagieux qui pourront donner la preuve de la nouvelle méthode, et de telles observations ne sont pas encore publiées.

Des expériences récentes ont mis en évidence une fois de plus la grande complexité régissant l'intéraction du bactériophage avec les différentes espèces de Shigella. Il est regrettable que ces résultats d'expériences récentes n'aient pas été confrontés d'une manière systématique avec les données de la sérologie moderne concernant le problème de la spécificité. Ceci serait d'une grande importance tant pour la théorie que pour la pratique, puisque — à notre avis — les possibilités thérapeutiques et prophylactiques du bactériophage n'ont pas été poursuivies à fond. Malgré quelques rapports optimistes sur son activité (139) et quelques résultats expérimentaux favorables, il faut bien constater qu'au moment présent, la valeur thérapeutique du bactériophage est loin d'être établie. Les expériences publiées sur les résultats obtenus par un phage de source allemande, (armée de Rommel du Nord de l'Afrique) ont été décevantes (143).

L'aperçu que l'on vient de lire aura démontré, nous l'espérons, que des progrès appréciables ont été réalisés dans le domaine de la dysenterie bacillaire. Des méthodes nouvelles ont été mises au point, permettant l'isolation et la détermination rapide des différents genres pathogènes. Plusieurs types et variétés nouveaux de Shigella ont été isolés, tandis que ceux déjà connus ont été mieux définis. L'antigène régissant les réactions d'immunité de l'organisme dans la dysentérie bacillaire a été définie comme étant un complexe moléculaire dont la spécificité dépend d'une componente polysacharide dans le molécule. Des analyses récentes sur la composition antigène du bacille Flexner semble avoir ouvert le champ aux travaux de grande portée dans le domaine de l'épidémiologie et de la prévention. Dans les sulfamidés, enfin, et spécialement dans la sulfadiazine, un moyen puissant nous a été donné tant pour la thérapeutique que pour la prophylaxie.