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EDITORIALS

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QUESTIONS OF SULFONE-RESISTANT TUBERCLE BACILLI

Although there are those who are not satisfied that BCG vaccination is of real value in leprosy prophylaxis because there is as yet insufficient statistically irreproachable evidence, there are others who hold that that measure should nevertheless be employed, especially for contacts. This matter has recently been discussed by Montestruc and associates in an article[1] of which there is an abstract in this issue. They doubt that reactivity to lepromin induced by lepromin injection is sufficiently strong and sustained to convey real resistance to leprosy infection, whereas the stronger and more persistent effects of BCG vaccination justifies the use of that measure for enhancing resistance.

They hold that all contacts, including recently-born infants, should be vaccinated. Pending the establishment by that means of the state of immunity (represented by lepromin reactivity), contacts of open leprosy cases, should also receive two or three months of preventive sulfone chemotherapy after the vaccination. They believe that the effect of this double treatment should not be influenced by a possible interference by the sulfone with the immunizing effect of the BCG, because sulfones are less active against the tubercle bacillus than against the leprosy bacillus.

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[1]MONTESTRUC, E., GARCIN, D., BERDONNEAU, R. and BENOIST, J. La prophylaxie de la lèpre par le BCG. Presse méd. **67** (1959) 1112-1113.

It may be noted that Vincent[2] (abstract in this issue) advises the combined prophylaxis for infants, using the sulfone because of doubt of the usefulness of vaccinating children so young.

In correspondence about the subject of the present note, William H. Feldman—who, closely following the pioneer work of Rist,[3] had a leading part in the extensive experimentation of the Mayo Clinic group with the effects of the sulfones in tuberculosis[4]—took exception to this last statement of Montestruc's, holding it to be "at least difficult to substantiate." He wrote:

> Many of the [sulfone] compounds studied were just as effective in suppressing experimental tuberculous infections caused by the human type of *M. tuberculosis* as streptomycin proved to be when studied later. Presumably the statement that sulfones are less active against the tubercle bacillus than against the leprosy bacillus refers to clinical infections in man due to these mycobacteria, but I fail to see how such a statement can be supported unequivocally.

Montestruc, to whom Feldman's letter was referred for comment, replied defending his position (see letter in the *Correspondence* section of this issue). That position would seem to receive support from a recent report by Watanabe,[5] of which there was an abstract in our last issue. She finds that the antileprosy therapy has little effect on tuberculosis in the leprosy patient whereas the usual antituberculosis therapy does. Nevertheless, there would seem to remain a possible question of whether the prophylactic administration of a sulfone at the time of BCG vaccination will permit the latter—in effect a new, experimental tuberculosis infection—to develop its full immunizing effect.

In the tuberculosis field it has recently been suggested by Spiess[6] that, for contacts, isoniazid chemoprophylaxis might be given until

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[2]VINCENT, M. Contribution a l'étude de la protection des enfants de lépreux contagieux vivant en leproserie. Mimeographed.

[3]RIST, N., BLOCH, F. and HAMON, V. Action inhibitrice du sulfamide et d'une sulfone sur le multiplication in vitro et in vivo du bacille tuberculeus aviaire. Ann. Inst. Pasteur **64** (1940) 203-237. (According to Montestruc, who supplied several references to pertinent reports by Rist, this article embodies the essence for the earlier ones.)

[4]FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. The effect of Promin (sodium salt of p,p'-diamino-diphenyl-sulfone-N,N'-dextrose sulfonate) on experimental tuberculosis; a preliminary report. Proc. Staff Meet., Mayo Clin. **15** (1940) 695-699. FELDMAN, W. H., MANN, F. C. and HINSHAW, H. C. Promin in experimental tuberculosis; observation on tuberculous guinea pigs before and after treatment with sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate (Promin). American Rev. Tubere. **46** (1942) 187-195; FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. Therapeutic effects of disodium formaldehyde sulfoxylate diaminodiphenylsulfone [Diasone] in experimental tuberculosis. Arch. Path. **36** (1943) 64-73; FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. Effects on experimental tuberculosis of 4,4'-diaminodiphenylsulfone. American J. Med. Sci. **207** (1944) 290-305; FELDMAN, W. H., HINSHAW, H. C. and MANN, F. C. Promizole in tuberculosis; effect on presumably established tuberculosis of guinea pigs of 4-2'-diaminophenyl-5'-tiazolylsulfone (promizole). American Rev. Tubere. **50** (1944) 418-440; FELDMAN, W. H. Chemotherapy of tuberculosis, including use of streptomycin. Harben lectures, 1946. J. Roy Inst. Publ. Hlth. & Hyg. **9** (1946) 267-288, 297,324, 343-363.

[5]WATANABE, Y. Clinical studies on the pulmonary tuberculosis complicated with leprosy. (Report I.) La Lepro **28** (1959) 258-267 (in Japanese; English abstract).

[6]SPIESS, H. Deutsche Med. Wchnschr. **84** (1959) 1410-1415 (abstract in J. American Med. Assoc. **173** (1960) 924).

BCG vaccination has induced tuberculin positivity. A further suggestion has been offered by Dormer and associates.[7] They had found that, although preventive isoniazid treatment almost completely protects babies from infection by their tuberculous mothers, they do not acquire immunity and are liable to contract tuberculosis when the drug treatment is stopped. They therefore proposed that all such infants should be vaccinated with BCG—but with an *isoniazid-resistant strain*, the effect of which would not be interfered with by the isoniazid chemoprophylaxis given concurrently.

This leads to a new question: Would or would not a *sulfone-resistant* strain of BCG be more effective in certain situations in leprosy than ordinary strains? Specifically, if one should attempt to make a lepromin-negative contact, or nonlepromatous patient, reactive to lepromin by BCG vaccination while giving a sulfone during the period required for the vaccination to develop its full effect, would there be an advantage in using a sulfone-resistant strain of BCG?

There follows the question of whether or not such a strain of BCG exists. Correlative to that question is this one: has anyone isolated a sulfone-resistant strain of the human tubercle bacillus from a long-treated leprosy patient with complicating tuberculosis, which resistant condition might have a bearing on the influence—or lack of it—of the antileprosy treatment on the complicating infection? An attempt was made to obtain information by correspondence. The questions aroused some interest in certain quarters.

Dr. Feldman was unable to answer the questions raised, which he regarded as intriguing and suggesting "an exciting research possibility." He referred the matter to Dr. Sol Rosenthal at the Tice Laboratory of the University of Illinois, which is in effect the BCG headquarters in the United States.

From there, Dr. Robert M. Bechtle wrote (in the absence of Dr. Rosenthal) that they have an isoniazid-resistant strain of BCG from which they have made vaccines that are now in experimental use, the results not yet reported. As for a sulfone-resistant strain they had no information, although he had an idea that some German workers might have one. Subsequently, Dr. Rosenthal offered to attempt to produce such a strain if the demand for it would justify the effort.

In England, Dr. J. R. Bignell, editor of *Tubercle,* who also thought the idea "intriguing," had no information about the existence of such a strain. He understood that the idea of using an isoniazid-resistant strain for vaccinating children against tuberculosis had originated with Dr. Georg Canetti, of Pasteur Institute, Paris, but although there had been quite a lot of talk about it he knew of no actual field trials.

Inquiries made of certain sources in Germany have yielded no trace of a sulfone-resistant BCG, but Professor Freerksen, director of the Institut fűr Experimentelle Biologie und Medizin, in Borstel, said that there should be no difficulty in producing one and offered to do that. He added, however: "It is to be considered that living BCG strains used for vaccination are not killed by sulfone therapy. If, for safety, you apply a larger dose than the usual one for BCG vaccination, you can without scruples employ also a sulfone, and the protective effect will nevertheless take place."

In Japan, Dr. Ken Yanagisawa, vice-director of the National Institute of Health, proceeded to ask all Japanese BCG researchers if a sulfone-resistant strain had ever been

[7] DORMER, B. A., HARRISON, I., SWART, J. A. and VIDOR, S. R. Prophylactic isoniazid; protection of infants in a tuberculosis hospital. Lancet **2** (1959) 902-903.

isolated, but there had not been. He himself had made efforts to isolate such a strain, without success. He felt it doubtful if any strain of the human tubercle bacillus with altered sensitivity had been isolated in any of the leprosaria from a leprosy patient with tuberculosis after prolonged sulfone therapy. He expressed the opinion that it is far more difficult to induce sulfone resistance in the tubercle bacillus than resistance to isoniazid or streptomycin.

The results of this inquiry do not give much encouragement for the idea that in leprosy work a sulfone-resistant strain of BCG might be used with benefit when sulfone chemoprophylaxis is given concurrently with BCG vaccination. Even the use of isoniazid-resistant BCG in tuberculosis work, which started us on this foray, seems little more than an idea as yet, for so far as has been learned it has been actually tried only in Chicago with as yet unreported results.

Nevertheless, there are points of interest in the results of the inquiry, although no indication of the existence of a sulfone-resistant strain of BCG has been elicited, or of sulfone resistance in human tubercle bacilli.

Freerksen is of the same opinion as Montestruc that the administration of sulfone would not inhibit the effect of BCG vaccination, but he suggests that for safety the dose of BCG might be increased. However, no mention has been made of actual observations in proof of that opinion.

Yanagisawa believes that it would be far more difficult to produce resistance in tubercle bacilli to a sulfone than to isoniazid or streptomycin. It should be of interest, as a research project, to determine how great that difficulty may be.

In view of evidence of renewed interest in certain quarters (see Karlson,[8] abstract in this issue) in the possibility of using sulfones in the treatment of certain cases of pulmonary disease (e.g., cases of infection by unidentified mycobacteria, and, presumably, of pulmonary tuberculosis resistant to the regular treatment), that information would be desirable. Particularly interesting would be information about the sensitivity of the tubercle bacilli in leprosy patients with active pulmonary tuberculosis who have long been under sulfone therapy, without ensuing benefit to that complication, especially in patients who have developed tuberculosis after prolonged treatment (Chenebault and Rollier,[9] abstract in this issue). If sulfone resistance proves difficult to induce in mycobacteria generally, that may perhaps explain why so little has been said of clinically observable sulfone resistance in leprosy patients.—H. W. Wade

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[8]Karlson, A. G. Diaminodiphenylsulfone (DDS): Preliminary observations on its effect in vitro and in mice infected with various species of mycobacterium. Trans. 18th Conf. Chemoth. Tubere., Veterans Administration and Armed Forces, St. Louis, Mo., 1959.

[9]Chenebault, J. and Rollier, R. Les manifestations pulmonaires au cours de la lèpre. J. Pneumo-Phthisiol. l'Afrique du Nord **1** (1958) 7-19.