EDITORIAL COMMENT†

DUPLEX ANTIGENS

Data, suggesting that a single protein molecule may stimulate the production of two qualitatively-different circulating antibodies, are currently reported by Smadel[1] and his coworkers of the Rockefeller Institute.

It was shown by Tanaka[2] and Freyer,[3] in 1902-4, that vaccine lymph gives specific flocculation reactions with vaccinia-immune serum. Two soluble antigens were afterwards demonstrated in this lymph[4]: a heat-labile (L) antigenic fraction readily destroyed at 56°C., and a heat-stable (S) fraction resisting heat to 95°C. By cross-absorption tests, Cragie[5] afterwards demonstrated that the same L- and S-antigens are also present in vaccine elementary bodies. There was suggestive evidence that the L- and S-antigens are conjugated, in the elementary body, to form a single protein complex, the so-called "LS-antigen," which is capable of reacting equally well with L- and S-circulating antibodies. It was suggested by Smadel and Rivers[1] that the serologically-active parts of this hypothetical protein conjugate (LS) undergo a series of independent degradations, giving rise to such fractionally-denatured complexes as L'S, L"S, LS', L'S', etc.

This theory of the nature of the natural antigen in elementary bodies is currently tested on vaccine dermal filtrates by the Rockefeller biochemists. Dermal pulp, from cutaneously infected rabbits, was extracted in a 1:50 dilution of standard phosphate buffer solution (pH 7.2). The extract was afterwards freed from cellular débris by centrifugation, followed by Seitz filtration. Electrophoretic analysis of the resulting filtrate demonstrated the existence of four distinct protein fractions. Fractionation was effected by altering the pH of the filtrate, by which means the dermal proteins were separated into three overlapping groups: A, proteins which remained in solution at pH 4.63; B, proteins precipitated at pH 4.63, but soluble at pH 6.31; and C, proteins precipitated at pH 6.31, but soluble at pH 8.56. On reprecipitation both A and C fractions were serologically inert, giving no test-tube reactions with either L- or S-antibody. The original reacting titer of the dermal filtrate, however, was found quantitatively in the B fraction. Physical and chemical studies showed this fraction to be a homogeneous protein, with a molecular weight approximately that of serum globulin. This B-protein is precipitated quantitatively with either L- or S-precipitin, from which they conclude that this natural antigen is "a single molecular substance containing both L- and S-activity."

They found that the L-portion of this native antigen can be partially (L') or completely (L") denatured by heat, without serological alteration of the S-portion. By means of enzymic digestion, the S-portion can be similarly degraded (S', S") without demonstrable alteration of the L-portion. Dissociation of the LS-molecule into free L- and free S-antigen, however, was not demonstrated, the allegedly free L- and S-antigens of previous investigators presumably being L"S, LS", or other unipolar degeneration products.

Demonstration of this duplex antigenic protein is not only a valuable contribution to the current theory of acquired immunity to vaccine virus, but is equally suggestive in numerous other infectious and allergic processes. Thus far allergists, for example, have almost invariably reasoned from the assumed one-to-one, antigen-antibody relationships of classical immunology, in spite of the reported synthesis of numerous "duplex" proteins of "hybrid" antigenicity.[6] For a decade the "emergent evolution" of new or "hybrid" blood specificities has been of speculative interest to geneticists.[7] The dual antigenic molecule of the Rockefeller biochemists, therefore, may also be of basic nonclinical biological interest.

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REFERENCES

1. Smadel, J. E., and Rivers, T. M.: Jour. Exp. Med., *75*, 151. Shedlovsky, T., and Smadel, J. E.: *Ibid.*, *75*, 165 (Feb.), 1942.
2. Tanaka, K.: Centralb. f. Bakt., *32*, 726, 1902.
3. Freyer, M.: Centralb. f. Bakt., *36*, 272, 1904.
4. Cragie, J.: Brit. Jour. Exp. Path., *13*, 259, 1932.
5. Cragie, J., and Wishart, F. O.: Jour. Exp. Med., *64*, 819, 1936.
6. Sox, H. C., and Manwaring, W. H.: Jour. Immunol., *22*, 237, 1932. Madison, R. R.: Proc. Soc. Exp. Biol. and Med., *32*, 641, 1935. Zoet, A. G.: *Ibid.*, *32*, 1469, 1935.
7. Irwin, R. R.: Proc. Soc. Exp. Biol. and Med., *29*, 850, 1932.

MALPRACTICE PROPHYLAXIS—MEDICAL DEFENSE*

A reduction in the number of malpractice actions can be effected only through the development of a strong defense. It is obvious that such actions would be discouraged if plaintiffs consistently failed to obtain favorable judgments.

Of course, it is not to be argued that a doctor who is actually guilty of malpractice should be allowed to go free of any penalty. There are meritorious claims, and these should be settled out of court—preferably before suit has been filed.

Unjustifiable claims, however, should be contested as thoroughly as possible. In such cases it is sheer folly to compromise, on the theory that a slight settlement would be less expensive than the cost of defense. Such a course serves as an

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* Third of a series of articles on Malpractice Prophylaxis (Article I, in July issue, on page 7. Article II, in August, on page 121.)

encouragement to others whose claims are not justified. This short-sighted view, which is so common today, is directly responsible for the rapid increase in the number of malpractice claims in some sections of the country. If cases based upon unjust or absurd claims are permitted to receive even a slight profitable return, there will be an incentive to bring more of them.

It is a great temptation for a doctor to rid himself of these nuisance claims by making a small settlement. The unfavorable publicity, the loss of time, and the mental and emotional strain involved in defending a malpractice suit may lead the physician to compromise. But, as is so often the case, the easiest way out of a situation is seldom the best. For the sake of both himself and his colleagues, the doctor should make a determined opposition to any unjustified claim.

The task of defending a malpractice case is one which requires a high degree of specialization, as well as a peculiar aptitude on the part of the attorney. He must be able to understand the medical problem presented in each case; for it is his duty not only to conduct the examination of the case, but also to cross-examine the plaintiff's witnesses, including the medical experts. If the attorney's medical knowledge is so limited that he is unable to comprehend the significance of the testimony, the defense will be seriously handicapped. Moreover, such an attorney would be incapable of the thorough analysis of the medical problem, which must serve as a basis for the construction and development of a sound and practical theory of defense.

The task of handling medical expert witnesses is also one which necessitates specialized training. Unless an attorney possesses an understanding of the psychology of medical expert witnesses, the defendant's own witness may do more harm than good. For one thing, medical experts are often accustomed to having their opinions listened to and accepted as authoritative. They are seldom prepared to be confronted with contradiction or expression of doubt as to their judgment. In addition, the expert may be definitely opinionated; and insistence upon personal preference in medical procedure may do much to injure the case. In many instances, the experts for the defendant have not had sufficient opportunity to discuss the case thoroughly and in a group before the time comes to go into court. In such cases, minor discrepancies may appear in their testimony, even though there is no actual disagreement which is of significance. Nonetheless, any such disparity in testimony is sure to be pounced upon by the plaintiff's attorney, and the effect upon the jury may be definitely prejudicial. Obviously medical experts must be encouraged to be fair and impartial. But they must also be simple and direct, they must employ phraseology which will be understandable to the jury, and they must be able to retain complete self-control under cross-examination which may be deliberately irritating.

Far too many malpractice actions have been lost through poor defense; this is an aspect of the problem which needs more attention, particularly in areas which have become virtual hot-beds of malpractice actions. Wherever a serious threat is made against a physician, a carefully-prepared procedure should be put into effect. Every phase of the case should be thoroughly investigated by experts. All available witnesses should be interviewed, and all records carefully examined while the case is comparatively fresh. It is particularly important that the physician or physicians who succeeded the threatened doctor in the care of the patient should be interviewed.

On the basis of all this evidence, the justice of the claim should be weighed. If the charge of malpractice seems justified, an attempt should be made to settle the case out of court. If the suit is to be fought in court, meticulous attention must be given to the method which is to be used by the defense in handling the medical facts. It is especially important that these facts be given the best possible sequential presentation. It is for this reason that the defense attorney must be equipped with a competent understanding of the medical problem involved. Far more often than not the defendant physician is too much involved emotionally to be able to give real assistance in the formulation of questions to be asked of medical expert witnesses for either side.

Through the development of a sound, capable and intelligent method of defense it will be possible to effect a reduction in the number of malpractice claims. Therefore, it would be difficult to over-estimate the importance of the way in which such claims are handled. Each step toward the formulation of better defense is a major contribution to malpractice prophylaxis.

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SULFONAMIDE RESISTANCE*

For four or five years it has been known that certain bacteria are capable of becoming resistant to the bacteriostatic action of the sulfonamides, a phenomenon similar in many respects to the development of drug-fastness during the arsenotherapy of syphilis. Sulfonamide resistance, at first a test tube curiosity, is rapidly becoming of considerable importance in clinical medicine.

Experimental studies have clarified certain aspects of the development of sulfonamide resistance.[1] Resistance has been demonstrated for many organisms commonly pathogenic for man, including streptococci, staphylococci, colon bacilli, gonococci, and Brucella. *In vivo,* sulfonamide-resistant pneumococci have been developed by serial passage through mice, treated with less than curative doses of sulfapyridine. Organisms made insensitive *in vitro* are also resistant *in vivo,* and vice versa. Although it may be lost when only partially developed, well established resistance is apparently retained indefinitely.

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