it would seem logical that even small amounts of estrin, not being inactivated by the liver would accumulate in the body and at the same time act as a chronic growth stimulant to the estrin-susceptible tissues, viz., the pelvic organs and possibly also the glands of the breast.

The fact that dietary errors tend to be chronic is shown in certain of our cancer cases, where even after cure, or a remission of months or years, they return to the same habits of diet and continue to show thiamine deficiency. While we must also consider the possibility of an internal metabolic defect leading to the deficiency, this would tend to be countered by the fact that with correction of dietary intake the deficiency was corrected in our cases. Whether or not these cases require an increased quantitative intake of these essentials to maintain a normal level remains to be investigated.

Conclusions

When we couple the findings with the background of what has been proven in animals, there appears to be excellent circumstantial evidence to suggest that the nutritional deficiency may have been a primary factor leading to the malignancy.

Whether this low thiamine excretion is due to an actual primary dietary deficiency or to some internal metabolic change is a subject for further investigation. In either case, if this hypothetical mechanism proves to be correct, it means that we are presented with the means not only of diagnosing uterine cancer by cytological findings but of actually detecting a potential cancer-producing mechanism even before the cancer develops! Two simple tests would be used: (1) a cervical cytology test, which would tell (a) if the person had uterine cancer, and (b) if not, whether the endogenous estrogen level was abnormally high, in which case the second test should be done; and (2) a test of the urinary thiamine level.

The finding of a combination of low thiamine and abnormally high estrogen could be recognized as a dangerous precancerous linkage. Recognition of this would permit correction and possible prevention of the cancer.

No single track of investigation yields a conclusive answer to the cancer enigma, but when we piece together the evidence of animal experimentation, cytopathological, hormonal, and nutritional findings, there seems to be evidence that progress in the right direction is being made.

References

1. Allen, E. *Amer. J. Anat.*, 1924, **34**, 133.
2. Allen, E. *J. Amer. med. Ass.*, 1935, **104**, 1496.
3. Biskind, M. S., and Biskind, G. R. *Endocrinology*, 1942, **31**, 109.
4. Biskind, M. S., Biskind, G. R., and Biskind, L. H. *Surg. Gynec. Obstet.*, 1944, **78**, 49.
5. Biskind, M. S., and Shelesnyak, M. C. *Endocrinology*, 1942, **30**, 819.
6. DeAllende, Ines, L. C., Shorr, Ephraim, and Hartman, Carl G. In *Contributions to embryology. Carnegie Inst. Publ. 557*, 1943, **32**, 1–26.
7. Ferrebee, J. W. *J. clin. Invest.*, 1940, **19**, 251.
8. Goldberger, J. Tice's *Practice of medicine.* (Rev. by W. H. Sebrell.) Vol. 9, 1932, p. 205.
9. György, P., and Goldblatt, H. *J. exp. Med.*, 1942, **75**, 355.
10. Henry, J. S. *Canad. med. Ass. J.*, 1945, **53**, 31.
11. Hodgson, J. E., Dockerty, M. B., and Mussey, R. D. *Surg. Gynec. Obstet.*, 1945, **81**, 631–642.
12. Kelly, A. O. J. *Osler's mod. Med.*, 1908, **5**, 775.
13. Krumm, J. F. *Amer. J. Obstet. Gynec.*, 1936, **31**, 1035.
14. Papanicolaou, G. N., and Traut, H. F. *Amer. J. Obstet. Gynec.*, 1941, **42**, 193.
15. Pincus, G., and Graubard, M. *Endocrinology*, 1940, **26**, 430.
16. Rhoads, C. P. *Bull. N. Y. Acad. Med.*, 1942, **18**, 53.
17. Robertson, D. C., Maddux, W. P., and Allen, E. *Endocrinology*, 1930, **13**, 77.
18. Singher, H. O., Kensler, C. J., Taylor, H. C., Jr., Rhoads, C. P., and Unna, Klaus. *J. biol. Chem.*, 1944, **154**, 79.
19. Wang, Y. L., and Harris, L. J. *Brit. med. J.*, 1943, 451.

The Antibacterial Activity of Protamine Zinc Insulin[1]

Carol Houck Bollenback and Sidney W. Fox

Chemistry Section, Iowa Agricultural Experiment Station, Ames

As part of a program of chemical and biological study of proteinaceous antibacterials (*3*), it seemed desirable to test the effect of protamine insulin combinations of the kind used routinely in the control of diabetes (*1*). The antibacterial property of the protamines, clupein (*5*), and salmine (*7*), had previously been reported. Protamine sulfate prepared from shad of the Sacramento River by one of us (S.W.F.) has also been found to possess comparable activity (*2*). The experiments recorded below indicate that protamine is able to act as an antibacterial, even though combined in a relatively insoluble form with insulin.

The tests were conducted on cultures of *Lactobacillus arabinosus, Staphylococcus aureus,* and *Escherichia coli.* Both the supernatant liquid of centrifuged protamine zinc insulin preparations and the whole suspension, with appropriate controls, were tested. All tests were run in solutions buffered by phosphate. The contents of the tubes were initially at pH 7.1–7.4. *Lactobacillus arabinosus* was cultured at 30° in the special Bacto-Peptone medium of McMahan and Snell (*6*) and in the synthetic medium of Kuiken, *et al.* (*4*). The other two organisms were cultured at 37° in the usual beef extract broth. The observations recorded in Table 1 were made at 24 hours from tube cultures. All results were confirmed by plate cultures read at 48 hours. These plate cultures were made from well-shaken suspensions after an initial growth in

[1] Journal Paper No. J–1288 of the Iowa Agricultural Experiment Station, Project 897, in cooperation with the Veterinary Research Institute.

tubes for 24 hours. In order to test the possibility that the cells are prevented from proliferating because of engulfment within the solid, shake cultures were run on *Lactobacillus arabinosus* with a suspension of protamine zinc insulin at a concentration that was close to the threshold value in tubes. Results comparable to those for cultures in tubes were obtained.

TABLE 1

LOWEST DILUTIONS OF PROTAMINE AND INSULIN PREPARATIONS PERMITTING GROWTH IN SEVERAL SPECIES OF BACTERIA

Microorganism	Protamine zinc insulin suspension	Protamine zinc insulin supernatant solution	Salmine	Zinc insulin
L. arabinosus on Bacto-Peptone medium	1/20,000	N.I.*	1/85,000	N.I.
L. arabinosus on synthetic medium	1/40,000	N.I.	1/200,000	N.I.
Staph. aureus Heatley	1/20,000	N.I.	1/50,000	N.I.
E. coli	1/10,000	N.I.	1/25,000	N.I.

* N.I. signifies no inhibition by the undiluted solution. The undiluted solution of zinc insulin contained 1.8 mg. of zinc insulin powder (Lilly) per cc. Dilution figures in the table refer to the fraction: weight of substance tested/weight of solution tested.

Effective concentrations were determined by testing successive twofold dilutions of the original solution or suspension. All solutions were sterilized by Seitz filtration, and all mixtures were aseptically prepared from such solutions. The protamine zinc insulin preparation was obtained from commercial ampoules. The zinc insulin powder and salmine sulfate were the gifts of Mr. George Walden, of Eli Lilly and Company, to whom our thanks are expressed.

The phenol used as a preservative in protamine zinc insulin preparations contributes but slightly to its antibacterial activity. The data in Table 1 indicate inappreciable antibacterial activity for the supernatant liquid of centrifuged preparations. Substantially the same antibacterial activity was recorded for protamine zinc insulin suspensions prepared in this laboratory without the inclusion of any added preservative. The observed antibacterial effects are therefore not attributable to the phenol found in commercial preparations.

The activity of protamine zinc insulin appears to be approximately equivalent to the activity of the contained protamine (3.5 parts of protamine zinc insulin contain 1.25 parts of protamine). It seems reasonable to conclude, therefore, that the salmine zinc insulin dissociates to liberate salmine. This behavior is comparable to the gradual release of insulin for its regulated action when administered in insoluble complex form with protamine.

These observations indicate that there may be a previously unrecognized medical utility in the inclusion of protamine in insulin preparations.

References

1. AMERICAN MEDICAL ASSOCIATION. *New and non-official remedies*, 1944, 431.
2. FOX, S. W., BOLLENBACK, C. H., and FLING, M. Unpublished experiments.
3. FOX, S. W., FLING, M., and BOLLENBACK, G. N. *J. biol. Chem.*, 1944, **155**, 465.
4. KUIKEN, K. A., NORMAN, W. H., LYMAN, C. M., HALE, F., and BLOTTER, L. *J. biol. Chem.*, 1943, **151**, 616.
5. MCCLEAN, D. *J. Path. Bact.*, 1931, **34**, 459.
6. MCMAHAN, J. R., and SNELL, E. E. *J. biol. Chem.*, 1944, **152**, 84.
7. MILLER, B. F., ABRAMS, R., DORFMAN, A., and KLEIN, M. *Science*, 1942, **96**, 428.

Scanning Science—

Almost the only power clearly and expressly vested in Congress by the Constitution which has remained practically unexercised to the present day is that of fixing the standard of weights and measures. For more than a generation we lived with no legal standard by which could be determined even the amount of metal which went into the coin that came from our mints. Gallatin procured from France a platinum kilogram and meter in 1821 and from England a troy pound in 1827, and in 1828 the latter was recognized as the standard for mint purposes. In 1830 the Senate directed the Secretary of the Treasury to have a comparison made of the standards of weight and measure used at the principal custom houses of the United States and report the same to the Senate. This was done, and large discrepancies and errors were found to exist. Varying scales and varying measures inevitably produced varying rates of duty. The Treasury Department, therefore, in the exercise of its executive power and as a necessary incident and means to the execution of the law and the observance of the Constitution, adopted for the use of that Department the Troughton scale, then in the possession and use of the Coast Survey, as the unit of length, and the troy pound of the mint as the unit of weight. From the latter the avoirdupois pound was to be derived, assuming that they were 7,000 grains in the pound avoirdupois to 5,760 in the pound troy. By the Act of March 3, 1881, similar sets of standards were directed to be supplied to the various agricultural colleges which had received land grants from the United States at a cost not exceeding $200 for each set. This law was complied with as best it could be under the limitation of cost prescribed.

—27 March 1896