

## ALLERGIC REACTION TO PROTAMINE: A LATE COMPLICATION OF ELECTIVE VASECTOMY?\*

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*ABSTRACT—Nucleoprotamines are a normal component of human sperm cells. Antibodies against these protamines develop in 22 to 33 per cent of patients undergoing elective vasectomy. These antibodies, in turn, have been shown to cross-react with medicinal protamines, which are extracted commercially from the testes of salmon and certain other fish. This cross-reactivity against protamines raises the possibility that patients who have undergone elective vasectomy may be at increased risk of an allergic reaction developing if they are later exposed to protamine as a medication. Since medicinal protamines currently enjoy widespread clinical use, this information should be borne in mind by those clinicians using protamine and by urologists when counselling patients concerning elective vasectomy for sterilization.*

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Protamine is a widely used medication which is administered after certain procedures to reverse heparin-induced anticoagulation. One would hardly suspect that undergoing an elective vasectomy would place a patient at increased risk of a serious allergic reaction to this medication. Yet, a series of studies from the Netherlands<sup>1-3</sup> now provides substantial evidence that, for vasectomized patients, such risk may indeed exist. The following case report is presented to bring further attention to this potential hazard.

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### Case Report

In April, 1982, a forty-two-year-old man underwent cardiac catheterization for evaluation of coronary vessel disease. Within five minutes after receiving an intravenous injection of protamine, pruritus and hives developed over his neck and face. There was no wheezing or change in blood pressure. The allergic reaction responded promptly to intravenous diphenhydramine hydrochloride (Benadryl). Several months later, at the termination of open heart surgery, protamine was again injected. To prevent another allergic reaction, methylprednisolone (Solu-Medrol) and 25 mg of diphenhydramine were injected first. The patient experienced no untoward reaction and has since done well.

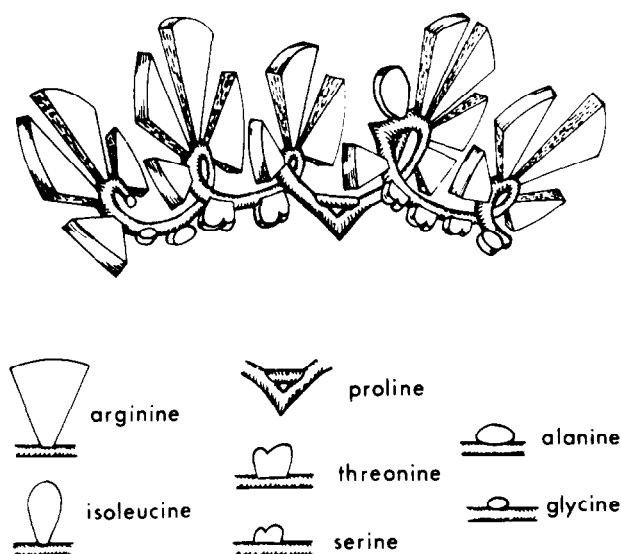


FIGURE 1. Schematic drawing of structure proposed for protamine-herring protamine (clupeine) Y-I. (From Ottensmeyer, Whiting, and Korn,<sup>10</sup> reproduced with permission.)

This patient had previously undergone an elective vasectomy for sterilization in 1967 and had required repeat surgery for sperm granuloma formation in 1975. In assessing the immunologic consequences of the vasectomy, a tray agglutination test (TAT),<sup>4</sup> a microimmobilization test,<sup>5</sup> and an antiprotamine immunofluorescence test<sup>6</sup> were performed. While results of the immobilization test were negative, the serum showed a sperm-agglutinating antibody titer of 1:1024. And, when swollen sperm heads that had been treated with triton X-100 detergent 1% and dithiothreitol (a reducing agent) were added to serum diluted 1:5 and 1:20, to demonstrate the presence of antiprotamine antibody, one of the most intense immunofluorescent reactions ever recorded in this laboratory occurred.

#### Comment

Several factors point to a relationship between this patient's history of vasectomy and his subsequent allergic reaction to protamine. First, we do know that vasectomy can lead to formation of systemic antibodies. The studies of several investigators<sup>6</sup> have shown that after vasectomy, agglutinating antibodies against spermatozoa develop in 60 per cent or more of the cases. Thus, men who have undergone a vasectomy are at risk of reacting to spermatozoa and their various components.<sup>7</sup> Protamine is one such component.

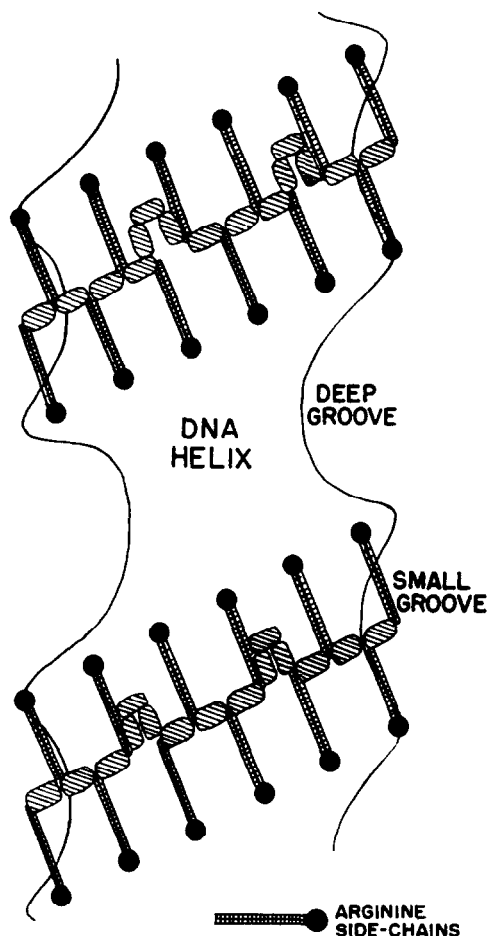


FIGURE 2. Schematic representation of spiraling chain of protamine interfacing with DNA helix. (From Felix,<sup>9</sup> reproduced with permission.)

Protamines are molecules of low molecular weight and consist chiefly of amino acids, most prominently arginine. The compound forms a helix, with arginine moieties facing away from the core (Fig. 1).<sup>8-10</sup> This configuration permits an intimate, spiraling interface with the nuclear DNA molecule<sup>10</sup> (Fig. 2). Protamines are related to nucleohistones. However, while nucleohistones are widely distributed throughout the animal kingdom, it is only in the developing spermatids that these nucleohistones are replaced by nucleoprotamines.<sup>2</sup>

The protamine used commercially for medication is extracted from sperm cells within the testes of salmon and other fish. These protamines are species specific, but there can be a strong crossover of antigenicity against the protamines of other species. Since in our patient antibodies to the protamine of his own sperm cells as a result of elective vasectomy had already developed, it would seem that subsequent

exposure to antigenically similar fish protamine triggered his allergic reaction.

To substantiate this hazard, Samuel<sup>2</sup> has undertaken direct immunofluorescence of the sera of 78 men who had undergone elective vasectomy; antibodies against protamine were uncovered in 17 of these patients (22%).<sup>1</sup> In other related studies, antibodies against protamine after vasectomy have been detected in 30 per cent (of 47 patients)<sup>3</sup> and 33 per cent (of 71 patients).<sup>7</sup> The observations that these antibodies (1) developed progressively during the year after vasectomy; (2) paralleled the development of antisperm agglutinating antibodies; and (3) were not found in prevasectomy samples, implicate vasectomy as the source of immunologic insult that stimulated antibody formation against protamine.<sup>1,7</sup> Patients in whom sperm granulomas develop postoperatively seem to be at increased risk.<sup>3</sup>

If these antibodies against human protamine, developed as a result of elective vasectomy, truly increase the risk of an allergic reaction on subsequent exposure to medicinal protamine, the clinical consequences could prove substantial. For instance: (1) patients such as ours who have undergone elective vasectomy might be at higher risk of mild allergic reactions developing on later exposure to protamine as an antiheparin agent; (2) more important, these patients might also be at higher risk of suffering an anaphylactic reaction; and (3) since use of protamine as a heparin antagonist is not limited to open heart surgery, patients exposed to protamine in other cardiovascular surgery, in dialysis, and in many leukopheresis techniques would also be at higher risk of allergic reaction if they had undergone prior vasectomy. Even diabetic patients, following vasectomy, might react adversely to protamine zinc insulin.

The exact mechanism by which antibody formation against protamine evolves is not well understood. Protamine itself does not appear to be antigenic; injections of purified protamines alone do not evoke an antibody response. However, protamines *in vivo* are intimately bound to the DNA helix (Fig. 2). Thus it is possible that antibodies are not developed directly against protamine, but rather against the protamine/DNA complex. If this is the case, there may be a risk that in vasectomy patients antibodies will develop not only against protamine, but also against the protamine/DNA complex, and, more specifically, against DNA

itself. And, if this is the case, the potential consequences could be far more serious.<sup>1,7</sup>

### Conclusion

The exact clinical consequence of postvasectomy antibodies against protamine remains uncertain. However, it clearly has been shown that antibodies against human protamine do develop in 22 to 33 per cent of patients undergoing elective vasectomy, and that these antibodies do cross-react with fish protamines now widely used in clinical medicine. This information and the clinical concerns it raises should be borne in mind by clinicians who are using protamine in their practice. The potential risk should also be kept in mind when urologists counsel their patients concerning elective vasectomy for sterilization.

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