

Four of the in the IRR group based upon the questionnaire data and the screening exam. Of these, two had substantial post-void residual volumes, one with low flow rate, one with reasonable flow rate, the examination indicating mild BPH. The other two patients in the IRR group were mildly symptomatic. One had a low voiding flow rate and the other a reasonable but not exceptional rate. Of the 4 "normal" individuals with >8 pg/ml NGF in the urine, two had previously undergone vasectomy, and the other two reported fathers with prostate cancer. It is possible that high rates of NGF in urine can indicate future medical problems.

The high NGF group contained two "mild" BPH cases with significant post-void volumes and one with a very low flow rate. Also, an apparently asymptomatic individual has a relatively low flow rate, residual urine and the highest level of NGF in the urine. One might predict that this person will begin to experience symptoms in the future.

EXAMPLE 8

URINE TESTS IN ANIMALS

Urine was collected from rats during experiments on other projects, those involving experimental obstruction and normal controls. The results parallel that from the patients: 33% of normal rats have detectable levels of NGF in the urine taken as a 24-hour sample from a metabolic cage, with a mean concentration of 5.6 ± 0.57 pg/ml (mean \pm SE). 75% of rats after one week of partial urethral ligation had detectable NGF, at 7.82 ± 2.47 pg/ml, a higher level and increased incidence. All of these animals were female, indicating that the source of NGF in the urine of laboratory rats is not exclusively the prostate and testis. Thus, NGF in the urine in these obstructed animals may derive from the bladder and the urine level rises with the large increase in production during obstructive hypertrophy. Furthermore, kidneys in these animals were not hydronephrotic. Because 2.5S NGF, the smallest active form, is a dimer with a molecular weight approximately 26,000 daltons, it is unlikely that the protein is filtered by the kidney. NGF does not cross the blood-brain barrier unaided. However, the molecular form of NGF in the urine is not presently known. The two-site ELISA depends upon immunoreactivity and might measure a smaller protein fragment generated elsewhere and filtered and excreted by the kidney.

The increased incidence of detectable NGF and increased levels in the urine of obstructed female rats can relate to other, more general changes in the urine protein content. This was tested by SDS-PAGE analysis of urine from normal and rats obstructed for 1-3 weeks. The gel patterns, total protein content and creatinine content of the two groups were indistinguishable. These results illustrate that obstruction does not result in a wholesale shift in the spectrum of proteins in the urine but that the alterations are more subtle than can be detected by SDS-PAGE. The ELISA for NGF exceeds 2 orders of magnitude greater sensitivity than that of a western blot from SDS-PAGE gel.

Neurotrophic factor production participates in neural plasticity following outlet obstruction and inflammation because the neurons in the micturition pathways respond to the factors with growth and altered function. The cellular pathways responsible for regulating the synthesis and transfer of neurotrophic factors are activated and stimulated by the disease conditions. NGF and bFGF appear in the urine of patients with voiding dysfunction and in experimental animals with induced disease models. Therefore, the symp-

toms associated with BPH and IC that cause most patient concern and dictate physician intervention may be directly related to the production of these neurotrophic factors.

Not all attempts to use the presence of specific growth factors in the urine for diagnosis have been successful. One group of urine samples taken during a prostate cancer screening was collected and stored using a very different protocol. When assayed for levels of NGF, very few samples contained detectable NGF. No attempt was made to correlate this NGF levels in this group with specific clinical findings. However, efforts are in progress to optimize the handling of urine samples after collection and prior to analysis to ensure that factors are not degraded or lost to detection. An entirely different approach was also taken. Urine samples from rat disease models and human samples were analyzed by polyacrylamide gel electrophoresis under denaturing (SDS) conditions (SDS-PAGE). This separates urine proteins based upon differential rate of migration through an acrylamide gel in response to an applied electric field, a separation method based roughly upon protein size. The gels were transferred to a membrane support and immuno-probed with antibodies against the factors of interest (Western blot). This detection method was not sensitive enough to detect or measure the urine neurotrophic factors.

Since other modifications and changes varied to fit particular operating requirements and environments will be apparent to those skilled in the art, the invention is not considered limited to the example chosen for the purposes of disclosure, and covers all changes and modifications which do not constitute departures from the true spirit and scope of this invention.

What is claimed is:

1. A non-invasive method of detecting lower urinary tract response to obstructive or irritative conditions comprising the steps of:

- collecting a sample of urine from a patient,
- determining the concentration of nerve growth factor present in said urine using an immunoassay,
- comparing said concentration of said nerve growth factor in said urine to a predetermined normal concentration, wherein the presence of an increased concentration of said nerve growth factor indicates the presence of irritative and/or obstructive conditions.

2. The non-invasive method of detecting lower urinary tract response to obstructive or irritative conditions of claim 1 wherein said predetermined normal concentration is approximately less than 8 picograms per milliliter.

3. The non-invasive method of detecting lower urinary tract response to obstructive or irritative conditions of claim 1 wherein said concentration of nerve growth factor present in said urine is determined through a two site ELISA.

4. A non-invasive method of detecting lower urinary tract response to obstructive or irritative conditions comprising the steps of:

- collecting a sample of urine from a patient at the onset of symptoms of said conditions;
- determining the concentration of nerve growth factor present in said urine using an immunoassay,
- comparing said concentration of said nerve growth factor in said urine to a predetermined normal concentration, wherein the increased concentration of said nerve growth factor indicates the onset of irritative and/or obstructive conditions.