UROLOGICAL PRACTICE AND BIOCHEMISTRY

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The marked advances in the medical sciences have been the result of cooperative efforts in the fields of clinical investigation and laboratory research. These achievements have been accomplished largely by tedious investigations which prove fruitless more often than fruitful. In the field of urology alone, in which we are particularly interested, many of the advances have been direct results of investigations in the chemical laboratory. Without any attempt to review the vast literature, some of the more practical results of collaborative efforts between urologists and biochemists will be discussed.

It is not possible here to mention the multitude of biochemical tests for the analyses of blood and urine which are of diagnostic as well as prognostic value in urological practice. Most of these tests are also useful in general medical practice. At present, we will mention only some of those tests which are of special urological interest.

Diodrast has been a very useful chemical in the making of pyelograms. It is nontoxic and its intravenous administration is not followed by any serious reaction. It can readily be used in the making of pyelograms in small children or infants. Under many circumstances when retrograde pyelography is contraindicated, a roentgenogram can be obtained following the intravenous injection of diodrast. When used in making retrograde pyelograms, it is much more satisfactory than sodium iodide because it is less irritating to the delicate mucous membranes of the urinary tract.

Various chemicals have been made which are of tremendous importance in the determination of kidney function. The use of indigocarmine enables the diagnostician to determine quickly individual kidney function when ureteral catheters are in place. The phenolsulphonphthalein test has been used to great advantage in the diagnosis of surgical diseases of the kidney. In patients suffering from nephrosis or one of the nephritides, total kidney function can be determined by the urea clearance test.

In the field of urinary antiseptics, much could be written in regard to recent chemical contributions. At one time, no thought was given to the probability of having specific chemotherapeutic agents. Treatment with sodium acid phosphate and urotropin, which is very valuable, was used in attempting to control any or all types of infection. It is now known that ketogenic diets and mandelic acid are particularly efficacious in combatting the colon bacillus and the streptococcus fecalis. The discovery of the usefulness of the sulfanilamide group has been of the greatest importance to the urologist. The first member of this group

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to come into common use was prontosil which was very useful in the treatment of streptococcal infections, as well as in other conditions. Recently, sulfanilamide and sulfapyridine have been widely used in streptococcal and gonococcal infections. Sulfapyridine probably is less toxic than most other available compounds of this type. Very recently, experiences with sulfathiazol indiate that it is probably very efficacious in regard to staphylococcal infections of the urinary tract.

In addition to the production of these antiseptics, the chemist plays a valuable role in controlling their proper therapeutic use. The mode of absorption and excretion has been studied. Quantitative methods for measuring the antiseptics in the blood stream have been developed. The mode of action on the organisms has been investigated. Methods for determining the most satisfactory quantities to administer have been devised.

During the past decade notable advances have been made in regard to our knowledge of urinary lithiasis. The gaps are so great that extensive researches still are necessary. It has long been recognized that infection and stasis are definite predisposing factors in the production of calculi, but it is only within recent years that the very important question of diet has received proper emphasis.

Vitamin A deficiency has been demonstrated to be a major etiological factor in the production of many stones, particularly of the phosphatic type. It is known that this vitamin is of great importance in the maintenance of epithelial structures. It seems that desquamated keratinized epithelium from the urinary tract provides a nucleus about which crystalline depositions readily form. The frequency of renal calculi in vitamin A deficiency has been demonstrated in experimental animals and in man.

For reasons other than vitamin deficiency, the diet is a very important consideration in regard to the formation of stones. By controlling the diet, it usually is possible to control the acidity of the urine over a considerable range of pH. This is very useful as a therapeutic aid because uric acid calculi are much more soluble in alkaline medium whereas phosphatic calculi increase in solubility as the urine becomes more acid.

Improved methods for the analysis of calculi have been developed. This has become a matter of importance because of the fact that many calculi tend to recur. If the nature of the stone is known, the recurrence can be combatted more readily.

By no means has the least of the biochemical contributions in the field of urology been in the investigation of the sex hormones. The literature on the subject is so tremendous that to summarize it briefly is impossible. The investigations of greatest interest to the urologist are

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those concerned with testicular disorders. In studying cases of impotence, sterility, or cryptorchidism, it frequently becomes important to know whether or not the condition is of endocrine origin. In addition, it is important to discover whether or not glands other than the testes are involved. In making such a diagnosis, laboratory studies to determine the amount of testicular and gonadotropic hormone being excreted can be of considerable assistance.

The assay for androgens (male sex hormones which directly stimulate male characteristics) can be carried out in numerous ways. No matter what method is employed, it is necessary first to separate the hormone from other urinary constituents. This concentration can readily be affected by the use of fat solvents. The hormone is recovered from the solvent and measured either by biological or by chemical methods. Numerous biological procedures have been used, including the effect of the androgens on the seminal vesicals, the prostate, and the production of semen in experimental animals. By far the most satisfactory biological method for routine clinical use is that based on the measurement of the growth of the comb of the capon after the bird has been treated with the hormone.

In the normal male, sufficient hormone is present in the urine to make it possible to extract it and inject it into capons in order to make this test. In children and in hypogonadal individuals, the amount of androgen present is lower and in order to accomplish a satisfactory assay, it is necessary to increase the sensitivity of the test. This can be done by inuncting the material directly onto the comb instead of injecting it into the capon.

Recently, considerable effort has been made to devise satisfactory chemical methods for measuring androgens in urinary extracts. The androgens which are quantitatively the most significant in normal urine are ketonic in nature and possess a chemical configuration which results in their reaction with meta-dinitrobenzene, to produce a red color. The depth of the color can be used as a measure of the amount of hormone present. Under certain circumstances nonketonic androgens are present in the urine. These cause growth of the capon's comb but do not give the color reaction. In such instances, they can be detected only by biological assay.

When the testes are not producing the normal amount of hormone, the pituitary gland becomes hyperactive. Several laboratory tests for overactivity of the pituitary gland are available. The pituitary sex hormones are known as gonadotropins because they stimulate the gonads. They are extremely complex chemical elements and chemists have not been able to devise a satisfactory chemical method for their detection. However, excellent procedures are available for the separation of these hormones from the urine. When separated, biological determination is

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possible. Most methods of bio-assay for gonadotropins are based on the fact that they stimulate the ovaries of experimental animals. The amount of stimulation is a measure of the amount of hormone present.

One of the very greatest chapters in chemistry has been that dealing with the sterols. Some of the adrenal substances, the ovarian hormones, and the androgens are all derivatives of the sterols. The isolation of these substances from their natural sources and the subsequent production of many of them from cholesterol and other sterols have been significant achievements of the chemists. The urologist finds the androgens of especial interest. The androgen which is in most common use therapeutically is testosterone propionate. It has been of very great value in the treatment of testicular deficiency. In addition, numerous reports have appeared in the literature in regard to its efficacy in the treatment of prostatic hypertrophy. However, further clinical research is necessary to determine its value, if any, in this group of cases.

The efforts of biochemists have been successful in the production of hormones for the treatment of certain forms of cryptorchidism and sterility. There is every reason to believe that they can contribute further to the treatment of these diseases. Although some reports would indicate that testosterone and possibly some of the other androgens are injurious to the testes, there is incontrovertible evidence that under certain circumstances the androgens are a very definite aid and a stimulant in the production of sperms. Following hypophysectomy in the rat, the testes become inactive very quickly, both in regard to sperm production and to hormonal function. However, if adequate doses of androgens are administered, normal production of sperms can be maintained for a long period. The proper clinical application of this principle has not yet been developed.

While considering testicular disorders, the fact that the testes produce a non-androgenic hormone known as inhibin seems worthy of mention. This hormone was discovered and has been studied by many investigators, using the rat. It is now known, however, that inhibin is present in bovine testes and is effective in human beings. This hormone was called inhibin because it seemed probable that its most important function was that of depression of the pituitary gland, particularly in regard to its gonadotropic function. In experimental animals, it has been shown that the hyperactivity of the pituitary gland which follows castration can be controlled by the injection of inhibin. When inhibin is injected into normal animals, it causes a decrease in the size of the prostrate gland presumably because of decreased androgenic production by the testes as the result of the lessened pituitary activity caused by inhibin. Because of this experimental finding, inhibin has been used in the treatment of prostatic hypertrophy in humans. Strangely enough, no one has yet been able to demonstrate any changes in the human

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prostate gland following treatment with inhibin. There is no question, however, that treatment with inhibin has greatly relieved the urinary retention in many instances. As in other instances of endocrine replacement therapy, the treatment appears to be effecive only as long as medication is continued.

In that inhibin was so effective in the male, its influence on the female was also studied. It acts as a very powerful sexual depressant in experimental animals. Normal female rats which have been observed to have regular sexual cycles every three or four days, as indicated by vaginal smears, can be forced to go into diestrus (the resting stage of the sexual cycle) as long as the injections of potent inhibin preparations are continued. Clinical experiments have been undertaken but reports are not yet available.

Conclusions

In this very brief review in which only a few of the pertinent facts have been mentioned, an attempt has been made to demonstrate how medical science definitely has advanced as a result of the collaboration of two of its branches. A multitude of such examples could be found to prove that no scientific specialty can function to greatest efficiency except by some such method of cooperation.

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