Heberden Society

Annual General Meeting, 1969

The following papers were presented at the annual general meeting on November 21 and 22, 1969.


Between the years 1958 and 1967, a series of 354 gouty patients was examined and investigated by one or both of the authors at one of three London hospitals: Hamme-smith, Charing Cross, and West London. The information for the survey was abstracted from the case records and recorded on a proforma which permitted 100 items of data to be assembled for each patient. These were then fed into a computer which cross-referenced each of these items with all the others, enabling the incidence of one feature in relation to any other feature to be readily assessed. The 5,000 items of information so obtained have been scrutinized and form the basis of this survey.

The data confirm what is already well-established knowledge concerning gout, such as the distribution of age at onset, the incidence of individual joint involvement, the comparatively high incidence of obesity, regular intake of alcohol, hypertension, proteinuria, and renal impairment, and the preponderance of gouty patients in the higher social classes.

A number of interesting and hitherto unrecorded facts came to light concerning the relationship between hypertension, renal failure, age at onset, and duration of disease.

Discussion

Prof. E. G. L. Bywaters (Taplow) One of the most interesting non-results of this interesting study is the failure to correlate hypertension or uraemia with duration of disease. It seems to me that this apparent negative correlation might be due to your sampling techniques. You have a good representation of gouty patients in the first 10 years of the disease, but a very poor proportion of that gouty population who have lasted longer than 10 years from onset; those in that latter group who are missing from your sample may well have died already from hypertension or uraemia or may already be under affective treatment elsewhere, having been recognized because of their referral for hypertensive treatment. A comparison therefore of hypertension between these different age-from-onset groups is vitiated by their essential non-comparability.

Dr. Grahame I think the sample of patients was biased towards those with shorter duration of disease by reason of anno domini. I think the patients' ages may have been operating here just as much as the other factors referred to by Prof. Bywaters.

Dr. J. S. Lawrence (Manchester) How helpful did you find the computer analysis in a study of this magnitude? You must have had a vast amount of results to wade through after the computer had done its work. Did you feel it was all really worth it?

Dr. Grahame Whether it was all really worth it I would prefer to leave to the audience to decide, but certainly we should not have been able to analyse the data as we did without the help of the computer. There were problems in sorting out the data received from the computer; but the computer was certainly invaluable to our minds.

Prof. J. H. Kellgren (Manchester) How meaningful is disease duration in this study? I think that 'duration' refers to the interval since the onset of articular gout or manifest renal stones, but the metabolic disease had presumably been going on for quite a long time before that and might have been affecting the kidneys in a silent way. It is not as if the hyperuricaemia and the hyperuric acid excretion started on the day when the first attack of gout occurred. I wondered if you had taken that into account?

Dr. Grahame We had no way of detecting the onset of hyperuricaemia in these patients. We had to fall back on the onset of clinical gout, but work from the Tecumseh study shows that the liability to gout seems to be directly related to the level of the uric acid, so perhaps this was not all that unreasonable.

Factors affecting the Binding of Urate to Plasma Proteins. By R. Bluestone, I. Kippen, J. R. Klinenberg, and W. M. Whitehouse (The Department of Medicine, University of California School of Medicine)

The ability of human plasma proteins to bind uric acid has been demonstrated by several techniques. Although the physiological significance of these observations has
not been established, they may be pertinent to the mechanisms of both tissue deposition and glomerular clearance of urate. We have studied plasma urate binding by a method of equilibrium dialysis. In this method aliquots of freshly obtained plasma were dialysed for 16 hrs at 4°C. against large volumes of 0·01 M phosphate buffer containing 15 mg. uric acid per 100 ml. buffer. After equilibration, the amount of uric acid within the dialysis bag in excess of that in the buffer was considered to be bound. The quantity of urate bound is dependent on the free urate concentration, the temperature, pH, and molarity of the buffer, and the protein concentration of the plasma. Other factors which appear to affect urate binding have also been studied in detail. Ingestion of aspirin, probenecid, and phenylbutazone impaired urate binding. The mechanisms of this impairment was studied in vitro using human albumin and dye displacement techniques. Likewise, very low plasma albumin levels resulted in a complete loss of urate binding capacity. Lastly, three patients with severe tophaceous gout had grossly impaired urate binding.

Discussion

DR. H. L. F. CURREY (London) I was trying to estimate the significance of this binding in terms of the actual percentage of urate in the plasma which might be bound. Am I right in thinking that if, in what you describe as the optimal conditions in your system, 30 μg./ml. urate is bound, this would suggest that about 2 per cent. of the urate might be bound in vivo? If one thinks that non-bound urate is the factor in the plasma which determines crystallization in the tissues, this would seem a very marginal and small influence even under the best conditions. I can understand this competitive binding might be important in the opposite direction in terms of the influence on drugs, but I am surprised that you place so much significance on altering the concentration of unbound urate by as little as 2 per cent. [Correctly calculated = 20 per cent.]

DR. BLUESTONE An estimate of the amount that might be bound in the physiological state in vivo was made by Dr. J. R. Klenenberg long before I joined him. From the relationship between bound urate and the concentration of urate in vitro, it was estimated that about 15 to 20 per cent. of the uric acid of a serum urate of 8 mg. per cent. could be bound; but of course this is partly guesswork and you cannot necessarily extrapolate direct from the state in vitro to that in vivo. This is where we are in grave difficulties because no one has yet thought of an unequivocal method of demonstrating urate binding in vitro.

PROF. E. G. L. BYWATERS (Taplow) Has anyone examined the interstitial or oedema fluid? This has a very low content, under 0·1 per cent., of protein and should reflect this binding and non-binding.

DR. BLUESTONE No, that would be very helpful, but I am not aware that it has been done. One idea was that we might study the renal tubular fluid by the micropuncture technique in a rat with chemically-induced hyperuricaemia in order to study urate binding in that situation, and this is the basis of a scheme we are now considering.

DR. J. T. SCOTT (London) This is interesting and important work, but I agree with Dr. Currey that one must be careful about some of the inferences that have been drawn. For example, it is unlikely that alteration in binding plays a significant part in the acute gout which sometimes follows the start of treatment, since you have shown that allopurinol, which tends to produce acute gout even more than uricosuric drugs, has no effect on urate-binding.

DR. BLUESTONE We absolutely agree, and there is no direct correlation between our experiments in vitro and the clinical situation. Nevertheless we might be throwing light on some factors that apply in some circumstances.

DR. A. S. RUSSELL (Taplow) In one of your latter Tables, when you were talking about the analogy with DNSA binding, I am a little confused as to the relative potencies of the different drugs. As I remember, indomethacin is the most effective in displacing DNSA—

DR. BLUESTONE The second most effective—

DR. A. S. RUSSELL (Taplow) And yet it did not figure in the uric acid displacement?

DR. BLUESTONE Yes; this is because when we give indomethacin to patients or to normal subjects the plasma concentrations obtained are very low. You get nowhere near the 0·2/0·3 millimolar levels we have in our system in vitro. The fact that phenylbutazone was so high up on the DNSA displacement table indicates that we have probably mapped out a specific binding site for that drug.

DR. A. S. RUSSELL (Taplow) What did you think about the urate binding reported by Kelley in the alpha2 globulin region? Did you do any studies putting just albumin in your dialysis bags or something of this sort?

DR. BLUESTONE Yes. The experiment we did in vitro was one with purified albumin. Coming back to the alpha2 globulin work, the whole year apart from this work was spent trying to confirm those findings and resulted in miserable failure. We could not demonstrate any significant urate-binding protein which lay outside the albumin/pre-albumin range, at least in terms of electrophysical properties.

DR. A. ST. J. DIXON (Bath) Neither the speaker nor the discussers seem to have mentioned the problem of the rate of urate-unbinding. What matters physiologically is not the equilibrium state so much as what happens when you change it. Supposing in your experiment you remove the 15 mg. per cent. urate from the surroundings, how soon does the urate which is bound to protein un-couple and become free again? This is important in considering the clearance of urate through the glomerulus.

DR. BLUESTONE The answer is, instantly. One of the things I tried to emphasize earlier is that the bond between protein and urate is a remarkably weak one and has foiled investigators for many years. Unless you provide a surrounding medium of free excess urate, the bond simply uncouples.

Sjögren's Syndrome in an Ophthalmic Milieu. By J. M. Gumpel and P. Wright (Royal Postgraduate Medical School and Moorfields Eye Hospital)

Since Sjögren drew attention to the association of joint disease and kerato-conjunctivitis sicca (KCS), this syn-
Factors affecting the binding of urate to plasma proteins.

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