DIABETES AND GOUT

Recent observations have shed new light on the well-known relation between diabetes and gout. It will be remembered that in 1943 Shaw Dunn made the interesting discovery that alloxan, when injected into rabbits in sufficient amount, altered the blood sugar, and after 24 hours a permanent diabetic condition resulted. The observation has appeared until recently to be no more than a curious phenomenon of no physiological importance. Several workers have investigated the mechanism of the action of alloxan and have shown that substances containing sulphydryl (–SH) groups are concerned. When alloxan was injected it was found to cause a rapid decrease in the amount of glutathione in the blood,[1] and Lazarow[2] made the complementary observation that when glutathione or cysteine was injected beforehand alloxan failed to cause diabetes. Evidence has been obtained that the protective action of cysteine is due to the reduction of alloxan to its close relation dialuric acid.[3] The latest developments, indeed, hinge on dialuric acid, for it occupies a position midway between uric acid and alloxan. In 1909 Ascoli and Izar[4] showed that dog's liver contained an enzyme which converts uric acid to dialuric acid, so that probably uric acid can be converted to dialuric acid in man. There has been a difference of opinion whether this substance causes diabetes,[5] and the outcome appears to be that if there is too little glutathione in the blood dialuric acid can be oxidized to alloxan, and then diabetes occurs. Thus glutathione can protect the body against alloxan by converting it to dialuric acid, but lack of glutathione allows dialuric acid, formed from uric acid, to be turned into alloxan.

The experiment of producing diabetes in rabbits by injecting them with uric acid has actually been done by Griffiths.[6] He fed rabbits on a diet deficient in methionine and cysteine, and in the course of six weeks the glutathione was reduced to half. When one gramme of uric acid was injected into the peritoneal cavity the mean blood-sugar changes of four rabbits were very similar to those observed in four other rabbits after the injection of alloxan. There was the same initial hyperglycaemia giving place to hypoglycaemia, and the prolonged hyperglycaemia at the end of 24 hours. The injection of uric acid had no action on the blood sugar of rabbits receiving the same diet plus a supplement of methionine.

Evidence indicating a connexion between purine metabolism and diabetes has also come from another direction. Conn and his colleagues[7] at Ann Arbor have shown that in man diabetes can follow the injection of purified preparations of the adrenocorticotropic hormone of the anterior lobe of the pituitary body. There is hyperglycaemia and glycosuria, and the sugar-tolerance curves become like those of a diabetic. The excretion of uric acid in the urine is increased, and the amount of glutathione in the blood falls progressively. If an injection of glutathione is given intravenously there is a rapid fall of the blood sugar, and the urine temporarily becomes sugar-free. The authors express the view that the primary disturbance is in purine metabolism and that a substance like alloxan is produced, which in turn causes diabetes. Other observations on the effect of the adrenocorticotropic hormone have been made by Hellmann,[8] who has injected it into patients with gouty arthritis. He found it caused a rise of uric acid in the serum and an increased excretion in the urine: he also observed glycosuria. The injection of this hormone would, of course, stimulate the adrenal cortex to increase the output of its own hormones, and when the injections were discontinued the output of these hormones would cease. Three days after the injections were stopped Hellmann's patients had an acute attack of gouty arthritis, and this attack was arrested by giving adrenocorticotropin once more. We have yet to learn whether treatment of rheumatoid arthritis with compound E ("cortisone"[9]), which is a hormone of the adrenal cortex, or with adrenocorticotropin causes glycosuria.

These observations indicate a close relation between purine metabolism and blood-sugar control. The importance of this relation is emphasized by the results of metabolic studies on birds.[10-12] In the duck and the chicken the largest doses of alloxan produce no blood-sugar change. In the pigeon there is some rise of blood sugar, but the bird dies from a deposit of sodium urate over all the serous surfaces. The facts suggest that the duck is immune to alloxan because it converts it to uric acid and excretes it; the pigeon is less immune because it carries out this process less efficiently.

VIRIDANS STREPTOCOCCI IN BACTERIAL ENDOCARDITIS

The viridans streptococci—so called because on blood-containing media they produce green pigment—are the most frequent cause of subacute bacterial endocarditis, and it has been a common assumption, since Andrewes and Horder's early work, that they are derived from the mouth, where similar streptococci are found normally or associated with dental sepsis. Strong support for this

[1] Leech, R. S., and Bailey, C. C., *J. biol. Chem.*, 1945, **157**, 525.
[2] *Proc. Soc. exp. Biol., N.Y.*, 1946, **61**, 441.
[3] Lazarow, A., Patterson, J. W., and Levey, S., *Science*, 1948, **108**, 308.
[4] *Z. Physiol. Chem.*, 1909, **62**, 347.
[5] Brückmann, G., and Wertheimer, E., *J. biol. Chem.*, 1947, **168**, 241.
[6] Ibid., 1948, **172**, 853.
[7] *Science*, 1949, **109**, 279.
[8] Ibid., 1949, **109**, 280.
[9] Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F., *Proc. Mayo Clin.*, 1949, **24**, 181. See also leading article in *British Medical Journal*, 1949, **2**, 24.
[10] Mirsky, I. A., and Foley, G., *Proc. Soc. exp., Biol., N.Y.*, 1945, **59**, 35.
[11] Scott, C. C., Harris, P. N., and Chen, K. K., *Endocrinology*, 1945, **37**, 201.
[12] Goldner, M. G., and Gomori, G., *Proc. Soc. exp. Biol., N.Y.*, 1945, **58**, 31.

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view came from Okell and Elliott,[1] who were able to culture non-haemolytic streptococci from the blood of 30 out of 40 patients immediately after dental extractions and from 12 out of 110 patients with gross oral sepsis. Further work showed that any trauma, however trivial, to septic gums or the removal of tonsils was likely to produce a temporary bacteriaemia, and that if there were diseased heart valves subacute bacterial endocarditis was a possible sequel. Among those interested in the pathogenesis of infection it is now accepted that some organisms which normally have a saprophytic existence in one part of the body may initiate infection in another part. The coliform group causing urinary infection is a good example, and the term "potential pathogen" is often applied to these bacteria. However, lessons learnt from the classification of proven pathogens, like the pneumococci, haemolytic streptococci, and staphylococci, suggested that a subdivision of these potential pathogens might yield useful information on certain points: whether, for example, a particular group within the species was most likely to be associated with infection, as happened with the Lancefield group A streptococci, and whether the strains causing infection could be more closely identified with saprophytic strains, as has proved to be the case with certain types of pneumococcus causing bronchopneumonia.

Attempts to classify bacterial species like the coliform bacilli or the viridans streptococci according to their biochemical properties have not been very successful, and the tendency lately has been to use the methods of antigenic analysis or susceptibility to specific bacteriophage for the subdivision of these families. In America attempts have already been made to classify the viridans streptococci serologically, and in this issue Professor Selbie and his colleagues report their findings in an antigenic grouping of over 200 strains of this organism from cases of subacute bacterial endocarditis and of some 50 strains each from normal throats and from dental extractions. Classification has been based on precipitation reactions with streptococcal extracts (prepared by the Fuller formamide method) against antisera to eight different strains produced in the rabbit by repeated injections of live or killed suspensions of the streptococci. By analogy with the Lancefield grouping of the haemolytic streptococci this method of antigenic analysis is likely to give only a broad grouping, dependent presumably on a carbohydrate fraction in the viridans streptococci. The authors found that most of their strains gave precipitation reactions with several antisera, and on the basis of these "pattern" reactions they have recognized three broad groups with two subgroups. Most of the endocarditis strains (181 out of 209) were distributed fairly evenly among the five groups, and all but nine of the 103 strains from teeth and throats gave positive reactions the majority of which fell into group IIa. These results indicate broadly that viridans streptococci associated with subacute bacterial endocarditis belong to the same family as the strains found in the mouth, but they do not necessarily mean that a group I streptococcus isolated from the blood is identical with a group I strain present in the throat or causing dental sepsis in the same patient; for that, more precise antigenic analysis like Griffith typing will probably be needed. It was usual to find strains falling into several groups among the streptococci isolated from the throat or from apical abscesses in individual patients, whereas strains isolated from the blood of relapsed cases of endocarditis treated by penicillin most often belonged to the same group as the original strain. These findings have been interpreted as an indication that the relapse was due to a recrudescence of the original endocardial infection and not to reinfection from the mouth, but it is doubtful if with this broad serological classification such a claim is justified, although it gains some support from the close similarity in the biochemical reactions of strains isolated from the blood of relapsed cases. No mention is made of the non-haemolytic streptococcus called by Kilian Clarke[2] *Streptococcus mutans* because of its variable morphology, and associated by him with the aetiology of dental caries. This streptococcus is a single serological type and has occasionally been found as a cause of bacterial endocarditis, which is further evidence of the close association between the organisms in the mouth and the endocardial strains, as is also the occurrence of *Haemophilus para-influenzae*, another inhabitant of the mouth, as a cause of infective endocarditis.

Penicillin therapy has profoundly altered the prognosis in this previously fatal infection, particularly if the dosage is increased to 2 million units a day for six weeks as recommended by Christie.[3] But it must be remembered that "cured" patients are often left with grossly damaged valves which usually impair cardiac efficiency and leave the patient a prey to subsequent infection. It would be interesting to know the after-histories over a five- to ten-year period of patients with infective endocarditis cured by penicillin. Much more needs to be done to prevent this infection. Rheumatic fever is the main predisposing factor, and its steadily diminishing incidence should reduce the number of young people with endocarditis; but given a patient with diseased valves—congenital defect and syphilis are the other main contributors—every effort should be made to prevent the superimposition of an infective endocarditis. Oral sepsis is a continual danger to such a patient and should be radically treated, while the

[1] *Lancet*, 1935, **2**, 869.
[2] *Brit. J. exp. Path.*, 1924, **5**, 141.
[3] To be published shortly.

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extraction of teeth, tonsillectomy, or indeed any manipulative measure that may result in a temporary bacteriaemia should be carried out only under a penicillin or sulphonamide "umbrella." This is a matter which vitally concerns the dental surgeon, who should become well acquainted with the risk of oral sepsis or of any dental operation in a patient with defective heart valves.

PENICILLIN IN EARLY SYPHILIS

Though nearly six years have passed since Mahoney and his colleagues successfully treated four seamen suffering from early syphilis with penicillin, international opinion on the optimum treatment of early syphilis is still divided. In the United States, where the records of well over half a million patients who have been treated with penicillin alone are being carefully followed and statistically investigated, adjuvant arsenicals and bismuth are held to be not only unnecessary but undesirable. In Europe, where penicillin has been available only since the end of the war, and until recently has been strictly rationed, there is a widespread unwillingness to accept it as proved on alien evidence that even in its earliest stages a grave, chronic, constitutional disease can be permanently cured by a few days' treatment. In this country, though penicillin is now accepted as an ideal treatment of attack, there is a not unnatural reluctance to abandon its well-tried predecessors. Most venereologists, with a few notable exceptions, still prefer to compromise and to consolidate their treatment with a standard course of about ten weekly injections of neoarsphenamine and bismuth, which would by itself, incidentally, cure at least 70% of early infections.

Elsewhere in this issue J. W. Eames and D. H. Miller have tried to assess the results of this combined treatment in the face of a high default rate from surveillance due to the rapid release of their patients from the Services. With statistical and actuarial aid they claim to have demonstrated a cumulative post-treatment relapse rate of 15% at 18 months in addition to a treatment failure rate (sero-resistance) of 3.9% in secondary cases and 0.9% in seropositive primary cases. That these results are appreciably worse than those reported after similar treatment by McElligott, Jefferiss, and Willcox[1] in this country and after penicillin alone by Sternberg and Leifer[2] and others in the United States is doubtless due to a laudable desire to take no chances with patients whose follow-up is likely to be jeopardized by an early return to civil life. Many will be surprised, however, to read that all patients whose blood tests were positive four months after the end of treatment were summarily classified as failures and treated again. Apparently no attempt was made to gain some idea of the serological pattern—to find out whether the titre of the test was rising, falling, or stationary. It is now well recognized that the serum reactions in treated early syphilis often take many months to revert to negative and that so long as the titre continues to decline a slow disappearance of reagin, even lasting a year or longer, is in no way suggestive of failure of treatment. Indeed in some cases of true relapse the initial serological response is often surprisingly rapid.

There is still a tendency for the clinician to place too blind a faith in blood tests and also perhaps for the serologist to believe too implicitly in his own technical modifications and in the specificity of his antigens. Until standard methods and, what is even more important, standardized reagents are employed it will still be possible for a patient to be cured in one clinic and not in another. The new cardio-lipin-lecithin antigen is becoming increasingly popular in the United States, and is said to be stable and unaffected by changes of climate or temperature. When its optimum level of sensitivity has been ascertained and its manufacture standardized and simplified the problem of the exact significance of serum reactions may perhaps be nearer solution than it is to-day.

That the toxic effects of arsenic are rarely seen in military patients is doubtless due to their age, sex, and good physical condition. A far greater toll is usual in civil clinics, where women, the undernourished, and men in the higher age groups are treated, and most venereologists would be glad to dispense with these potentially toxic drugs. If consolidation treatment in early syphilis has any advantage, and this is generally denied in the United States, weekly injections of bismuth, or of procaine-penicillin with aluminium monostearate, or of both concurrently would seem to be safer and equally efficacious for this purpose. Be this as it may, a few weeks' consolidation treatment of any kind has the advantage of impressing the patient with the gravity of his disease and will underline the importance of adequate observation after treatment.

The accurate assessment of a new therapeutic agent in a disease so chronic and so protean in its manifestations, as well as in its reactions to treatment, is a difficult task. Prolonged and careful clinical observation and serological studies are important, but in addition that unpredictable element, the host factor of the individual patient, can never be neglected. It is easy to acclaim a dramatic cure or a failure of treatment, but more difficult to state dogmatically to what extent the treatment, or the lack of it, has been responsible for the result. It is only by careful observation of a large number of patients over a long period, and by careful comparison with the results obtained by treatment with the arsenicals, that we can even begin to come to a decision. Meanwhile the Syphilis Study Section of the National Institute of Health, of the United States Public Health Service, has been carrying out a carefully controlled experiment on a vast scale for more than three years. Up to the present these American workers are increasingly convinced with each succeeding year that penicillin alone with adequate surveillance is the best known treatment for early syphilis.

[1] *Brit. J. vener. Dis.*, 1948, **24**, 45.
[2] *J. Amer. med. Ass.*, 1946, **133**, 1.

VITAMIN B_{12}

In previous annotations[1] we have commented on the isolation from large amounts of liver of minute quantities of a red crystalline compound containing cobalt and having great anti-pernicious-anaemia activity. This substance has also been isolated from fluids in which certain micro-organisms, notably *Streptomyces griseus*, have been grown.[2] Dunlop

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