from all causes at the same ages. Of the whole number, out of 141 gouty men, 8, or 5.7 per cent., died of phthisis, while 651 free from gout, 12.3 per cent., died of that disease. We are therefore, I think, warranted in concluding either that the gouty habit tends to prevent the development of phthisis, or, conversely, that phthisical subjects are less liable to gout, or (and this is, I think, the most probable explanation of the fact), that the causes of the two diseases are antagonistic or in some degree mutually incompatible.

Lastly, we may some of us, perhaps, find comfort in the observation that the gouty habit is, in the case of a temperate man, at least, no hindrance to the prospect of attaining extreme old age.

In class C indeed the evidence looks strong against the gouty but this class is an ill-defined one, and probably the gouty members of it were also the less temperate.

In the statistics which I have been able to adduce perfect accuracy was not attainable, and, moreover, the numbers are insufficient for the complete elimination of chance. Nevertheless, after full allowance has been made on these grounds, sufficient evidence will remain to support the conclusions which I have drawn from them.

THE RELATIVE VALUE OF OPIUM, MORPHINE, AND CODEINE IN DIABETES MELLITUS.¹

By THOMAS R. FRASER, M.D., F.R.S., F.R.C.P.E.,
Professor of Materia Medica, and of Clinical Medicine in the University
of Edinburgh.

SINCE Pavy's recommendation of codeine as a remedy having advantages over opium and morphine in the treatment of diabetes mellitus, codeine has been much used, and has even to a large extent displaced opium and morphine in the treatment of this disease.

There are at the same time no clear pharmacological data in support of this preference. Indeed, the data are not even such as to suggest it; for notwithstanding assertions of a like superiority in the relief of various symptoms of other diseases, the facts, so far as we know them, seem to show that, pharmacologically, codeine is in its most important actions merely a weak morphine. This conclusion is supported by the circumstance that in its chemical structure it differs from morphine only in containing methyl—that in fact it is morphine diluted by the addition to it of the relatively inactive substance, methyl.² In regard to its therapeutic effects in those conditions, other than diabetes, in which it is now commonly used, I have also failed to obtain any evidence that it acts otherwise than a weak morphine; for example, in the relief of cough, the production of sleep, or the removal of pain whether in the abdomen or elsewhere.

These considerations, as well as the special suitability of the disease for such comparison, and the probable value to therapeutics of any decisive results that might be obtained, induced me, several years ago, to make some observations for the purpose of comparing the effects of codeine with those of opium and morphine upon the more important of the phenomena of diabetes mellitus.

Observations of a detailed character have been made on four patients, with results of a concordant kind; but I propose to describe, by way of illustration, the results that are of most importance in one of these patients only, on whom, incidentally, some observations were also made with atropine.

This patient, M. B., aged 26, came under my care in the Royal Infirmary of Edinburgh, on October 5th, 1887, suffering from thirst and frequent micturition. None of her immediate relations had suffered in a like manner. She was a nursery maid, and had lived in comfortable houses, and been supplied with abundant and good food. The first symptom of her illness was thirst, which showed itself about seventeen months prior to her admission, and had led to the discovery that she was suffering from diabetes mellitus. She was treated for this illness, but without much

effect, and she soon became very weak, and lost flesh, so that in twelve months her weight was only eight stone, whereas immediately before this illness it had been ten stone. Notwithstanding careful and strict dieting, the emaciation advanced, and she weighed only seven stone four pounds when she entered the Royal Infirmary. She was then dyspeptic, and moderately anæmic, but she did not suffer from constipation, nor was the liver enlarged. There was no disease of the respiratory or circulatory systems. The eyes were hypermetropic, the skin dry, and the temperature slightly subnormal.

The patient was in the hospital from October 6th, 1887, to July 10th, 1888, and the observations to which I shall now draw attention occupied the whole of this time. The general plan followed was to allow the patient ordinary diet for one period; then to adopt a carefully restricted diet; then this diet with codeine, in doses varying from half a grain to five grains thrice daily, and for a short time with one-sixtieth and one-thirtieth of a grain of sulphate of atropine thrice daily; then restricted diet alone; then restricted diet, first with opium alone, in doses of half a grain to one grain and a half, and afterwards with opium and sulphate of atropine; and, finally, restricted diet with hydrochlorate of morphine. The administration of morphine was not preceded by an interval in which restricted diet alone, and without any medicinal treatment, was adopted; as in the period immediately preceding that of the administration of morphine, in which no medicine was given, the patient had become dull, languid, and sleepless, she had complained of sickness and loss of appetite, and in a few days had been unable to leave her bed.

During the whole of the nine months in which the patient was under observation and treatment, with the exception of only a few days occurring now and then, the quantity of fluid drunk, the quantity of urine voided, and the specific gravity of the urine and the amount of urea and of sugar contained in it, were each day recorded. The weight of the patient was ascertained from time to time, and a careful record was made of her diet, and also of her general state of health. In the labour that was necessary I had the hearty and able co-operation of Messrs. C. G. Gibson and W. H. Bunting, clinical clerks, and Dr. Mackness, resident physician. The daily observations are too numerous to be communicated to the Section. I shall, therefore only state the averages for each period and condition of treatment. (The table of averages communicated to the Section is here omitted, as the general results shown by the table are included in the immediately following statements).

To state the results in another way:

1. The case was one in which mere restriction of diet did not have so marked an effect as occurs in many cases. The prospects of successful treatment were not, therefore, very hopeful.
2. Codeine had a very decided effect in reducing the quantity of urine, sugar, and urea. When contrasted with the reduction produced by restricted dietary alone, the addition of nine grains of codeine in the day lessened by about one-third, and of fifteen grains of codeine in the day by about one-half, the quantity of fluids drunk, and the quantity of urine, sugar, and urea, and it slightly reduced the specific gravity of the urine.
3. The addition to fifteen grains of codeine of the one-twentieth, and afterwards of the one-tenth, of a grain of sulphate of atropine, caused a still further, though not a large, reduction.
4. After the administration of codeine had been stopped, an interval of six days on restricted diet, without any medicinal treatment, was not sufficient for a deterioration to occur to the conditions present before codeine had been given.
5. The subsequent administration of half a grain of opium thrice daily produced a considerable reduction. With one grain of opium thrice daily the reduction was to less than one-half, when contrasted with the amounts during a restricted diet alone, and before any medicinal treatment had been adopted. One grain and a half thrice daily produced a further reduction; and when to it was added one-twentieth of a grain daily of sulphate of atropine, a still further reduction occurred.
6. Restricted diet, with one-third of a grain of hydrochlorate of morphine thrice daily, or one grain daily, also produced a marked reduction; and the conditions relative to the points under investigation were even more satisfactory than when fifteen grains daily of codeine were being administered. While this small quantity of morphine was being taken, the fluids drunk by the patient were only one-third, the urine and sugar less than one-half, and the urea about one-half of the amounts during the period of restricted diet alone, before medicinal treatment had been commenced.

¹ Read in the Section of Pharmacology and Therapeutics at the Annual Meeting of the British Medical Association, held at Glasgow, August, 1888.

² Expressing the relation in more exact terms, codeine is to be regarded as a methyl-morphinate, in which the hydrogen of the hydroxyl in morphine is replaced by an atom of methyl.

As to the general state of the patient during each of these conditions of treatment, restriction to an antidiabetic dietary produced improvement in thirst and mental activity. So long as the quantity of codeine was limited to six grains daily, this improvement was maintained; but when nine grains, and even more, when fifteen grains were being taken daily, the appetite failed, she became listless and apathetic, vertigo was occasionally experienced, and the patient remained for a considerable part of each day asleep in bed. The addition of atropine to the codeine did not produce any improvement, but rather added to the discomfort by impairing vision; and even when only one-sixtieth of a grain was being taken thrice daily, the pupils became slightly dilated. When codeine and atropine were stopped, and a restricted dietary alone adopted, the health was not improved. The symptoms referred to became, indeed, worse, and prevented a prolongation of the period of restricted diet without medicine to the extent that seemed desirable before a new plan of treatment was adopted. When opium was now given a marked improvement occurred, but the larger doses caused some drowsiness during the day. With one grain daily of hydrochlorate of morphine the condition of the patient became more satisfactory. The drowsiness soon disappeared, the appetite improved, and she became sufficiently active to engage in ward work. Constipation of the bowels was not produced by any of the medicinal agents employed.

A consideration of these averages seems to show that, under a daily administration of one grain of hydrochlorate of morphine, the quantity of fluids drunk, and of urine, urea, and sugar voided, was rather less than when three grains of opium, and decidedly less than when fifteen grains of codeine were being taken. In three other cases in which I have instituted a comparison between these substances in diabetes mellitus, morphine also showed a marked, though not so great, superiority over codeine. After this note had been prepared, I have seen a recent paper by Dr. Bruce, of London, in which similar results were obtained in two very carefully observed cases. So far as I know, also, the favour with which codeine is regarded in this disease has not been supported by any observations calculated to show its value relatively to opium or morphine so clearly as in the cases to which I have referred.

The evidence, therefore, seems to indicate that codeine is a less powerful remedy in diabetes than either opium or morphine, and to confirm the view that in its therapeutic value it ranks as a weak or diluted morphine.

The conclusion receives an importance (no doubt a subsidiary one) from the circumstance that codeine is about three times as expensive a substance as morphine. The great demand for it has led to its being manufactured from morphine so largely, that probably one-fourth of the codeine in the market is an artificial substance. When we consider the large doses that are required in diabetes mellitus, and the generally protracted duration of this disease, we are, I think, justified in asking for more clear evidence of its superiority over morphine than has as yet been produced.

NOTES ON THE VALUE OF SOME NEW DRUGS.¹

By JAMES F. GOODHART, M.D., F.R.C.P.,

Physician to, and Lecturer on Pathology at, Guy's Hospital.

THE drugs that I purpose to say a word or two about to-night are paraldehyde, urethan, antipyrin, and pilocarpin; and perhaps, in dealing with antipyrin, I may say a word or two upon my experience with other antipyretic drugs. In these go-ahead days I may be taken to task for calling these new drugs, and I had some doubt how to name my paper; but if I cannot call them new I most certainly cannot call them old, and no equivalent to the "subacute" of medicine came ready to my hand. Let me also say that I do not propose to treat of these drugs from any other than my own standpoint; it is simply my object to say in what I have found them useful, and ask you for such experience as you may have of the same agents in similar or other fields. Thus I shall hardly, if at all, discuss the actions of the remedies, nor is it my object to give even a summary of the diseases in which they have been used or recommended.

Now, first of all, *paraldehyde*. It has been *out*, so to speak, for several years, but I do not think it is at all in common use. I am rather fond of it, and have given it frequently now certainly for three or four years, and that means in a large number of cases. Originally recommended, I believe, as a hypnotic, one that combined the advantages, to the exclusion of the disadvantages, of chloral and bromide of potassium, I tried it first of all in cases of insomnia. I do not consider it at all a reliable drug for that state of things; but it is a drug of unquestionable value in the restlessness and cardiac asthma so often seen in aortic disease, and in the labouring dilated heart of chronic Bright's disease. I well remember the first case in which I gave it some years ago, a man who had long been subject to gout, and who had a granular kidney and a large dilated heart. His distress was extreme, and I had exhausted all the old-fashioned remedies (than which few are better), and many new, including caffeine, and with a marked condition of Cheyne-Stokes's breathing, he had all the aspect of speedy dissolution. As a last resource I gave him half-drachm doses of paraldehyde, with marked relief to the end of the case, which occurred about a fortnight later. I have also found it occasionally useful in the headache of renal disease. In two cases, where this was especially troublesome in the early morning, it was taken on and off for many months, with great relief. As a general rule, nitro-glycerine is the more reliable remedy for the headache of Bright's disease, but the symptom is often a troublesome one, and paraldehyde may well be kept in memory for occasional cases. But there is another class of cases in which I think it of even more use. It was recommended some few years ago, I think by Dr. Strachan, for certain cases of mania, and some three years or so ago I had to deal with a very troublesome case of alcoholic delirium. The patient was a very free drinker, had had delirium tremens twice before, and was now in a low, muttering, sleepless condition, which nothing seemed to quiet or control. He had been in a semi-comatose state already for five days. He was quite unheeding of anyone about him, talked in an unintelligible mutter, and his muscles were tremulous, flabby, and wasted. As his wife was his equal, if not his better half, in drinking capacity, he was sent into Guy's Hospital, and for eighteen days he remained in much the same state. During that time his treatment consisted of free aperients, iodide and bromide of potassium, opium, and latterly of subcutaneous injections, first of $\frac{1}{10}$ grain, and then of $\frac{1}{20}$ grain of hyoscine; none of them seemed to do him any good. I then tried half a drachm of paraldehyde three times a day, and within a day or two he was much clearer in his mental condition, and before a week was out he was practically well. He remained somewhat feeble-minded for some little time, but he quite recovered eventually. Since then I have given it in similar cases several times. Whether it acts as a stimulant or a sedative I do not know, but it certainly sometimes quiets the delirium and clears the mental faculties. My friend Mr. Wornum lately ordered it in another such case, but it was only given in ten-minim doses. The general condition improved decidedly, but the mental condition still remains cloudy. However, the patient has come out of a semi-comatose state, and is now sitting up, although she still suffers from delusions.

Another case of what I think may be called a similar ailment was treated in a similar manner. A young fellow, aged 27, had typhoid fever badly; he became excessively emaciated, and not long after the fever left him he went off his head; he was very delirious and troublesome. Free stimulation failed to restore him, and he was, therefore, ordered half-drachm doses of paraldehyde. This was on the 8th of the month. The stuff was so nasty, he said, that he would take no more, and when I again saw him, on the 11th, it had not been persevered with. He then began it regularly, and within four or five days he was much clearer and less delirious, and at the end of a week he was practically well.

I suppose that the state of malnutrition after a prolonged attack of typhoid fever is not very unlike that produced by alcoholic poisoning, and, if so, might be expected to be benefited by the same remedy. The main objection to paraldehyde is its strong taste. I have usually given it with almond mixture, but it is, after all, not so very nauseous combined with some tincture of orange and syrup and water. The patient taking paraldehyde emits a very peculiar and characteristic odour, which is very tenacious, and I have known it to linger about the person two or three days after the drug has been discontinued.

Of *urethan* I have not much to say, but that little is in its favour. I have used it in a large number of cases as a hypnotic, and although it often fails, I think it is one of the best remedies

¹ Read before the North London District meeting of the Metropolitan Counties Branch at Tottenham.