

terms of actual oxybutyric acid which has an optical activity of  $24.1^\circ$  as against that of dextrose  $52.5$ , by multiplying the above difference by  $2.2$ .<sup>2</sup>

In connexion with the very large quantity of oxybutyric acid that has been stated by some authorities to have been found by the above-described method of estimation, Magnus-Levy<sup>3</sup> in an elaborate dissertation on oxybutyric acid and its relation to diabetic coma, has raised the question of the validity of the process. He brings forward work conducted upon other lines and states that the quantity of oxybutyric acid that can be extracted by ether from the acidified urine comes out much less than that deducible from the difference between optical activity and cupric oxide reducing power, but agrees fairly with the amount given by calculation founded on determining the saturating capacity of the bases and noting the deficiency in the mineral acids present to effect saturation, the deficiency being reckoned as due to oxybutyric acid. Many elements of consideration, with risk of error, are here involved and the results must be looked upon as blended with uncertainty. He points out that the levo-rotatory effect of the urine is increased by an excess of the lead acetate used in the preparation for examination. This is easily shown by observation to occur, even to a considerable extent, when much lead acetate is present and unless guarded against may give rise to considerable error. Possibly some of the earlier results recorded may have been vitiated in this way and too high figures given, but the fallacy may be escaped from with proper procedure as regards the amount of lead acetate used, and frequently the urine is sufficiently devoid of colour for filtration alone to suffice, in which case there can be nothing to interfere with correctness of result.

Should it be thought desirable the dextrose may be fermented off so as to leave the oxybutyric acid with its levo-rotatory power freed from any neutralising influence when a simple polarimetric reading suffices to give the information required. The process, however, is lengthy and tedious and, I cannot help thinking, involves the risk of a certain amount of loss of the oxybutyric acid present. I am of opinion that with recourse to the cupric oxide reduction and optical activity method we need not go further and that information is supplied by it upon which reliance may be placed.

We come now to the question of harm inflicted by this chain of principles. None of them, as shown by experiment, is capable *per se* of exerting any pronounced or immediate toxic effect and to none of them can diabetic coma be considered directly attributable. Acetone being volatile has a channel of escape by the lungs in addition to that afforded by the kidney. As is well known in the bad form of diabetes it is strongly perceptible in the breath.

(To be continued.)

## THE SUBCUTANEOUS INJECTION OF CINNAMATE OF SODIUM: A NEW DEPARTURE IN THERAPEUTICS.

By LOVELL DRAGE, M.D. OXON.

*With a Note on the Preparation of Cinnamate of Sodium Solutions suitable for Hypodermic Injections*

By GILBERT T. MORGAN, D.Sc. LOND., F.I.C.

AFTER many years' wandering in search of an explanation of the intravascular clotting which is observed in the human body in connexion with a variety of conditions I have come to the conclusion that a partial explanation only can be found on strictly chemical and physical grounds. There has always appeared at the moment when a complete "explanation" has seemed possible a factor of unknown quantity. The same difficulty appears in all phenomena when a vital process is involved. We are, indeed, very far off an accurate conception of the meaning of the term *life* and one is forced to the conclusion that when a process is connected intimately with living cells there is a limit to human comprehension.

Speculation leading to a working hypothesis seems at the present moment the only means within our reach of arriving at solutions of many of the phenomena, if not all, which are connected with disease. Having arrived at a working hypothesis as to the causes of the intravascular clotting which occurs during the lying-in period of women I have been led into a speculation as to what is the constituent of the blood which is the cause of the *impasse* at which I had arrived. What is the constituent which shows pre-eminently the phenomena associated with living cells? Surely, it is the white blood cell.

Accepting as I do the conclusions to which Dr. J. G. Adami arrived in his article on Inflammation in Dr. Clifford Allbutt's "System of Medicine," it is no matter of surprise that I have been assiduously looking out for weary years for a gleam of light which would help me to understand the reason why certain drugs have an influence upon such diseases as cancer and tuberculosis. A recent article in the *Journal of Pathology* on the leucocytic changes following injections of cinnamate of sodium has given me a clue. Inflammation, in the words of Dr. Adami, is the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part—or, briefly, as the local attempt at repair of actual or referred injury.

The injection into veins of cinnamate of sodium has now been shown by Dr. H. Batty Shaw—as it had been previously by Richter and Spiro—to produce a general leucocytosis, not by depriving the blood of a certain amount of liquid, but by stimulating the simpler lymphocytes to transformation into polymorphonuclear cells and intermediate forms. The oil of cinnamon was one of the drugs the action of which I was previously not in a position to understand, and I naturally inclined to a trial of the cinnamate for the same conditions of disease as those for which I had previously exhibited the oil. A drug capable of producing leucocytosis, such as the cinnamate of sodium, appeared to me to be the very one which would be likely to be of avail in the repair of tissue damaged by inflammatory, tuberculous or cancerous processes, because it is the leucocyte of one kind or another which is at once the agent of destruction and repair.

It is the purpose of this paper to place before my professional brethren (having briefly indicated the foundation of my belief in the efficacy of my method of treatment) the result of my observations of the action of the cinnamate of sodium in various conditions of disease. For purposes of administration I use a 10 per cent. solution of cinnamate of sodium in glycerine. This was prepared for me by Dr. Morgan of the Royal College of Science, South Kensington, who has very kindly promised to write a note dealing with the chemistry of the subject.

CASE 1.—The first case which I selected for trial was that of a man, over 60 years of age, who was much emaciated and who was apparently dying from tuberculosis of the lungs. His weight was only seven stones and 10 pounds at the time of the commencement of treatment; he had lost two pounds at the end of the next fortnight. After this he ceased to lose weight. The expectoration was excessive in amount, but was reduced after one injection of 15 minims of the solution into the skin close to the edge of the scapula, and is now, a month later, very small in amount.

CASE 2.—The next case treated was that of a man, over 60 years of age, who was going downhill very rapidly. He is, I believe, suffering from cancer of the pancreas; at all events he has had the symptoms usually noted when this organ is so affected. At the time of the first injection into the abdominal walls vomiting was incessant and he suffered great pain. He was very much emaciated. He has had two injections of 30 minims each twice a week. Vomiting has been completely controlled, the pain is very much alleviated, and the delirium, which was beginning to be troublesome, is now, after three weeks' treatment, absent.

CASE 3.—The next case was that of a man about 30 years of age, suffering from chronic inflammatory mischief connected with the middle ear. This man came under my care some months ago with a history of inflammatory trouble connected with both ears, following upon influenza. He had been treated by throat and ear specialists. The tympanum on one side was perforated and he used this ear alone with the aid of a trumpet. He was completely deaf on the other side and suffered acute pain; having reduced the pain with leeches I persuaded him to consult Mr. Cumberbatch who gave a very gloomy report of the condition of the ear and suggested continuous blistering and the use of a spray for the nose. The patient did not improve and I persuaded him

<sup>2</sup> Magnus-Levy: *Archiv für experimentelle Pathologie und Pharmacologie*, Band xlv., 1901.

<sup>3</sup> *Ibid.*, Band xlii., 1899.

to allow me to inject 30 minims of the cinnamate solution behind the mastoid. In a fortnight's time he returned for a second injection in high spirits; the improvement in hearing was very marked and I now look forward to a complete cure.

I have now under treatment one early case of laryngitis, almost certainly tuberculous, in which the evening temperature was at once lowered after an injection of 30 minims and there was a diminution in the amount of expectoration.

I am quite aware that these preliminary and unfinished cases do not furnish absolute evidence as to ultimate success, but the results have been so extremely striking to me that I have felt it my duty to give my professional brethren the opportunity of extending observations upon the value of the drug. There are many points connected with the use of the drug which require time and the efforts of a large number of observers. I have not injected more than 30 minims of the 10 per cent. solution, but it is probable that a much larger dose can be used safely. I have not at present done so because the dose with which I have worked gives good results and causes no unpleasant symptoms to the patient. It is probable that there are many other chemical substances which may be used to produce similar effects. I feel some degree of assurance that the lines upon which such diseases as cancer and tuberculosis can be treated successfully are those based upon the principle of administering drugs which by their action on the white blood cells will assist repair in the cells damaged. At any rate I am confident that I am calling the attention of the medical profession to a valuable therapeutical method.

NOTE BY DR. GILBERT T. MORGAN.

The therapeutic application of sodium cinnamate described in the preceding communication was rendered practicable by the discovery that this salt dissolves in glycerine to form a clear solution which can be easily manipulated in the hypodermic syringe. This observation was the outcome of my own experiments on the solubility of the substance in various media, an investigation which was undertaken at Dr. Lovell Drage's suggestion.

This preparation is more reliable than the emulsions already employed in physiological research, inasmuch as these mixtures alter in composition by subsidence in a comparatively short space of time, whereas the glycerine solution remains unchanged for an indefinite period. The glycerine solution is prepared by heating dry powdered sodium cinnamate with the pure solvent at a temperature of 180° C. (about 360° F.), and in this way from 10 to 11 per cent. solutions are readily obtained. It is important that the salt should be finely divided in order that the dissolution may proceed as quickly as possible because prolonged digestion of the solvent at the temperature indicated leads to the formation of acrolein (acetaldehyde), a substance having very irritating properties. More concentrated glycerine solutions may be produced but these exist at the ordinary temperature in a state of supersaturation and the salt gradually crystallises out, the separation being accelerated by agitation. The high temperature required for the preparation has the useful effect of ensuring the sterilisation of the solution.

Further experiments showed that sodium cinnamate is almost insoluble in chloroform, acetone, ether, absolute alcohol, and other low boiling-point organic solvents. Boiling water dissolves a large amount of the salt (about 25 per cent.) but the greater portion of the substance crystallises out on cooling; a sediment is slowly formed in 10 or 12 per cent. solutions, the supernatant liquid being distinctly alkaline to litmus paper.

Ethyl acetate, ethyl benzoate, and ethyl cinnamate dissolve appreciable quantities of the salt, but the solutions are too dilute for practical purposes. Hot oleic acid takes up a large amount of the cinnamate, but the greater part of the salt separates out again on cooling to form with the solvent a viscous emulsion.

It is, indeed, a fortunate circumstance that glycerine is the most suitable solvent for the cinnamate, because this liquid has other properties which combine to make it a particularly useful medium for the subcutaneous introduction of the drug: firstly, it is very inert; and, secondly, it is miscible with water or aqueous solutions. A gradual addition of water to the glycerine solution would take place in the tissues into which the liquid is injected, bringing the salt into intimate contact with the parts affected.

The further study of other preparations of cinnamic acid and its derivatives is in progress.

## THE HETOL TREATMENT OF TUBERCULOSIS.

By DR. O. AMREIN.

IN 1888 Professor Landerer of Stuttgart proposed a new treatment of tuberculosis and 10 years afterwards he published in a large volume<sup>1</sup> his technical and physiological observations and the results which he obtained. Landerer holds the opinion that the tuberculous affections have little tendency to heal owing to the want of blood-vessels, which is very unfavourable to the process of cicatrization. Therefore he tries to provoke an artificial "hyperæmia" in the neighbourhood of the tubercle nodules by injecting "cinnamylic acid"<sup>2</sup> into the circulatory system, and he observes an inflammation and accumulation of leucocytes round the tuberculous foci (state of leucocytosis). The next stage is emigration of multinuclear leucocytes into the alveolar septa and organisation of blood-vessels (state of organisation). In the next place new vessels and fibrous tissue grow through the tubercle nodules (state of vascularisation); and, finally, this new fibrous tissue becomes solid and the result is a cicatrice (state of cicatrization and retraction). He thinks that this healing process is similar to the natural one, only quicker and more solid. Instead of the cinnamylic acid Landerer afterwards used the cinnamylic soda salt and called it "hetol." Further publications (Krämer) show that the principal action of the hetol treatment is the leucocytosis (therefore everything causing a leucocytosis would be a help in combating tuberculous diseases). This method of Landerer has been tried by a great many physicians and notwithstanding great opposition at the time of its introduction it has become a very well-known one in Germany and Switzerland. But up to the present time much discussion, favourable and unfavourable, has occurred. As against the good results published by Landerer himself and other authors (Heusser, Krämer, &c.) is to be set the fact that other physicians did not find the expected effect. I mention here especially the publication by Dr. H. Staub (at the sanatorium Wald-Zürich) in No. 12, 1901, of the *Correspondenzblatt für Schweizerärzte* and the discussion between him and Dr. Heusser of Davos in the same medical paper.

As the observed results of many cases can alone enable medical men to decide as to the efficacy of the treatment I here bring forward my results obtained by hetol treatment in the period 1899-1901. I learned the method (intravenous injections) at the Sanatorium Wald in 1899 and I have used it in the manner described by Dr. Staub. In the first place, I may say that I have never observed any harmful influence either on the local state of the lungs or on the general state of health of the patient. There was never any inflammation at the place of injection. In one case, however (Case 13), every injection caused pruritus cutaneus on the chest after from three to four hours, lasting about half an hour, accompanied by fever. I always began with one milligramme (0.001 gramme). I injected the hetol every third day and increased the dose after two injections of a similar dose by one milligramme until 10 milligrammes had been reached, then by two and a half milligrammes until from 20 to 25 milligrammes (maximal doses) had been reached, using a solution of 1 per cent. up to 10 milligrammes and a solution of 5 per cent. from 10 milligrammes to from 20 to 25 milligrammes. A stasis of blood in the veins of the arm was caused by an elastic ligature, and after disinfection by spiritus saponatus and sublimate the injection was made into the vena mediana cubiti. The temperature was taken at 7 A.M., 9 A.M., and at 12 noon, and at 2.30 P.M., 4 P.M., 6 P.M., and 9 P.M. in the mouth (10 minutes), and the above-mentioned dose was increased only after the temperature did not exceed 37.3° C. During menstruation the injections were not stopped on female patients.

The accompanying table, constructed after the example of Dr. Staub, gives all the observed effects of the treatment and also all details—the state of the disease and its complications, the number of days of general treatment, the number and dose of the special injections, the temperatures

<sup>1</sup> Die Behandlung der Tuberculose mit Zimmtsäure.

<sup>2</sup> A constituent part of "Peruvian balsam" which was recommended for the treatment of tuberculosis a long time ago.