with were (1) an infant in 1873, the child of a chemist, who had semiconfluent small-pox, and whose wife (then seven months' pregnant) was in constant attendance upon him. She had been vaccinated well in infancy but was revaccinated in two places, with the result of very large well developed vesicles. In this case vaccination of the infant gave no result. (2) A woman contracted small-pox during pregnancy, and vaccination of the infant gave no result. For efficient vaccination four good vesicles were required. If all were placed on one arm, the vesicles should be placed at a sufficient distance to allow of an areola round each vesicle without the areolæ impinging one on another. The lymph used should be taken directly from arm to arm, or, if desired, gratuitous calf-lymph vaccination should be allowed. If there were an epidemic of small-pox in a district, every adult over 12 years of age should be revaccinated.

Dr. E. HAUGHTON (Upper Norwood) objected to Mr. May's statement that small-pox was now "the greatest scourge of the human race," as it was only the thirty-fifth on the list of causes of death. The death-rate—40 per cent.—put down for the unvaccinated was also incredible, when it was remembered that the statistics of Jenner (*Rees's Cyclopædia*) showed that about 18 per cent. was the small-pox average death-rate when everyone was unvaccinated. It was also unsatisfactory—in a paper professing to tell what was efficient vaccination—that no definition was given of what was vaccination, and from what source lymph should be obtained. Mr. May seemed to be of the same opinion as Dr. Warlomont, who held that small-pox was modified variola, and both appeared to claim credit for the results of other kinds of lymph of totally different origin and nature as though speaking of the same thing. A Royal Commission was sitting on this question, but in any case professional opinion had largely departed from that of Jenner, and, in Dr. Haughton's opinion, did so more widely every day.

Mr. C. H. WATTS PARKINSON ventured to suggest an improvement in the form of certificate issued by the addition of the words to the form thus: "I certify that —, the child of —, of —, has been successfully vaccinated by me in — places."

REMARKS ON THE TOXICITY OF THE URINE CONSIDERED AS A GUIDE TO THE DIAGNOSIS AND TREATMENT OF DISEASES.

*Read in the Section of Medicine at the Annual Meeting of the
British Medical Association held in Bournemouth, July, 1891.*

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Naples; Senator of the Kingdom of Italy.

Up to the present time the chemical analysis of the urine in different diseases has been considered an important aid to diagnosis; and, indeed, the search in urine for albumen, glucose, allantoin, uroerythrin, biliary pigments, etc., undoubtedly affords in many cases valuable help to the clinician, enabling him to complete or clear up an obscure diagnosis, to modify the prognosis, and to lay down indications for treatment, which, without the knowledge derived from such analysis, would have been impossible to obtain. The discovery of leucomaines and ptomaines has notably increased the clinical importance of precise chemical notions as to the composition of urine in different diseases, and especially in acute disorders. Unfortunately for clinical medicine, however, these analytical studies regarding the presence of the most diverse toxic elements which may be found in the urine of man, both in health and disease, are as yet too imperfect—being for the greater part hardly sketched out as yet—for chemical investigation of these principles (leucomaines and ptomaines) to be used with satisfactory results as a guide to diagnosis and treatment. The reasons of this are very simple: First, the large number

and great mutability of these toxic principles in relation to the course of the disease, and even to different phases of health; secondly, the extreme imperfection of our knowledge, and also in many cases the impossibility of isolating these various principles as well as the slowness and the complicated nature of the methods of research necessary to arrive at results which are not always strictly correct; thirdly, our complete ignorance of the relations existing between the various toxic principles which can be isolated from the urine and the clinical form of intoxication to which each one of them gives rise.

This being the state of affairs, it seemed to me clear, from the clinical point of view, that while on the one hand the discovery of ptomaines opens to the practical physician a vast horizon for the perfecting of diagnosis and treatment, on the other the direct search for these principles being so difficult—indeed, almost impossible—in the short time which the clinician has at his disposal to obtain the information which he requires—the time being in some cases limited to a few hours, inasmuch as the clinical forms of acute disease are the more changeable the more serious the illness is—it was necessary to find some other way in which real profit could be drawn from this brilliant page of modern pathology. It occurred to me to substitute biological for chemical analysis, as what the clinician wants to know is whether the particular toxic substances manufactured in the organism are capable of producing the clinical symptoms which he sees, so that he may be able to say with certainty that this or the other serious phenomenon is the effect of an intoxication rather than of a local morbid process with corresponding anatomical changes.

It concerns the clinician but little to know whether it be muscarin, neurin, neuridin, gadinin, cholin, saprin, etc., which in the particular case before him is producing coma or convulsions or other clinical phenomena. Assuredly he would be glad to have precise notions on that point also; but in default of that, what it is essential for him to know is that in the patient A. or in the patient B., during the evolution of the biochemical morbid process, toxic principles have been formed which are really the exciting cause of the functional disorders which he has before his eyes.

It is evident, therefore, that to-day, in order to complete the diagnosis of an acute illness the good clinician must not rest content only with the knowledge which analytical chemistry can give him, but he should supplement the chemical analysis of the urine with a biological examination of its properties, that is to say, by injecting, according to the method of Bouchard and others, the urine of the patient into animals (rabbits, dogs, etc.), with the view of determining not only the urotoxic coefficient in general, but more particularly the clinical signs of that toxicity, and comparing them with the clinical picture presented by the patient, and thus following *pari passu* those two factors which are capable of throwing a vivid light on the diagnosis, prognosis, and treatment.

The results of these analyses are naturally much more prompt and decisive than any chemical analysis conducted even by the most able chemist, for the simple reason that the cellular elements of animal organs react towards the circulating chemical principles with infinitely more sensitiveness than the most delicate reagent *in vitro*. And these minute chemico-vital reactions, imperceptible from the chemical point of view even to the most skilled observer, may, on the other hand, be read very distinctly on the dial of the functions where the long gnomon multiplies them, and allows us to observe them in the same way as the microscope enables us to detect in tissues apparently healthy degenerative changes which no clinical eye could ever have discovered.

Four months ago a series of researches on these lines were made under my direction on various acute diseases, which I propose to publish with all the clinical and experimental details. In this preliminary communication I wish to call the attention of clinicians to this new direction of experimental research applied to clinical medicine, and in order to make its great importance apparent I will only refer to two clinical cases in which these biological analyses of urine gave me extremely valuable results. The first case was that of a vast phlegmon in the right arm of a man, aged 70, with serious general and especially cerebral symptoms; the other was one

of extensive fibrinous pneumonia, certainly of infective nature.

In the former case, besides the diagnostic indication supplied by the biological analysis of urine, which in the rabbit reproduced the toxic symptoms in a more serious form than in the human patient, the knowledge thus gained was extremely useful to me from the point of view of prognosis and treatment. With regard to prognosis, I was able to foretell that improvement would take place at a time when the urotoxic coefficient of the urine was diminished in spite of the fact that, owing to an intercurrent attack of diarrhoea, the patient's general condition seemed to be worse, and when the clinical prognosis therefore was extremely doubtful. From the therapeutic point of view while the treatment (consisting of very large doses of hydrochlorate of quinine) employed before I was called in had been of little service, as soon as I had satisfied myself as to the close resemblance, as revealed by biological analysis, between the experimental results and the clinical picture presented by the patient, I ordered copious draughts of sulphuric lemonade with the object of destroying the circulating ptomaines and favouring their elimination.

In the second case—one of fibrinous pneumonia following influenza—whilst the specific inflammatory process successively invaded new zones of pulmonary tissue, there supervened suddenly eclamptic and tetanoid symptoms which made the medical attendant suspect the onset of infective cerebro-spinal meningitis. The condition of the patient was most serious; a temperature of 40.07° C, pulse 125, respirations 55; fluid yellowish-green expectoration, profuse sweating, etc., in short the classic picture of a most violent acute infection. The doubt as to the diagnosis was fully warranted, and it will readily be understood of what importance that was relatively to prognosis and treatment. I did not, however, feel justified in accepting without much reserve the diagnosis of cerebro-spinal meningitis, and before giving my opinion I caused experiments to be made in the laboratory of my Clinical Institute on the biological analysis of the urine which the patient had passed in the last twelve hours. The experiments were conducted by my able assistant Dr. Traversa and my demonstrator, Dr. Falcone.

The result of that biological analysis as well as of the chemical analysis was as follows: Urine deep yellow in colour, clear, acid, specific gravity 1020, containing no chemically appreciable pathological elements, no uroerythrin, biliary pigments, or ethyl-diacetic acid. The injection of 5 cubic centimetres of this into a guinea-pig weighing 250 grammes, and of 10 cubic centimetres into a rabbit weighing 1.050 grammes, was immediately followed by general tremors, alternating with tonic convulsions and extreme dyspnoea, exactly resembling the clinical symptoms and convulsions seen in the patient, and clearly showing that part of the dyspnoea, the severity of which was certainly disproportionate to the extent of the pneumonic process, was of bulbo-paralytic origin. I no longer hesitated as to the diagnosis, but declared that the convulsions did not indicate an attack of cerebro-spinal meningitis, but simply a most acute intoxication, due to the formation of new special ptomaines in that great and mysterious biochemical laboratory of which the human organism when attacked by influenza is the seat.

Such being the diagnosis, the prognosis naturally became less serious, and, instead of antiphlogistic treatment directed to the new seat of the supposed morbid process, I pursued my ordinary method of treatment in such cases, especially giving large doses of iodide of sodium, which I look upon as a powerful means of elimination in the treatment of infective diseases. The further progress of the disease completely confirmed this diagnosis; the convulsive attacks completely ceased twenty-four hours after their onset, and the urine passed after their subsidence, although the pneumonic process continued with hardly any appreciable improvement, and the temperature persisted at 40° C., showed itself on biological analysis to be inoffensive. In fact, the injection of 90 cubic centimetres into a rabbit did not induce the slightest toxic manifestation referable to the classic clinical type already described.

I do not think I need add other details to show the great assistance which may be derived in clinical work from the biological analysis of the urine, and I believe that these

analyses should be made *pari passu* with other semeiotic researches, since the results thereby obtained will enable one to foretell the impending development of serious clinical symptoms in the course of certain acute febrile infections, which begin suddenly with very high fever, and of which it is impossible in the earlier days of the illness to determine the nature.

I think it necessary before concluding to remind all those who propose to adopt this new diagnostic method of one thing, and it is this. There are two indispensable conditions for attaining all the clinical advantages which may be looked for from biological analysis: 1, the researches should be carried out by assistants thoroughly versed in pharmacological experiments, especially those concerning the nervous and muscular systems; 2, the experiments should be begun with small doses of urine (always having regard to the body weight of the animal), because in acute infective diseases the organism sometimes gives rise to the formation of most powerful poisons, with regard to which it would be impossible to obtain a precise knowledge of the clinical symptoms of intoxication produced by them unless one proceeded step by step. Lastly, the reader need hardly be reminded that the total quantity of urine passed in the twenty-four hours should be taken into account wherever it is possible to do so.

ON WOOLDRIDGE'S METHOD OF PRODUCING IMMUNITY AGAINST ANTHRAX BY THE INJECTION OF SOLUTIONS OF TISSUE FIBRINOGEN.

Being a Paper Communicated to the Bacteriological Section of the International Congress of Hygiene.

By A. E. WRIGHT, B.A.CAMB., M.D.DUBL.

ACCORDING to Wooldridge¹ rabbits which have received an intravascular injection of a solution of tissue fibrinogen, which has been sterilised by boiling, are thereby rendered immune against anthrax when it is subcutaneously inoculated. Wooldridge, however, described certain difficulties to exist in the application of this method. He found that when "strong alkaline solutions," that is, solutions in which no coagulation took place on boiling, were employed, the solutions did not possess any immunity-conferring power (this power having presumably been lost by the action of heat in the presence of free alkali). On the other hand, when the alkali of the solutions was reduced to a point which permitted of coagulation taking place on boiling, that coagulation tended to be too complete, and the filtrate in consequence to become inert, because entirely free from tissue fibrinogen.

The purport of this communication is to make a contribution towards defining the expression "tissue fibrinogen" from a chemical² point of view, and to report a few experiments upon the immunity-conferring power of a solution of tissue fibrinogen sterilised by passing it through a Chamberland's filter.

Method of Preparing the Fibrinogen Solution.—The perfectly fresh cellular organs (testicles, thymus, etc., in the experiments to be reported the fluid was always prepared from bulls' testicles) are reduced to a pulp in a mincing machine, and are extracted for twelve hours with water to which, for antiseptic purposes, an addition of 1 in 200 of chloroform has been made. The watery extract is then either centrifugalised or filtered, or simply decanted. It is then precipitated by the addition of 0.5 cc. of 33 per cent. acetic acid to every 100 cc. of the extract employed. The precipitate is collected and washed with NaCl solutions of moderate strengths, and lastly with distilled water. (All these washing fluids are rendered slightly acid by the addition of a trace of acetic acid.) The precipitate is now dissolved in a 1 per cent. solu-

¹ Arch. J. Anat. u. Phys., 1888.

² I have devoted a considerable portion of this paper to the discussion of the chemistry of the tissue fibrinogen, because the obscurity which surrounds it appeared to me to be responsible in great part for the fact that Wooldridge's experiments upon immunity do not appear to have been verified by subsequent observers.