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The Present Position of Tuberculin Therapy.

By.

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The Present Position of Tuberculin Therapy.

Tuberculosis has been known from very remote times. Hippocrates (460 - 376 B. C.) was the first to give an intelligent description of phthisis though the disease had been recognised before his time. He and his followers believed that it was curable in all stages and recommended change of residence as the chief element in the treatment. Since then many methods of treatment have been suggested, none of them proving satisfactory. Most of them have been merely symptomatic and have been valuable in so far as they have relieved distressing symptoms and rendered the patient's condition more tolerable; they have however done little towards producing a cure of the disease. Substances such as creosote and its derivatives have been administered in the hope that they might kill the bacilli without injuring the patient but have proved unsuccessful. A greater measure of success has attended the hygienic-dietetic method of treatment. This, briefly, consists in keeping the patient as much as possible in fresh air, both night and day, in regulating his exercise according to his condition and in giving him nourishing food in suitable quantities. Thanks chiefly to this method it has been proved that if taken sufficiently early the disease is not incurable.

A very considerable decrease in the death rate from tuberculosis has taken place chiefly as the result of the zeal of legislative bodies in improving sanitation and general hygiene and erecting hospitals for the segregation of infected individuals. In England the death rate from this cause has decreased from 247 per 100,000 in 1851 to 136 per 100,000 in 1900. It must be noted however that this decrease is due not so much to the cure of cases already infected as to prophylactic measures abolishing conditions favourable to the propagation of the disease and to the isolation and more particularly education of individuals capable of infecting others.

Until the introduction of tuberculin by Koch in 1890 however, nothing had been found which could in any way claim to be specific. In its first form, now known as tuberculin (T.O.) to distinguish it from newer forms, it was tried by Koch chiefly in lupus cases and was announced by him as a certain cure. It was received enthusiastically and subjected to extensive clinical trials but unfortunately proved very disappointing. The reason for this lay not in the tuberculin itself but in the method of using it. The doses employed were much too large and the cases selected were often quite unsuitable; consequently too severe a reaction was obtained and in many cases its use was attended by very harmful results.

This caused it to fall into disrepute and it was given up almost entirely as a therapeutic agent though it was still recognised as a valuable means of diagnosis. It has long been the chief instrument in diagnosis in veterinary practice and as a result of the researches of Von Pirquet, Calmette Wolff Eisner and others it is coming into more general use in ordinary medical practice.

A few workers who had been more moderate in their dosage obtained results which, though far from being uniformly successful, were still sufficiently encouraging to warrant the continuance of its use. They continued to advocate it but for years were practically unheeded by the majority of the profession. Recently however the interest in the subject has been revived by the brilliant work of Wright and his colleagues. Wright has shown that the immunising properties of the blood depend chiefly on certain bacteriotropic substances in the serum to which he has given the name of "opsonins". He has devised a means of estimating the opsonic power of the blood and has thus been able to determine the effect of tuberculin injections. The chief result of his work has been to show that small doses are sufficient and that they need only be repeated at intervals of ten or fourteen days.

He has thus, by replacing the former uncertainty of dosage by some degree of exactitude, placed the treatment on a more scientific basis and it has again been taken up, this time with more caution and in a fuller knowledge of its powers and limitations.

To what extent tuberculin may prove useful it is yet impossible to say. Before its action is thoroughly understood much work must be done in the study of the composition and mode of action of those substances at present vaguely termed bacteriotropic and more attention must be paid to the other factors in the production of immunity. Different workers give varying reports of the degree of success which they have had with it but practically all agree in considering that it is much superior to all other means of treatment and that it holds out great promise for the future.

The history of the subject dates from the discovery of the tubercle bacillus by Koch in 1882. This was only acheived after much patient and difficult research. The bacillus would not stain with ordinary water solutions of aniline dyes and it was only after staining for twenty-four hours in methylene blue to which caustic potash had been added that Koch succeeded in demonstrating its presence. In attempting to cultivate it outside the body he failed to get

results with any of the ordinary media. This difficulty however was also overcome by growing it for ten days on a specially prepared medium of solidified blood serum. He then carried out a series of inoculation experiments and demonstrated the causative relationship between the bacillus and the disease so completely that little of importance has since been added to his discoveries. Having thus discovered the cause of the disease he immediately set about trying to find a remedy for it. It had previously been stated by some observers that recovery from a localised tuberculous affection of the glands or skin seemed to confer immunity to pulmonary tuberculosis and this suggested to him that a specific curative agent might be found in the bacilli themselves or in the products of their metabolism. He found (1) that if a guinea-pig were inoculated subcutaneously with tubercle bacilli a module developed at the site of inoculation, ~~were made in another part of the body~~ broke down, and remained as an open sore till the death of the animal. If however a second inoculation were made in another part of the body an inflammatory reaction took place about the primary sore resulting in superficial ulceration and necrosis. The necrotic mass was finally cast off and healing occurred. He concluded from this that the bacilli secreted a substance which had a necrotic action on the tissues and that the

injection of bacilli increased the quantity of this substance about the tubercular mass and caused it to be thrown off. His attempts to isolate this substance led to the discovery of tuberculin. This was prepared from pure cultures of tubercle bacilli grown for from four to six weeks in 5% glycerine broth. These were filtered and the filtrate concentrated to one tenth its volume by boiling. It thus consisted of a 50% glycerine medium containing the soluble substances which were secreted by the bacilli and were not destroyed by boiling. The excellent results got from it in cases of lupus led to an over-estimation of its powers. It was used very extensively but the large doses which were employed caused very violent reactions and frequently led to dissemination of the disease. Cases were soon reported in which a rapidly fatal general tuberculosis resulted and the treatment was abandoned.

Koch (2) continued his researches. He injected dead bacilli in the hope that they might induce immunity to the organism as well as to its toxin. In this however he was disappointed; the bacillary bodies were not absorbed but remained at the site of inoculation and gave rise to suppuration. He next attempted therefore to obtain in an absorbable form all the substances contained in them. He tried first to

extract them by means of chemicals but was unsuccessful. Finally in 1897 he announced his new tuberculin which was prepared as follows:- Young and virulent cultures were dried in vacuo and thoroughly disintegrated by grinding in a mortar. The pulverised mass was then treated with distilled water, centrifugalised and the supernatant fluid drawn off. This process was repeated till practically no residue remained and the collected fluids formed the new tuberculin called by Koch Tuberculin Rückstand (T.R.) It was made of such a strength that 1 c.c. contained 2 mgms. of dried tubercle powder and 20% of glycerine was added as a preservative. Experiments with it have shown that it has a high immunisung value and causes much less reaction than old tuberculin. It does not cause suppuration at the site of inoculation. Its introduction caused some renewal of interest in the subject in Germany but in this country it did not receive much attention.

More recently in studying the agglutinative properties of the blood in tuberculosis Koch (2a) found that a certain relationship existed between the agglutinative powers and the degree of immunity. Believing that agglutination ~~powers of immunisation~~ was part of the complicated process of immunisation he concluded that the higher the agglutinative power of the blood could be raised the greater would be the

degree of immunity obtained. His experiments showed that high agglutinating values were obtained more rapidly and with greater certainty with ground bacillary mass than with T. R. and this led to the introduction of another form of tuberculin called Bacillen-Emulsion (Tuberculin B. E.) This is prepared by drying the bacilli in vacuo, pulverising and treating with distilled water. It is made of such a strength that 1 c.c. contains 5 mgms. of dried tubercle and 50% of glycerine is added to ensure preservation. It is questionable if much benefit is derived from obtaining high agglutinating values but by this method of preparation tuberculin has been brought more into line with other vaccines, and, assuming that it acts in the same way as other similar substances, it should prove the best form. In practice it has given very satisfactory results; it has a high immunising value and, given in small doses, it neither causes violent reaction nor suppuration.

Many attemps have been made to improve on the preparations of Koch. Denys (3) has prepared a tuberculin by filtering cultures through porcelain. He has avoided boiling the filtrate believing that boiling destroys useful toxins. His tuberculin is therefore practically Koch's old

tuberculin unconcentrated. It has given good results but seems to possess no advantage over the concentrated form.

Landmann (4) in an attempt to obtain both the extra and intra-cellular toxins prepared, in the following manner, a substance which he called Tuberculol. He took broth cultures of highly virulent bacilli, freed them entirely from fat and powdered them. He then extracted the soluble substances with normal saline solution or dilute glycerine at 40°C. He repeated this extracting process several times with fresh fluid at temperatures increasing gradually up to 100°C. The extracts mixed and concentrated in vacuo at 37°C. constitute tuberculol. By this process he claims to have obtained ~~without damage~~ the toxins extracted both at low and at high temperatures. Several observers have reported good results with this preparation but it has not yet been subjected to very extensive trials.

Klebs has prepared four different substances. He believes that along with the curative agent harmful toxins are present in tuberculin and his first preparation which he called Tuberculocidin (5) was the result of an attempt to remove these toxins by treatment with alcohol and bismuth. Not satisfied with this he prepared another substance which he

called Antiphthisin (6) by precipitating the filtrate of a tubercle culture with sodium-bismuth-iodide in acetic acid and absolute alcohol.

Finding that the Diplococcus Semilunaris was frequently present in mixed infections he prepared a substance from it which consisted of a solution of the bodies of the cocci with the toxins extracted by hydrogen peroxide. This he called Selenin and he used it along with tuberculocidin (7) in cases of mixed infection.

Finally he prepared another substance, Tuberculosozin (8) by extracting dead bacilli with glycerine. He recommends that it be employed after tuberculocidin - selenin has been used to the limit of its action. Good results have been reported with these preparations but most observers have been unable to confirm them.

Beraneck (9) has prepared a tuberculin containing both extra and intra-cellular toxins the latter being extracted from the bodies of the bacilli with 1% phosphoric acid. He claims for it that it contains all the substances having immunising properties but does not contain the other harmful substances. It has been largely used in Germany and very favourable opinions are expressed of it.

Behring (10) by a very complicated process consist-

ing partly in the treatment of bacilli with chloral hydrate has obtained a substance called Tulase which contains the somatic substance of the bacilli which takes up the stain in the Gram and Ziehl-Nielson methods. It has been very little used and Bandelier and Roepke (13) state that Behring himself has now given it up.

Many other forms of tuberculin have been devised most of them more or less similar to the preparations of Koch and possessing no advantages over them. Efforts have also been made to produce immunity by the injection of attenuated living bacilli. Experiments on cattle and other animals have been very satisfactory and the results obtained with human beings, although very few cases have as yet been reported have been sufficiently encouraging to justify the hope that this line of treatment may prove very valuable.

Maragliano (11) Marmoreck(12) and others have attempted to produce passive immunity by means of antitubercular sera. Good results with this method have been reported by some observers but others have been unable to confirm them It has recently however been receiving a great deal of attention and it is probable that it may yet take a prominent place in the treatment of the disease.

Of the various methods of administration which have

been tried that of subcutaneous injection has proved most satisfactory and is the one most generally employed although the method of oral administration finds favour in some quarters.

Intravenous injection was recommended by Koch in the belief that a higher degree of immunisation could be obtained than by the subcutaneous method. This has now been disproved and as its only advantage, that of rapidity of action, is more than counter-balanced by the dangerously violent reactionssometimes produced, the method has been abandoned.

Jacob (14) recommended intra-bronchial injection in lung cases, his aim being to bring the drug into the closest possible contact with the focus of disease. The action of tuberculin however is chiefly systemic and as moreover the local reaction induced would be of extremely short duration owing to the high absorptive power of the bronchial mucous membrane this method has little to commend it. It has, besides, the objection of being very disagreeable to the patient. Tuberculin inhalation has been advised also with a view to direct local action. It possesses no advantages and has the great disadvantage of uncertainty of dosage.

The method of administration by the mouth in the form of keratinised pills is one on which a definite opinion cannot yet be pronounced. Many workers claim to have obtained good results from it and Clarke cites cases to prove that the opsonic index is affected quite as markedly by it as subcutaneous injection. Some observers however condemn it believing that, provided the epithelial lining of the alimentary tract be intact, very little absorption of the toxin takes place and that it is probably destroyed or greatly altered in the process of digestion. The subject requires more study. Should the method prove successfulit would possess the great advantage that where regular supervision of the treatment was impracticable the patient, his progress having been carefully watched during the first few weeks, might be given a number of small doses with instructions as to their use. It would also be much more acceptable than subcutaneous injection. Several of my patients have refused to undergo the treatment on learning that the drug was to be injected under the skin and others, though it had been explained to them at the commencement that the treatment would have to be continued for months, have grown tired of it after a few weeks and declined to submit to further injections. I am quite certain that had the tuberculin been administered orally these

difficulties would not have arisen.

Administration per rectum in the form of suppositories and enemata has also been advised but has little to commend it.

Administration per cutem by inunction has been practised and it is claimed for it, that, owing to the small amount of absorption which takes place from the skin surface it is specially suitable for infants and patients exhibiting hypersensibility to the toxin. Here again the great objection is the absence of absolute control over the dosage. By means of suitable dilutions the toxin can be administered in these cases in sufficiently small doses and with much greater precision by the subcutaneous method so that there is nothing to warrant the continuance of administration by inunction.

Paterson's (15) method of administration by means of auto-inoculation has given very good results. The inoculations are induced by means of exercise and the dosage is increased by gradually increasing the exercise from short walks up to hard manual labour. The great danger in this method is the liability to overdosage and I do not think that it should be taken unless the patient can be kept under constant supervision and his progress regulated by means of frequent opsonic index determinations or observations of the temperature,

pulse, etc. In view of the experiments of Spengler and others to which reference will be made later, it seems doubtful whether any advantage is gained by thus treating patients with the toxins elaborated by their own bacilli.

Subcutaneous injection ensures exactitude of dosage and absorption in an unaltered form and is, at any rate for the present, the most suitable method of administration.

With regard to dosage and frequency of administration two distinct methods are in vogue, the German and the English.

The German method aims at producing as high a degree of immunity as possible and towards this end rapidly increasing doses are given at short intervals. The doses of T.R., for instance are raised quickly from $\frac{1}{1,000}$ mgm. to 20 mgms. The guide to treatment is the patient's condition as evidenced by his temperature, pulse and other symptoms. Formerly injections were given everyday but it has been recognised that this course is dangerous owing to the occasional occurrence of delayed reaction and a longer interval is now allowed between successive injections. A small initial dose is given and, if no reaction occurs it is followed by a slightly larger one two or three days later. This process is continued till the maximum dose is reached longer intervals being allowed

between successive injections as the dosage is increased. If any dose produces a violent reaction the treatment is suspended till the temperature has returned to normal and has remained at that for a few days. The same dose is then repeated or a smaller one given. It is usually found that the second injection is well borne but occasionally it happens that it is followed by a more violent reaction than that caused by the first. This is due to hypersensibility to the toxin and when it occurs the treatment is entirely suspended for some months and then much smaller doses are exhibited. When the maximum dose is reached it is repeated at intervals of about a month or the treatment may be suspended for some time and then the whole course repeated.

In the English school a different method is followed based on the teaching of Wright and his co-workers.

Wright and Douglas (16) in their researches on the role played by the serum in phagocytosis found that washed leucocytes free from serum were non-phagocytic but were reactivated by the addition of normal serum. If the serum were first heated to 60-65°C phagocytosis did not take place. If however the serum and bacteria were mixed and kept at a temperature of 37°C for 15 minutes then heated to 60°C., phagocytosis would still take place on the addition of washed

leucocytes. They thus demonstrated that normal serum contained a substance which could be destroyed by heat and which acted on the bacteria in such a way as to render them suitable for ingestion by the leucocytes. To this substance they gave the name "Opsonin" (Greek opsono = I prepare food for) and they have devised a method of estimating whether the quantity of it in the blood be above or below normal.

To do this three things are required, washed leucocytes, serum from the blood to be tested and bacterial emulsion. These are prepared in the following manner. A quantity of fresh blood is taken and mixed with a weak solution of sodium citrate to prevent congulation. This is centrifugalised and the citrated plasma pipetted off. Normal saline solution is then added to the mass of red cells and leucocytes and this is also centrifugalised and the supernatant fluid removed. This washing process is repeated several times, till, finally a mixture of red cells and leucocytes is got entirely freed from plasma. A small quantity of the blood to be tested is drawn off and allowed to coagulate and the serum is separated. A control serum is similarly prepared from the blood of a normal individual. The bacillary emulsion is prepared by emulsifying in distilled water and centrifugilising to throw down any clumps which may be present.

Equal quantities of the washed cells, bacterial emulsion and serum to be tested are drawn up into a suitable pipette and, after thorough mixing, incubated for 15 minutes and 37·C. A control specimen in which normal serum is used is prepared and incubated in the same manner. Films are then prepared from each on ordinary glass slides, fixed and stained and the number of bacilli ingested by not less than 50 leucocytes counted. The ratio of the average number of organisms per leucocyte in the patient's serum to the number in the normal serum gives the patient's opsonic index.

Wright (17) and his followers after estimating the index in a large number of cases have found that in normal individuals it is fairly constant but is subject to considerable variation in infected patients. They have studied the effect of the introduction of tuberculin into the system on the opsonic content and have found that on injection a decrease occurs. This is called the negative phase; it lasts for three or four days and is followed by an increase or positive phase lasting six or seven days. The index then slowly returns to normal the whole cycle lasting from ten to fourteen days. They have found also that a similar series of changes occurs as the result of auto-inoculations.

After treating a large number of cases and controlling the treatment with opsonic index determinations they have come to the

conclusion that the maximum benefit for the patient is derived from keeping the index as far as possible within normal limits and that to do this only small doses are necessary. They also believe that harmful results are caused by giving a fresh injection during the negative phase induced by the last and that no advantage is gained by giving a fresh injection before the end of the positive phase. The method they advise therefore is that small doses be given at intervals of ten or fourteen days and this is the method generally adopted in this country.

It is questionable whether Wright's deductions are absolutely correct. The results got by the German method seem to indicate that he has at least over estimated the danger of the negative phase. His work however has been of great value in increasing our knowledge of the nature of bacterial injections and the method by which the body defends itself against them. To it we owe practically all we know of the process of immunisation and it has led us to a better understanding of the immediate effect of our injections and of the dangers to be avoided in the treatment.

The opsonic index has been much criticised both as regards its accuracy and its value in regulating the dosage even if it be admitted that it can be accuratelely determined.

Its detractors maintain that in a process so complicated and delicate the liability to error is so great as to render the results very untrustworthy. If this were the case one would expect widely differing readings to be got in the determination of the indices of normal individuals. Bullock (18) however, has found, and his results have been confirmed by many other observers, that the index for normal individuals varies only between the limits of ·8 and 1·2. Fleming (19) has also shown that the amount of variation in the results got by different observers examining independently the same specimen is very slight. These facts prove I think that if sufficient care is exercised the amount of experimental error if not entirely negligible is at least too small to seriously affect the conclusions drawn from the readings. It must be admitted however that the liability to error is so great that much experience and an intimate knowledge of the technique are required before dependable results can be got and this unfortunately limits its use to the skilled laboratory worker who has made it a special study.

Possible sources of error are met with in connection with all three of the elements used. The most important of these as pointed out by Fleming (29) are as follows. If the red cells mixed with the washed leucocytes are agglutinable

an abnormally high reading will be got and a too high delution of the washed cells, will give a similar result. If care is not taken in the preparation of the serum to obtain it entirely free from red cells a low reading will be got as their presence seems to hinder phagocytosis. Care must also be taken not to allow the serum to remain exposed to the air for any length of time as this decreases its opsonic power. The presence of clumps of bacilli in the bacterial emulsion may also lead to considerable error.

The objection that where spontaneous auto-inoculations are frequent their occurrence render it practically impossible to obtain a correct estimation of the patient's immunising powers is more serious and the value of opsonic index determinations in such cases is extremely doubtful. These auto-inoculations however can be greatly controlled and in some cases entirely prevented by absolute rest.

Many observers maintain that, as a guide to treatment, the local symptoms at the seat of disease and the general condition of the patient are quite as reliable as the opsonic index. With this I cannot agree. The action of tuberculin is primarily systemic and the condition at the seat of disease, which is to some extent cut off from the ~~greatest~~ general circulation, gives no immediate indication of the patient's anti-bacterial power. After a considerable time, of course,

the local condition will indicate the effectiveness or otherwise of the treatment but, as pointed out by Wright, (20) if we depend on local symptoms alone we may treat a case for some months only to find that our treatment has been quite ineffective and even then we cannot tell in what way we must alter it to get better results. Neither can the general symptoms be accepted as an absolutely reliable guide. Excessive dosage is not necessarily indicated to a rise of temperature. Lawson and Stewart (21) in an investigation of 120 cases of phthisis found that in 50% the temperature gave no response during the negative phase. Even when it does respond the warning given, while it serves to indicate alteration in the future treatment, comes too late to prevent the harm done by the last dose. The effects of inter-current affections, also, may lead to erroneous conclusions.

Nevertheless experience in Germany and to a lesser extent in this country shows that as a rule the clinical symptoms form a sufficiently reliable guide to enable the treatment to be carried out without serious harm being done. The work of Inman (22) and others on the co-relation between the temperature and the opsonic index enables us to interpret with some degree of accuracy the patient's opsonic power from

his clinical condition and I do not think that the general practitioner should be deterred from carrying out the tuberculin treatment by the inability to have opsonic index determinations taken. He must be content however to proceed very slowly and to use very small doses and he must not expect to obtain results as rapid or as satisfactory as those got by observers who use the opsonic index as their guide.

The exact nature of opsonins and their relationship to other anti-bodies such as alexins, agglutinins, cytotoxins, etc. has not yet been determinedand probably will not be till they have been isolated in a state of purity. Wright considers them to be substances quite distinct from all others but Metschnikoff and other observers do not accept this view. It is held by some that they exist in the blood as pre-opsonins and only become specific after stimulation by bacteria. The experiments of Muir and Martin (23) and of Cowie and Chapin (24) seem to prove conclusively that they have a double structure consisting of a non-specific, thermolabile complement-like substance and a specific thermostable amboceptor-like substance. The latter is present only in very small quantity in normal sera but is abundant in immure sera. Little is known yet of the seat of their elaboration. Allen (25)) believes that they are formed in the muscles and subcutaneous

tissue but there is little evidence to prove this.

Till their exact nature is more thoroughly worked out and the part played by them in the cure of the disease is better understood it will be impossible to say whether the German method of producing a high degree of immunity or the English method of simply keeping the index as far as possible within normal limits is the better. Meantime we must base our opinion on the results got by the two systems. In comparing the results of different observers a difficulty arises in the fact that there is no universal method of classification of cases, each observer having a system of his own. So far as can be judged however the two methods of treatment give about equal results the balance being perhaps slightly in favour of the English method. From this it seems probable that the maximum benefit is obtained by keeping the opsonic index at a normal level and that the Germans gain no advantage by giving doses greater than are necessary to do this. Clarke (26) who has used both methods considers that the German is the better but gives no reason for his belief. It is noteworthy that in Germany the view is gaining ground that the present system of pushing the treatment to its utmost limits is unnecessary and there can be no doubt that it is much more dangerous than the system adopted in this country.

Of the various forms of tuberculin those of Koch, especially T. R. and B. E. have been most widely used and seem to give results at least as satisfactory as those got by any of the others. Opinions differ however as to the relative merits of vaccines prepared from the bovine and human types of bacilli. In the treatment of other bacterial diseases it has been found that the best results are obtained by using a vaccine prepared from the patient's own infecting organism and a priori one would expect the same to hold for tuberculosis. Several distinguished observers who have experimented on the subject however have been led to a very different conclusion. It has been shown that though cattle are practically never infected by human bacilli they can be most completely immunised to their own form by using a vaccine prepared from the human type, and some observers, notably Spengler (27) and Pottenger (28) believe that in treating human beings, the best results are obtained by using a bovine vaccine ~~of the analogous type~~ where the infection is the human type and vice versa. In support of this view Spengler states that when a pyrexial case is treated with a vaccine of the opposite type the temperature is reduced and when a vaccine of the analogous type is used it is increased. Pottenger states further that if the injection

of tuberculin prepared from one type of bacilli causes a rise in temperature the injection of that prepared from the other type will immediately reduce it, the one apparently acting as an antedote to the other. Allen (25) argued from this that if equal parts of human and bovine tuberculin were mixed together they would neutralise each other and give no result on injection. He has used such a mixture in a large number of cases but instead of finding it inactive has obtained results so satisfactory that he has now discarded in its favour the ordinary tuberculin.

Tuberculin is a very complicated substance and little is yet known of its composition. Most observers agree however that its opsonising and fever producing agents are different substances and I suggest as a possible explanation of the above phenomena that the opsonising elements in human and bovine tuberculin have a similar action while the toxic-fever-producing elements are reciprocally antagonistic. This would explain the satisfactory results got by Allen with his mixed tuberculin and would also explain the fact pointed out by Spengler that the prognosis is more hopeful in the case of patients infected by both types of bacilli than in those in whom only one type is present. Should this theory prove correct then a tuberculin prepared from the opposite type

of organism to that infecting the patient must clearly be the more beneficial since it will act not only as an immunising agent but also as an antidote to the toxin already present in the body.

Of the value of tuberculin there can now be little doubt. Satisfactory results of its use in all forms of tuberculosis have been published and those who have used it extensively are practically unanimous in considering it superior to all other methods of treatment. What form it may ultimately take it is at present impossible to say. A great step in advance would be made if a vaccine could be prepared free from toxic elements and in this direction the methods of treatment of Spengler and Allen are interesting and worthy of further investigation. Unless such a vaccine is discovered I think it probable that the best results may be got by a combination of active and passive immunisation as suggested by Bandelier and Roephe.

In pulmonary and laryngeal tuberculosis in which the treatment has been largely used we find from statistics published by various observers that about 20% more cures are got where hygienic dietetic and tuberculin treatments are carried out together than where the former is used alone.

The difference is most marked in moderately advanced cases, incipient cases doing almost as well under sanatorium treatment alone. Excellent results have also been got in cases treated at home often amid very unhygienic surroundings. The results got in the treatment of tuberculosis of other organs have been very encouraging but so far the number of cases reported has been small. Most observers agree that in surgical tuberculosis the use of tuberculin tends greatly to lessen the necessity for operative interference and to hasten the healing process where operations have been performed.

Opinions differ greatly as to the selection of cases suitable for treatment most observers holding that it should not be used in very advanced cases. Bandelier and Roepke (13) however advocate a wider use and state that it is only contra-indicated in the case of greatly debilitated patients with severe mixed infection. They claim that in severe uncomplicated cases with extensive lung destruction, though a cure cannot be hoped for, the patient's condition may be frequently ameliorated and in some cases the disease may be rendered quiescent.

In no case should the tuberculin treatment be used to the exclusion of all others. In all cases it should be com-

bined, where possible, with the hygienic-dietetic system and in surgical cases it should be used in conjunction with operation, Bier's passive congestion and other methods which in the past have proved servicable.

The preparation which I have used in my own practice is B.E. and I have relied on the patient's clinical condition as my guide. My patients have all been members of working-class families living in the country and in most cases in fairly comfortable homes. The plan I have adopted is to start with a dose of $\frac{1}{20,000}$ mgm. B.E. and if no reaction occurs repeat it in about 10 days. If this is also well borne I give at the next injection a slightly larger dose and go on in this manner gradually increasing the dose and giving each dose twice till a moderate reaction is induced. I then return to a dose slightly smaller than that which caused the reaction and remain at this level.

Case 1. W.B. aged 28 years.

Plurisy with effusion. Slight evening temperature. Von Pirquet's reaction positive. On January 16th clear fluid was aspirated from the chest. Two days later tuberculin treatment was commenced. Patient ~~is~~ improved rapidly. There was no return of the fluid, his temperature became normal and his

his general condition improved greatly. After five injections he returned to work feeling perfectly well and up to the present (May 10th) has had no return of his illness.

Case 11. J. C. aged 19 years.

Cough, languor, and evening rise of temperature. No sputum and no localising symptoms. Family history of tuberculosis and positive reaction by Von Pirquet's test. Tuberculin treatment commenced on December 8th. After about 2½ months patient felt perfectly well and the treatment was suspended. She is still under observation and has had no return of her symptoms.

Case 3. W.T. aged 15 years.

Tuberculosis of the right hip joint of five years duration. Three operations have been performed. I have been unable to obtain details of these but from the statements of the patient's parents it seems that they have simply consisted of the opening and draining of abscesses. The right leg is somewhat stunted in growth, movement at the hip joint is limited and there is a discharging sinus in the front of the thigh. Staphylococci are present in the discharge. Tuberculin treatment was commenced on February 3rd and is

still being carried out. Patient has gained considerably in weight and his general condition is very much improved; his parents state that he is now in better health than he has been since the commencement of his illness. No change is visible so far in the local condition but this may possibly be due to the fact that no staphylococcic vaccine has yet been used.

Case 4. M.W. aged 18 years.

Tuberculous adenitis of about 16 years duration. Some months ago the patient had an acute attack of rheumatism and since then the glandular condition has been much worse. Tuberculin treatment was commenced on March 8th and though the dose has never been increased beyond 1/20,000 mgm. very great improvement has taken place. There has been a marked reduction in the temperature the affected glands are much smaller and the general condition is much improved.

Case 5. M.S. aged 29 years.

Slight consolidation at the right apex., Tubercle bacilli in sputum. Tuberculin treatment commenced on January 30th, ~~for about two days, at the site of inoculation~~ The injections were very well borne but caused some pain, lasting usually for about two days, at the site of inoculation and

this coupled with the fact that there was no immediate benefit disheartened the patient and she declined to continue the treatment. Four injections were given but no improvement was manifest.

Case 6. R.C. aged 18 years.

Necrosis of terminal phalanx of right great toe after injury. Abscess on right thigh and on left side of neck. Von Pirquet's reaction positive. Necrosed bone was removed on March 10th, and tuberculin treatment commenced on March 14th. Iodoform dressings locally. Patient is still under treatment. His general condition is very much improved; The abscess in the neck is quite healed and the one on the thigh almost healed. The toe is still discharging probably owing to necrosis of the second phalanx though I have been unable to detect dead bone with the probe.

Case 7. S.C. aged 4 years. (sister of Case 6).

This patient fell and injured her forearm early in March. On April 12th her mother drew my attention to a large fluctuating swelling,,on the extensor aspect of the forearm. This was opened and a quantity of cardy material evacuated on April 16th. No necrosed bone could be found. B.E. $\frac{1}{20000}$ mgm. was injected on April &6th but as it caused a very violent

reaction I did not consider it advisable to continue the treatment.

Case 8. A.D. aged 24 years.

Tuberculosis of left knee joint. Diagnosis confirmed by Von Pirquet's test. Bier's passive congestion and tuberculin treatment commenced on February 26th. After five injections patient declined to continue the tuberculin treatment. No improvement. Temperature in this case was normal throughout with only slight elevations on injection.

Case 9. T.R. aged 11 years.

Tuberculosis adenitis of six years duration. Tuberculin treatment commenced on March 26th. Patient still under treatment. Temperature reduced and general condition slightly improved but no change in the glandular condition.

Case 10. G. M. W. aged 21 years.

Consolidation at both apices. Marked debility night sweats, cough. Sputum abundant and contains tubercle bacilli. High evening temperatures. Patient confined to

bed and tuberculin treatment commenced on 21st. Temperature greatly reduced and general condition improving. Patient still under treatment.

Case 11. G.B. aged 9 years.

Tuberculosis of left ankle. This patient was in a very weak condition when she first came under my care and I did not consider it advisable to use tuberculin immediately. The ankle was fixed in plaster of Paris and after two months her general condition being much improved, tuberculin treatment was commenced. After three injections the plaster was removed. Ankle apparently cured. This case shows nothing decisive as the improvement was probably due chiefly to the fixation of the joint, and attention to the general health.

Case 12. T.C. aged 14 years.

Tuberculosis of left knee joint. Treated by Bier's method and tuberculin injections. Treatment commenced on March 16th. Condition slightly improved. Patient still under treatment.

Conclusions.

Tuberculin therapy now occupies an assured position.

It has already given better results than any other method of treatment and as it is still in the experimental stage we may hope that further research will render it even more efficient. It is probable that a method of preparing tuberculin free from toxic elements will be discovered which will greatly lessen the danger of its use and that a deeper insight into the process of immunisation will be obtained which will enable us more accurately to regulate our dosage both as regards quantity and frequency of administration.

Of the preparations now in use the T.R. and B.E. of Koch have been most widely tried and seem to have given the best results. The relative ~~results~~ merits of preparations from the human and bovine types of bacilli is still an open question.

With regard to administration the method of subcutaneous injection finds most favour. Oral administration would be more convenient but opinions differ as to its efficacy and a final verdict on it cannot yet be pronounced.

The treatment should be commenced as early as possible and it should be aided by such other methods of treatment as will tend to improve the patient's general health and increase his powers of resistance. Till further research decides what method of treatment is most suitable the English

method should be adopted. It is safer than the German and has given quite as satisfactory results.

The accuracy of opsonic index determinations in experienced hands and their value both in diagnosis and in the regulation of dosage has been fully proved and where practicable the treatment should be carried out under their guidance. Experience has shown however, that in the majority of cases the patient's clinical condition forms a sufficiently reliable guide and the treatment may be undertaken with this control alone.

Tuberculosis is one of the most widespread and fatal of all diseases, but, with such a means of treatment and with the possibility of very early diagnosis by means of the opsonic index and the cutaneous tuberculin reactions at our command it is not too much to hope that the time is not far distant when it will become one of comparitive rarity. Before this can be attained however the general practitioner must take a much more prominent part in the treatment than he does at present. The unfortunate results which attended the use or rather abuse of tuberculin when it was first introduced have impressed him more with its dangers than its utility and he is inclined to regard it as of very doubtful value and at

the best suitable only for hospital practice. Hospital accomodation however is too limited to deal with more than a very small proportion of those affected and the great majority of cases must be treated by him. He must be taught therefore that it is of undoubtable value, that its sphere of use is much wider than he at present considers and that it is his duty to acquaint himself thoroughly with its action and to use it in every suitable case which comes under his notice.

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(2) Koch. " " " 1897. No. 14.

(2a) Koch. " " " 1901. No. 48.

(3) Denys. Le bouillon filtre du bacilli de la tuberculose. 1905.

(4) Landmann. Zentralblatt fur Bakteriologie. vol. XXVII.

(5) Klebs. Wiener medizinische Wochenschrift. 1891. No. 15.

(6) Klebs. Zentralblatt fur Bakteriologie. 1896. vol XX.

(7) Klebs. Deutsche medizinische Wochenschrift. 1907. No 15.

(8) Klebs. Deutsche " " 1908. No. 3.

(9) Beraneck. Comptes rendus de l'Academie des Sciences. 1903. vol. CXXXVII.

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(10) Behring. Beitrage zur experimental Therapie part II.

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(11) Maragliano. Tuberkulosis. 1906. vol V.

(12) Marmorek. Berliner Glinische Wochenschrift. 1903. No. 48.

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(13) Bandelier and Roepke. Tuberculin in diagnosis and treatment. 1909.

(14) Jacob. Deutsche medizinische Wochenschrift. 1904. Nos. 26-28.

(15) Paterson. "Graduated Labour in Pulmonary Tuberculosis". Lancet January 25th, 1908.

(16) Wright and Douglas. Lancet October 22nd, 1904.

(17) Wright. Lancet December 2nd, 1905.

(18) Bullock. Lancet January 21st, 1905.

(19) Fleming. Practitioner. May 1908.

(20) Wright. Practitioner. May 1908.

(21) Lawson and Stewart. Lancet. December 9th, 1905.

(22) Inman. Proceedings of the Royal Society of Medicine. April 1908.

(23) Muir and Martin. British Medical Journal. 1906. No. 11.

(24) Cowie and Chapin. Journal of Medical Research. October 1907. February 1908.--------

(25) Allen. "Vaccine Therapy and the Opsonic Method of Treatment.)

(26) Clarke. "Studies in Tuberculosis." 1909.

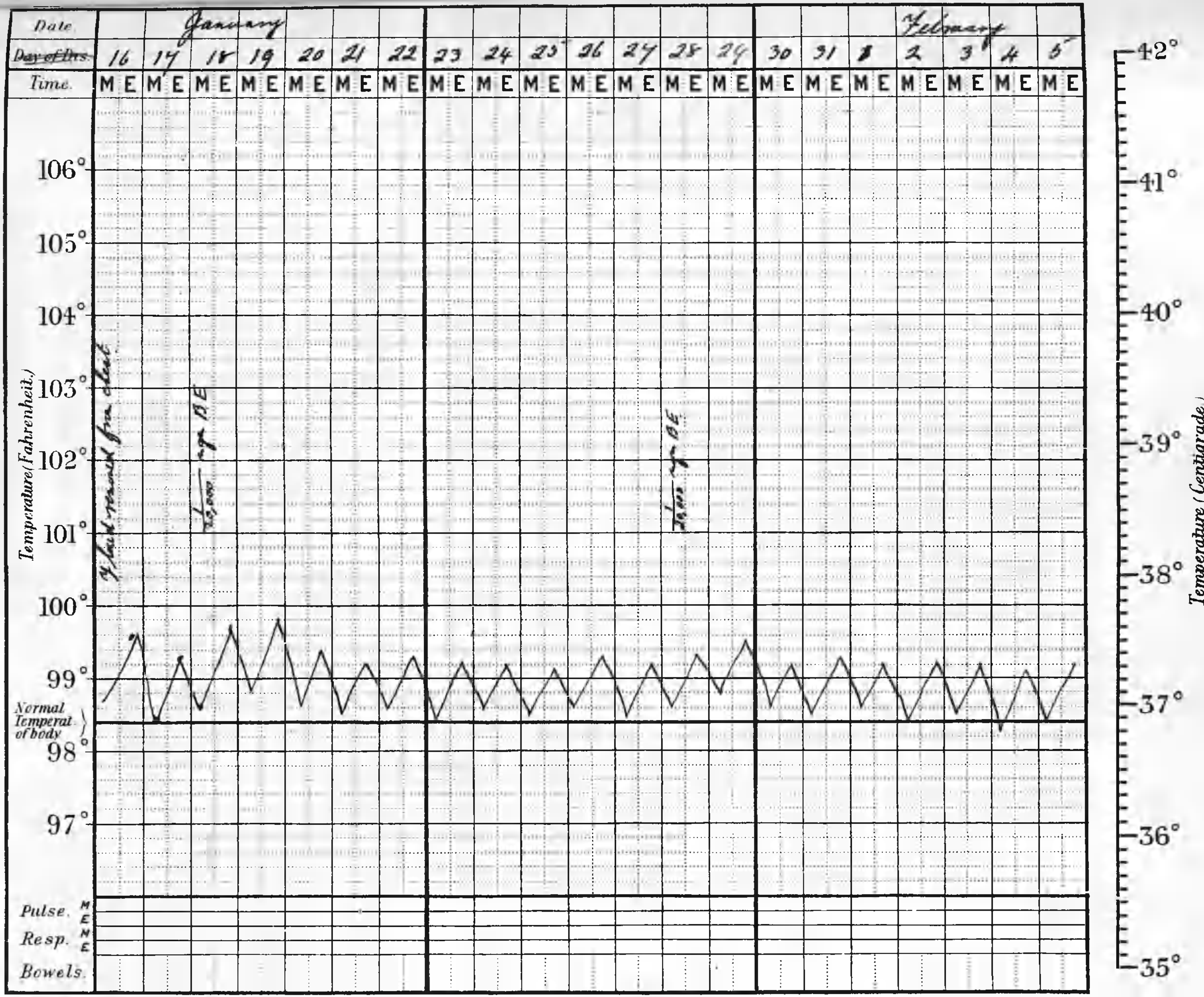
(27) Spengler. Deutsche medizinische Wochenschrift. 1904. No. 31.

(28) Pottenger. The Diagnosis and Treatment of Pulmonary Tuberculosis 1908.

(29) Fleming. Practitioner. May 1908.

Notes of Case.

Diet, etc.

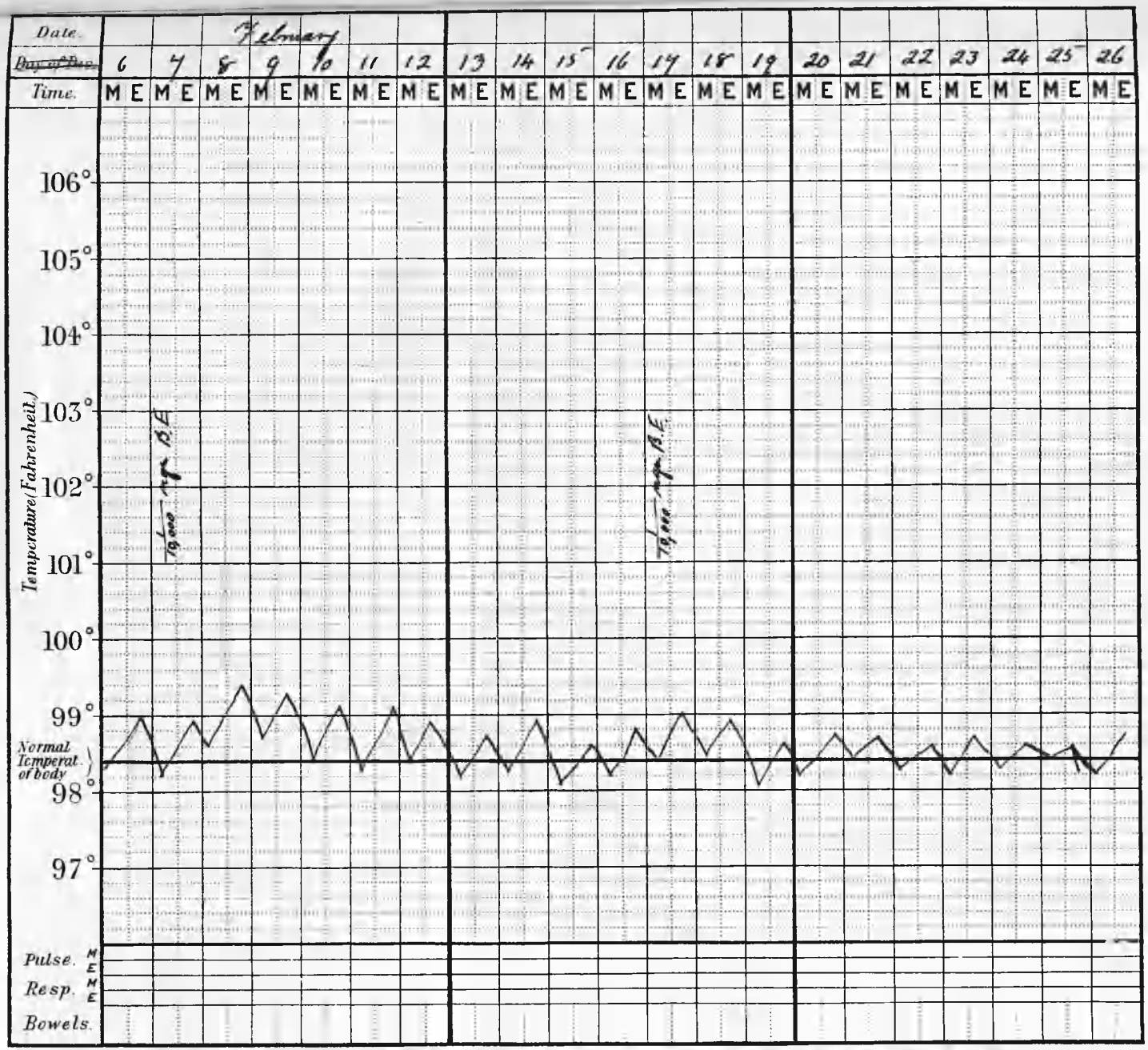


Result ....

(COPYRIGHT) (LONDON [illegible]) RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.



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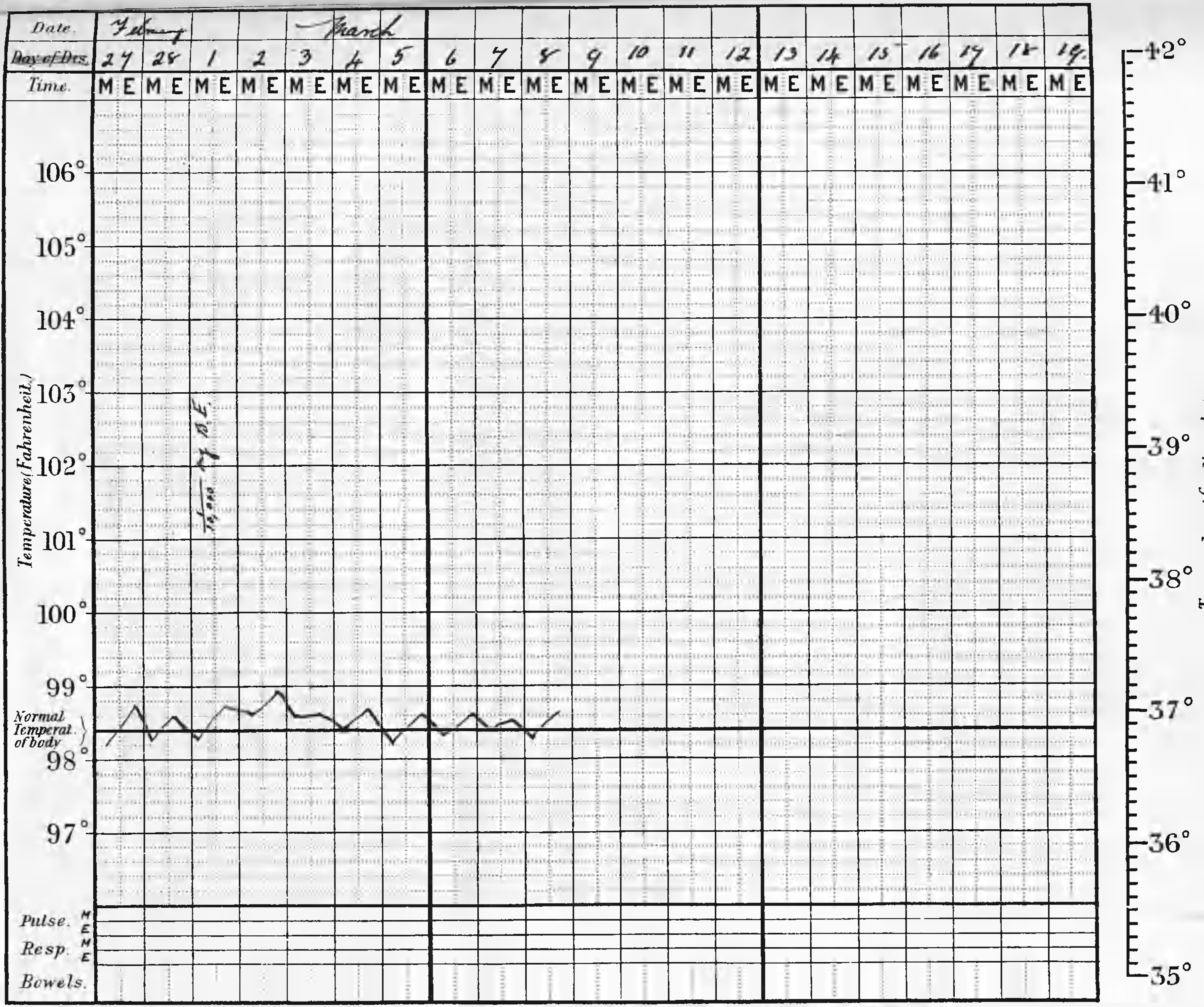
Notes of Case.

Diet, etc.



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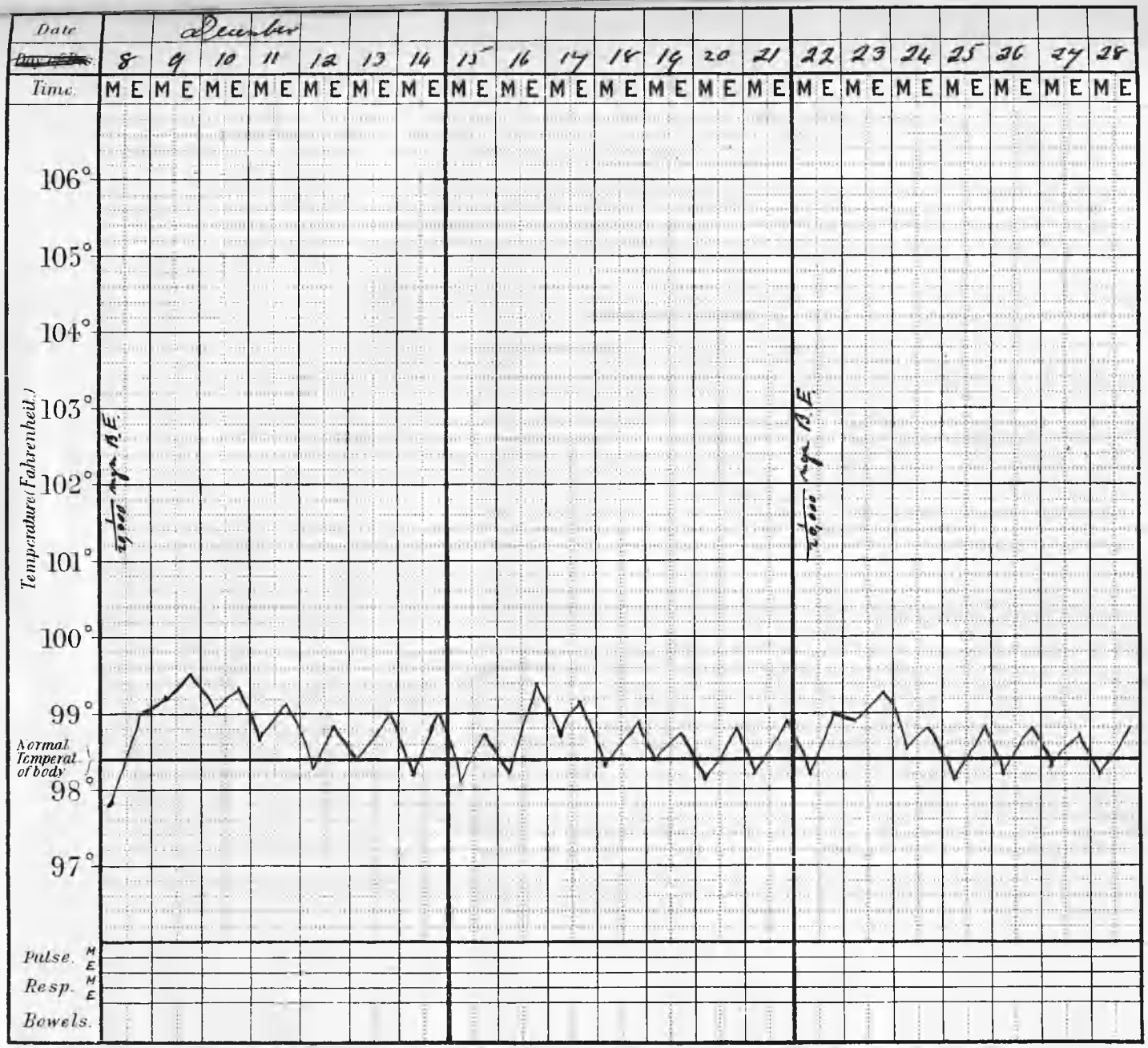
Notes of Case.

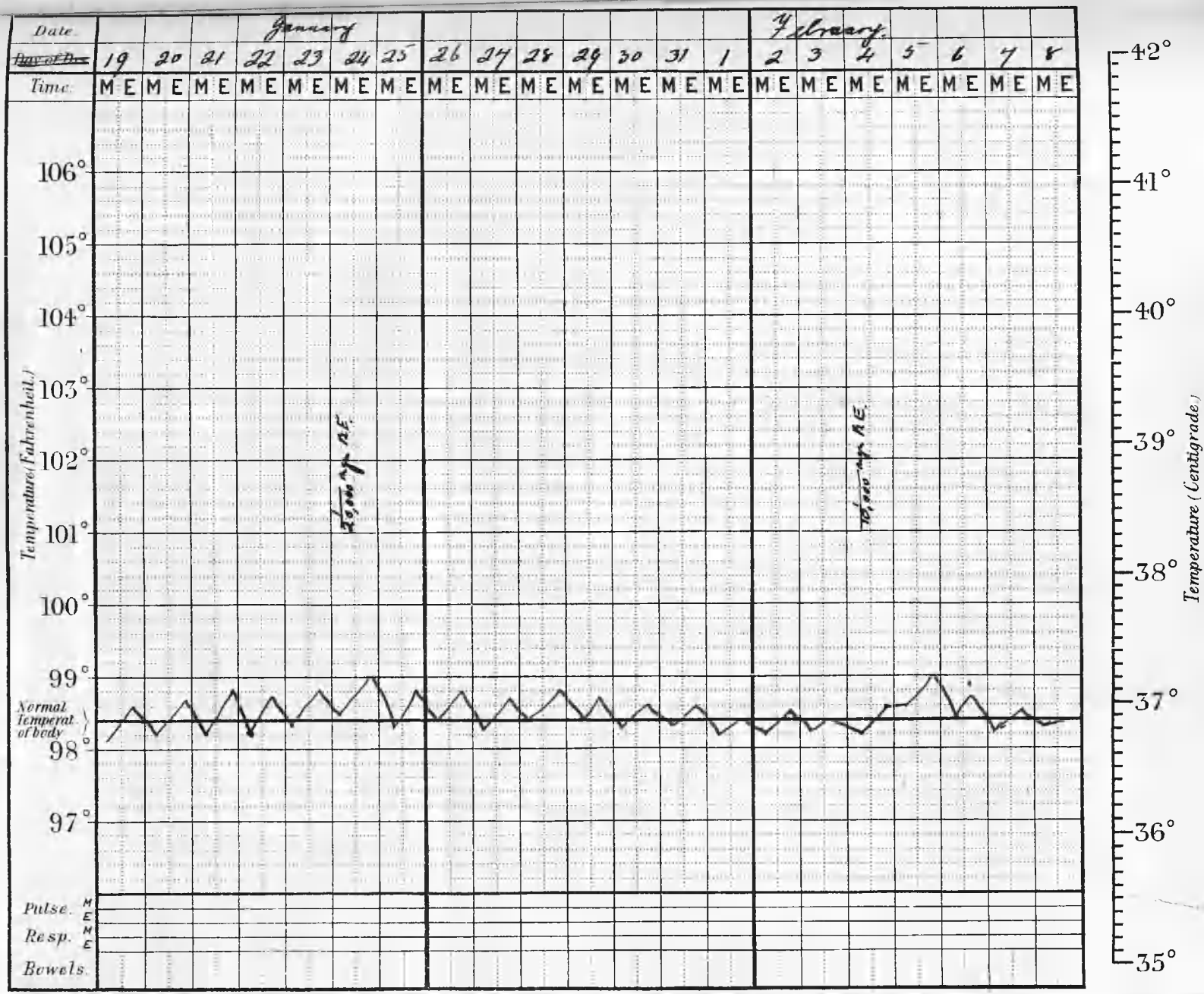
Diet, etc.

Result



Notes of Case.

Diet, etc.



Result .....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result .....

Date	February																								
~~*Day of Dis.*~~	9		10		11		12		13		14		15		16		14		18		19		20		21
Time	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E

22		23		24		25		26		27		28													
M	E	M	E	M	E	M	E	M	E	M	E	M	E												

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat of body

Temp on A.E.

Pulse. M E

Resp. M E

Bowels.

Temperature (Centigrade.)

42° 41° 40° 39° 38° 37° 36° 35°

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result .....

Date	February																						
~~Day of Illness~~	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23		
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E		

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

Temperature (Centigrade.)

42° 41° 40° 39° 38° 37° 36° 35°

Pulse. M E

Resp. M E

Bowels.

RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result .....

Date			February							March														
Day of Dis.	24	25	26	27	28	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E			

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperal. of body

Pulse. M E

Resp. M E

Bowels.

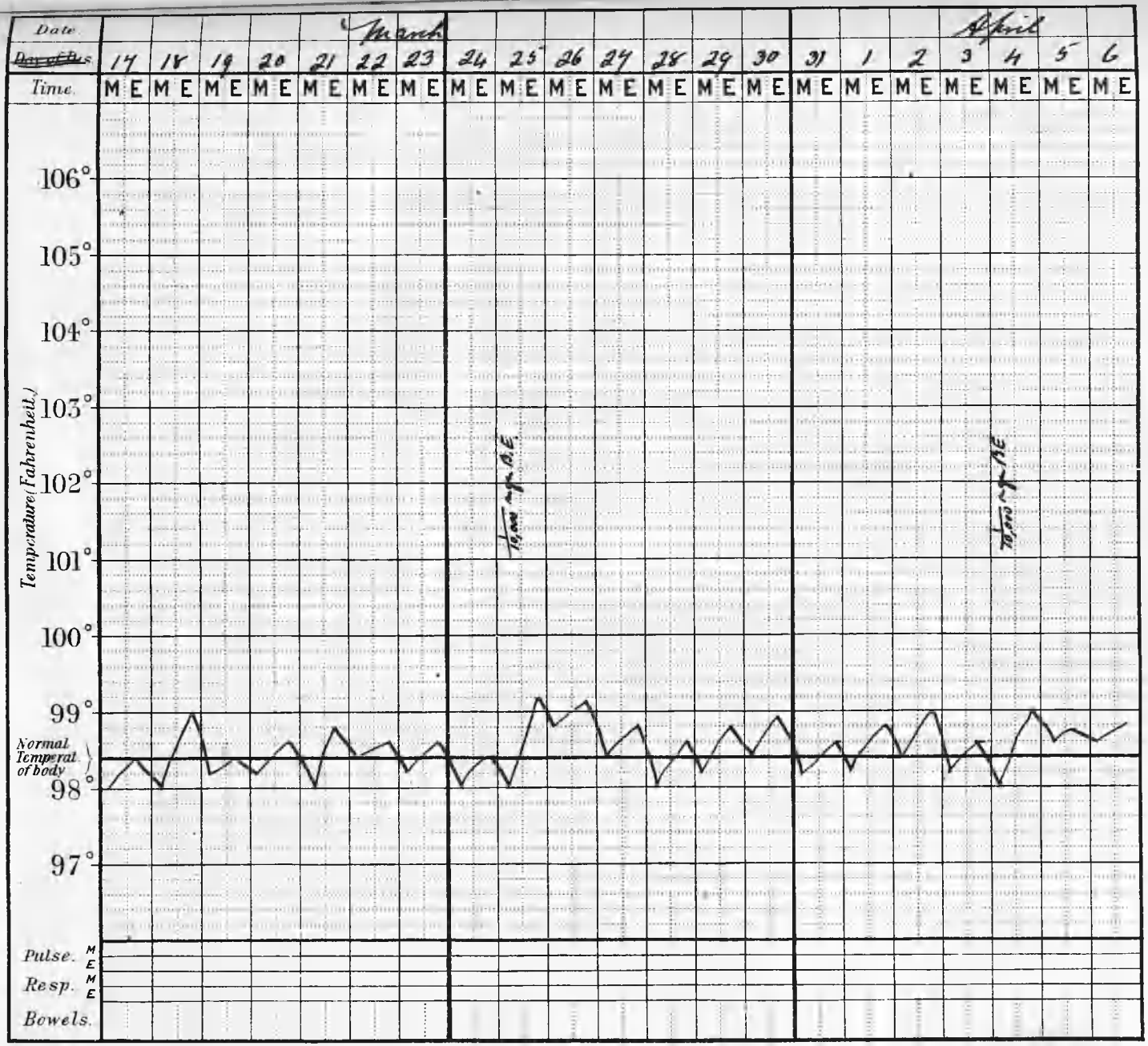
Temperature (Centigrade.)

42° 41° 40° 39° 38° 37° 36° 35°

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE

Notes of Case.

Diet, etc.



Result .....

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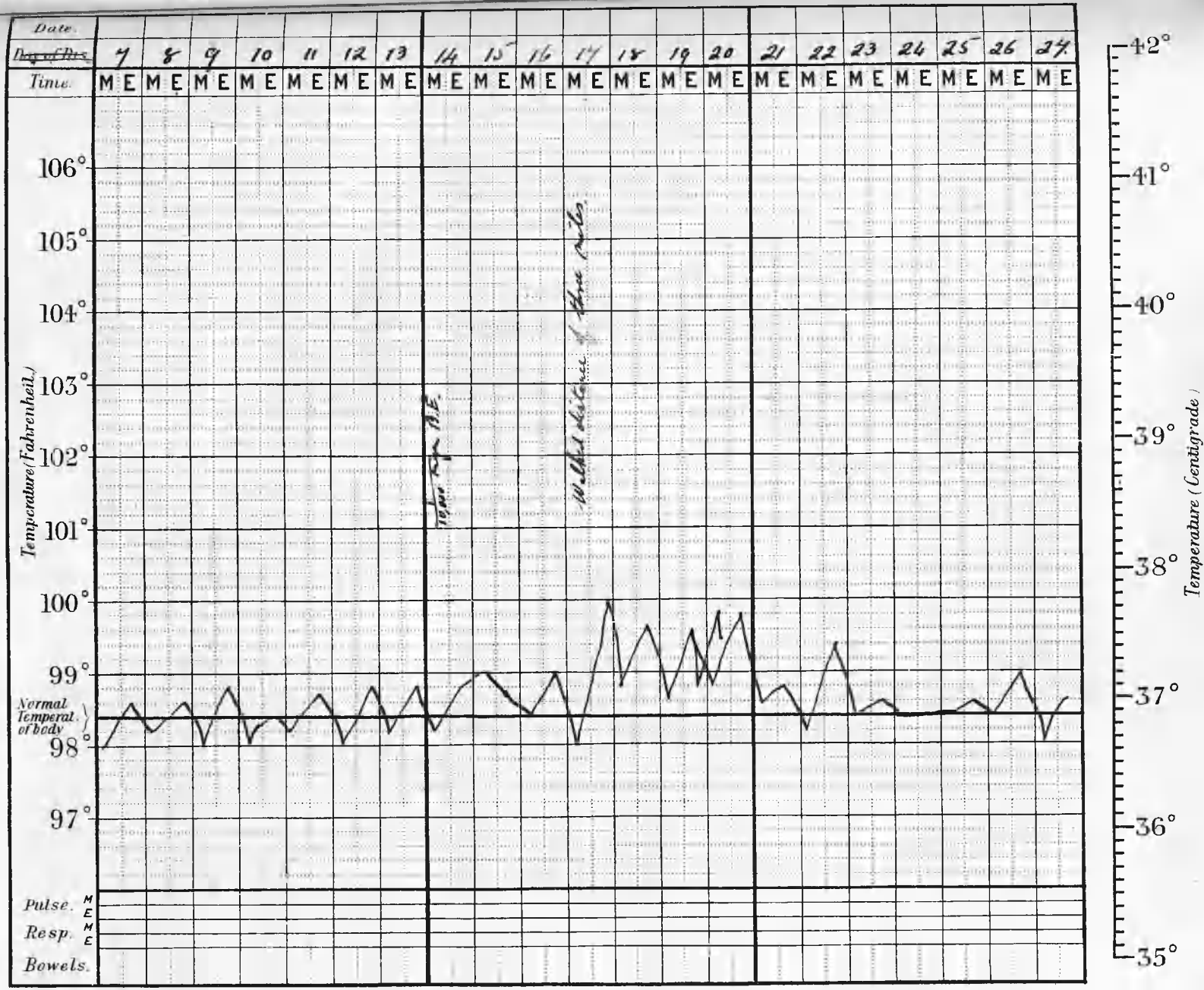
Notes of Case.

Diet, etc.



Result .....

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Notes of Case.

Diet, etc.

Result .....

Date.	April							May													
Day of Dis.	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

Temperature (Fahrenheit)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

1/1000 Hyd. Perchl. M.E.

1/1000 Hyd. Perchl. M.E.

Pulse. M E

Resp. M E

Bowels.

42° 41° 40° 39° 38° 37° 36° 35°

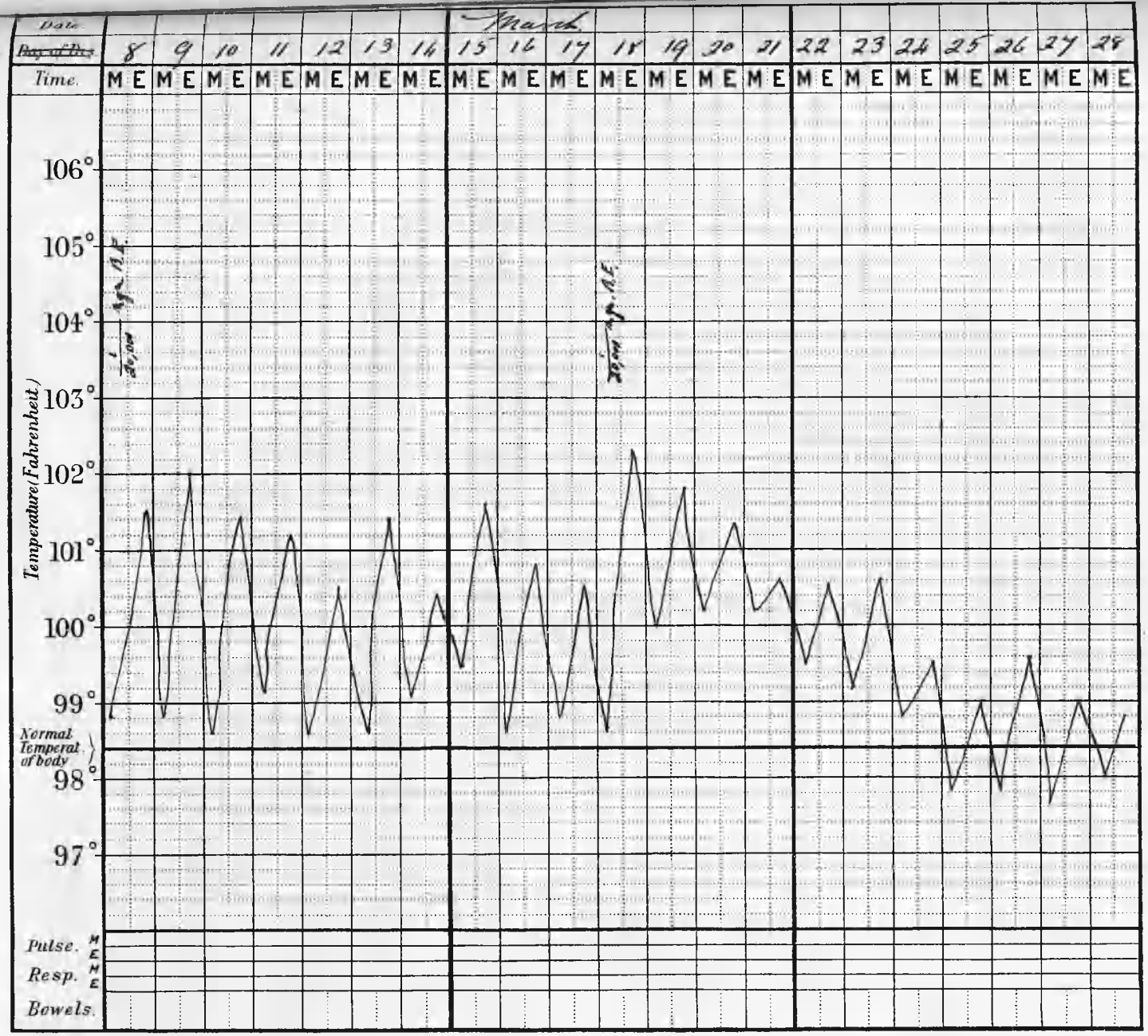
Temperature (Centigrade)

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result .....



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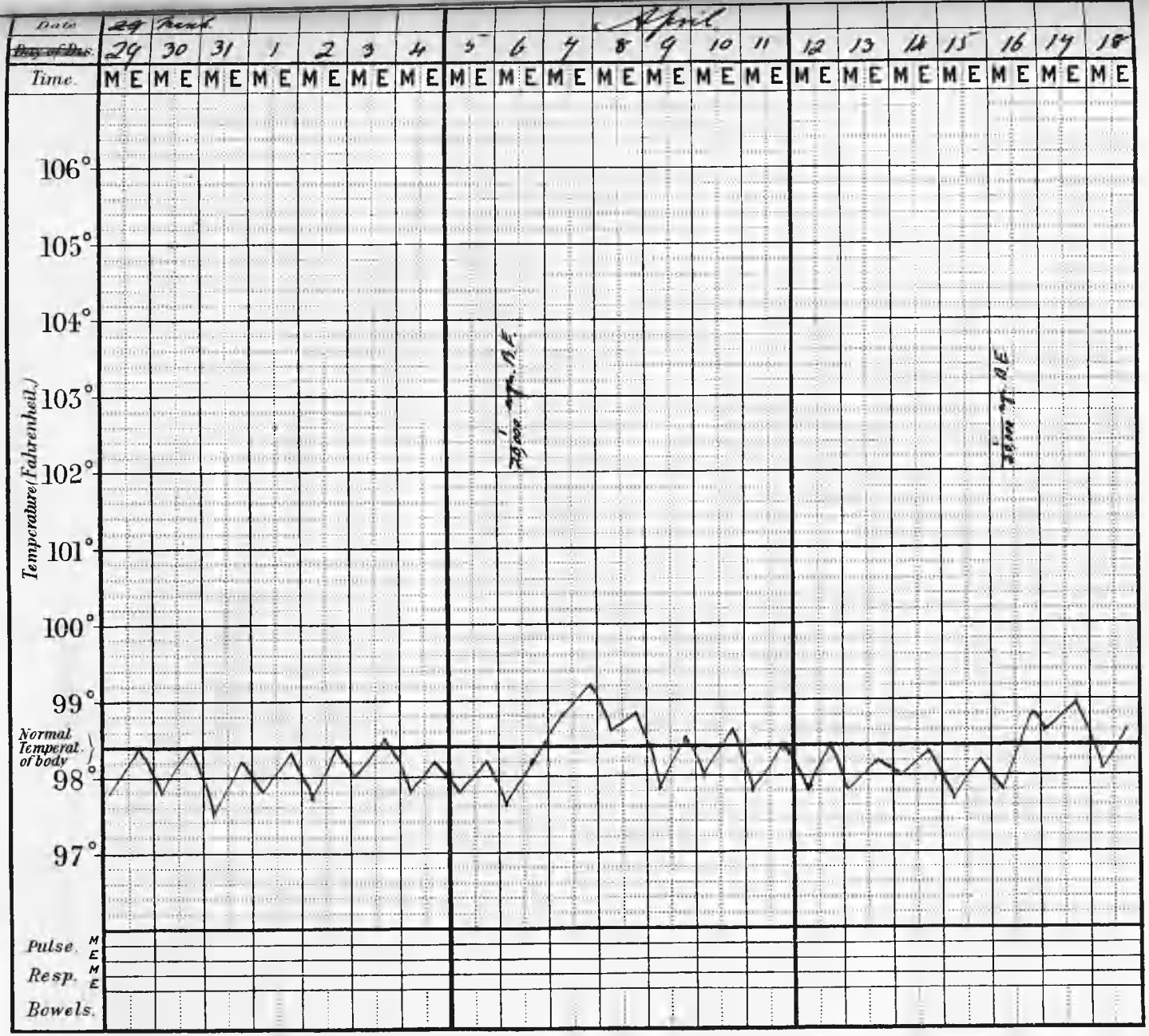
Notes of Case.

Diet, etc.



Result .....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Date	April													May							
Day of Dis	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

28 Jan 95

29 Jan 95

Pulse. M E

Resp. M E

Bowels.

42° 41° 40° 39° 38° 37° 36° 35°

Temperature (Centigrade.)

Result .....

Notes of Case.

Diet, etc.

Date.			Prep.																													
~~Day of Dis~~	10		11		12		13		14		15		16																			
Time	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

Pulse. M E

Resp. M E

Bowels.

Temperature (Centigrade.)

42° 41° 40° 39° 38° 37° 36° 35°

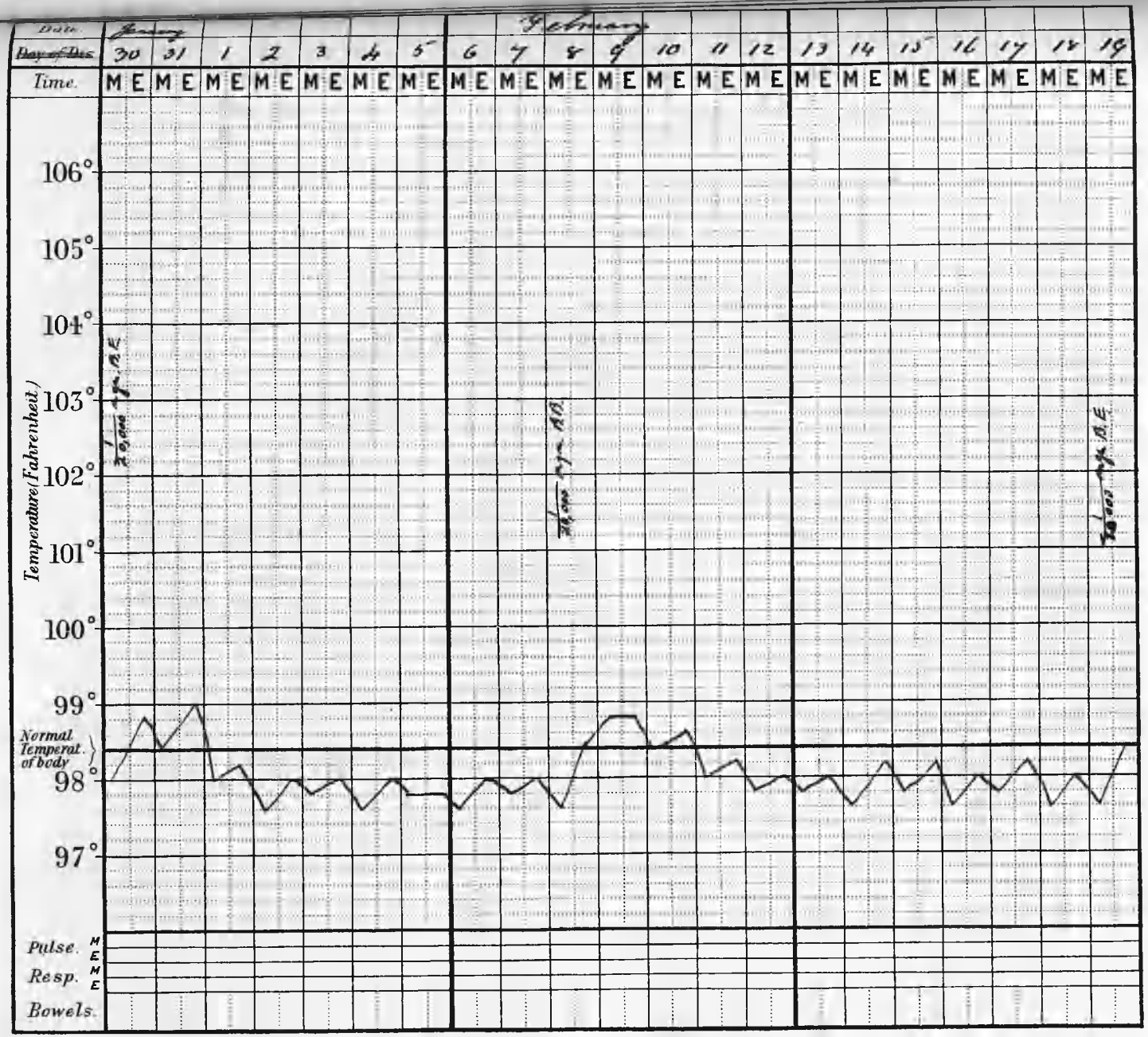
Result .....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result



 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Result .....

Date	February														March										
~~Day of Dis~~	20	21	22	23	24	25	26	27	28	1	2	3	4	5	6	7	8	9	10	11	12				
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E				
106°																									
105°																									
104°																									
103°																									
102°																									
101°																									
100°																									
99°																									
98°																									
97°																									
Pulse. M E																									
Resp. M E																									
Bowels.																									

Temperature (Fahrenheit.)

Normal Temperat. of body

42° 41° 40° 39° 38° 37° 36° 35°

Temperature (Centigrade.)

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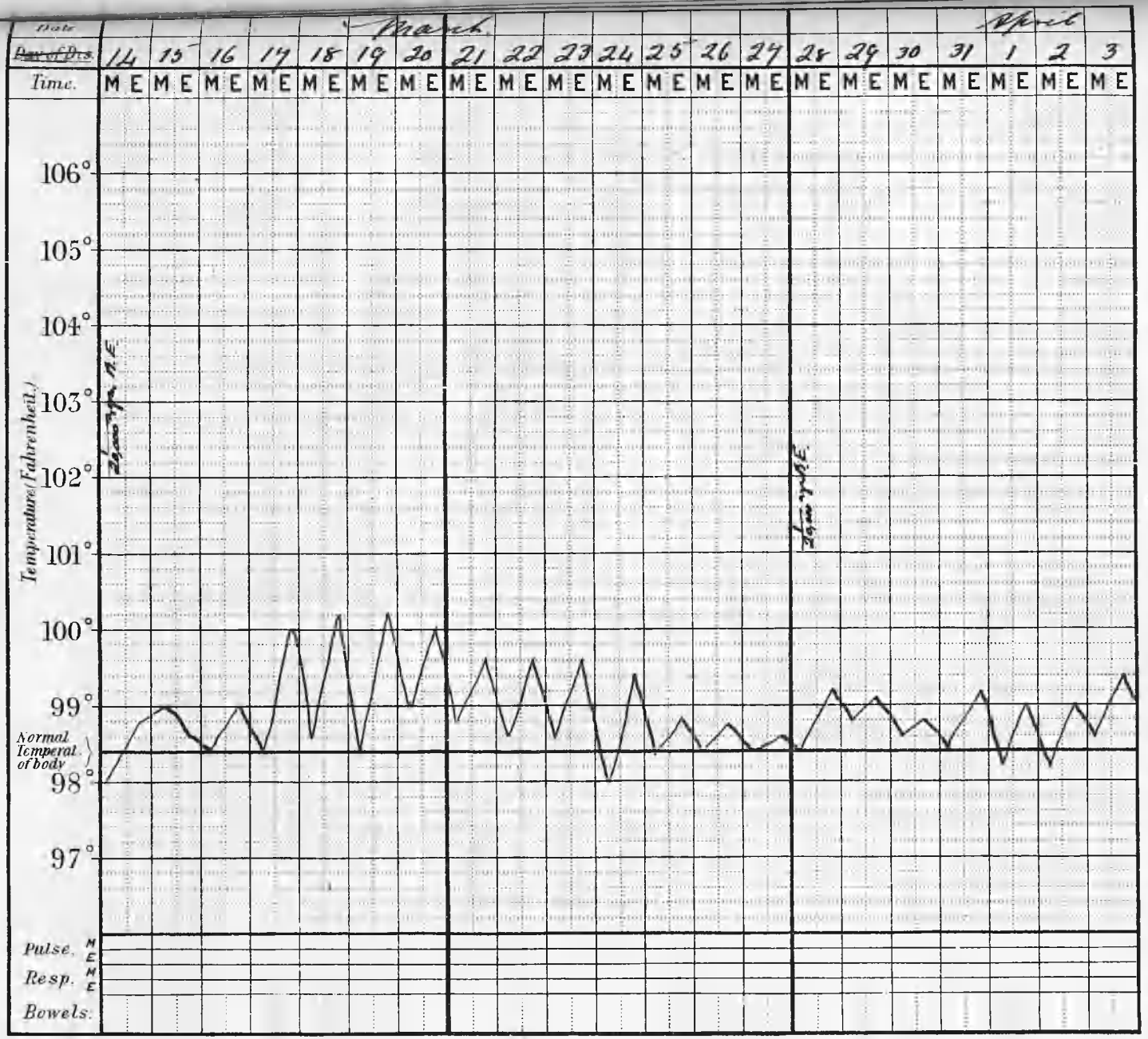
Notes of Case.

Diet, etc.



Result .....

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Notes of Case.

Diet, etc.

Result .....

Date.																									
Day of Dis.	4		5		6		7		8		9		10		11		12		13		14		15		16	
Time.	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E

17		18		19		20		21		22		23		24											
M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E										

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

42° 41° 40° 39° 38° 37° 36° 35°

Temperature (Centigrade.)

Pulse. M E

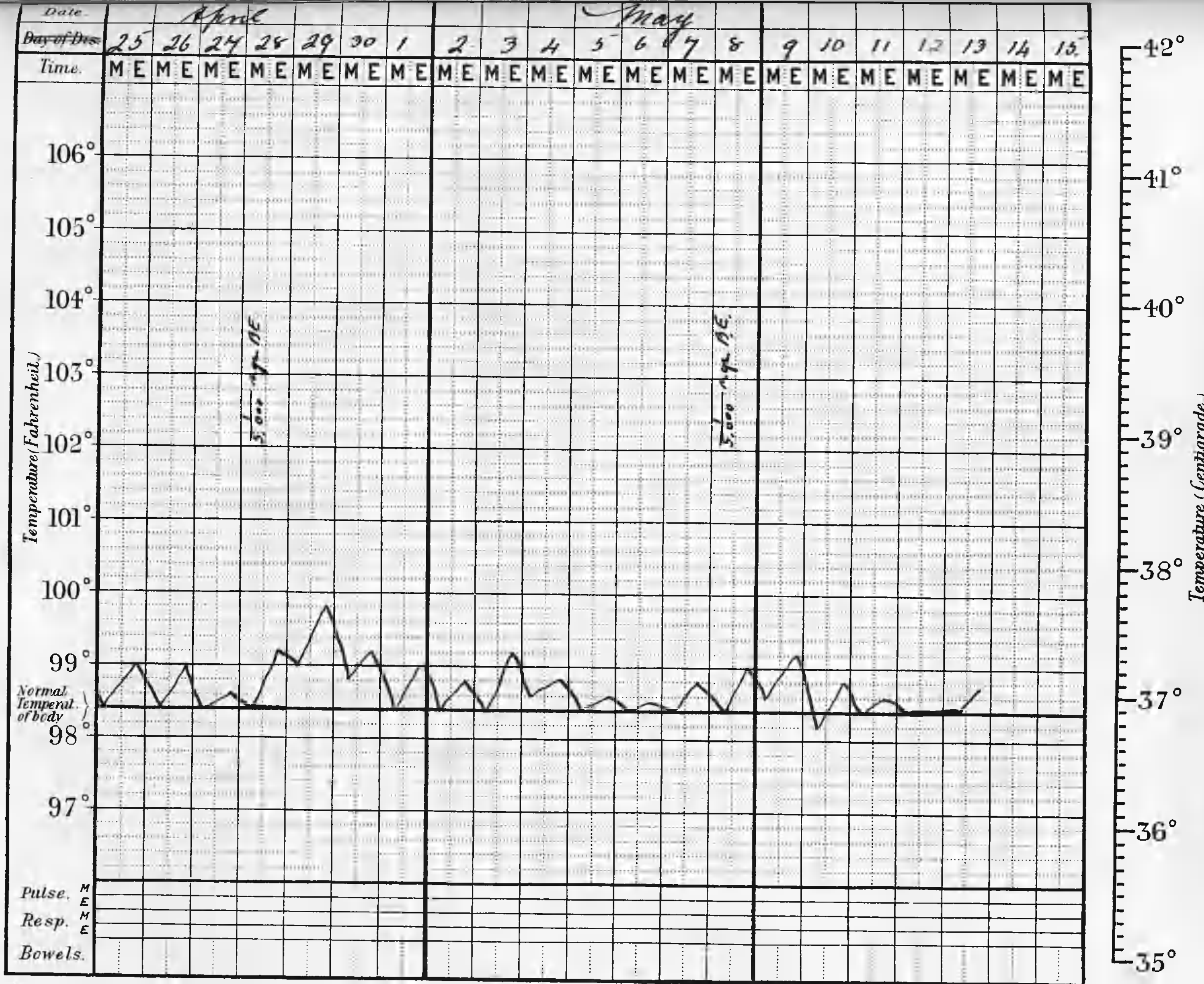
Resp. M E

Bowels.

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.



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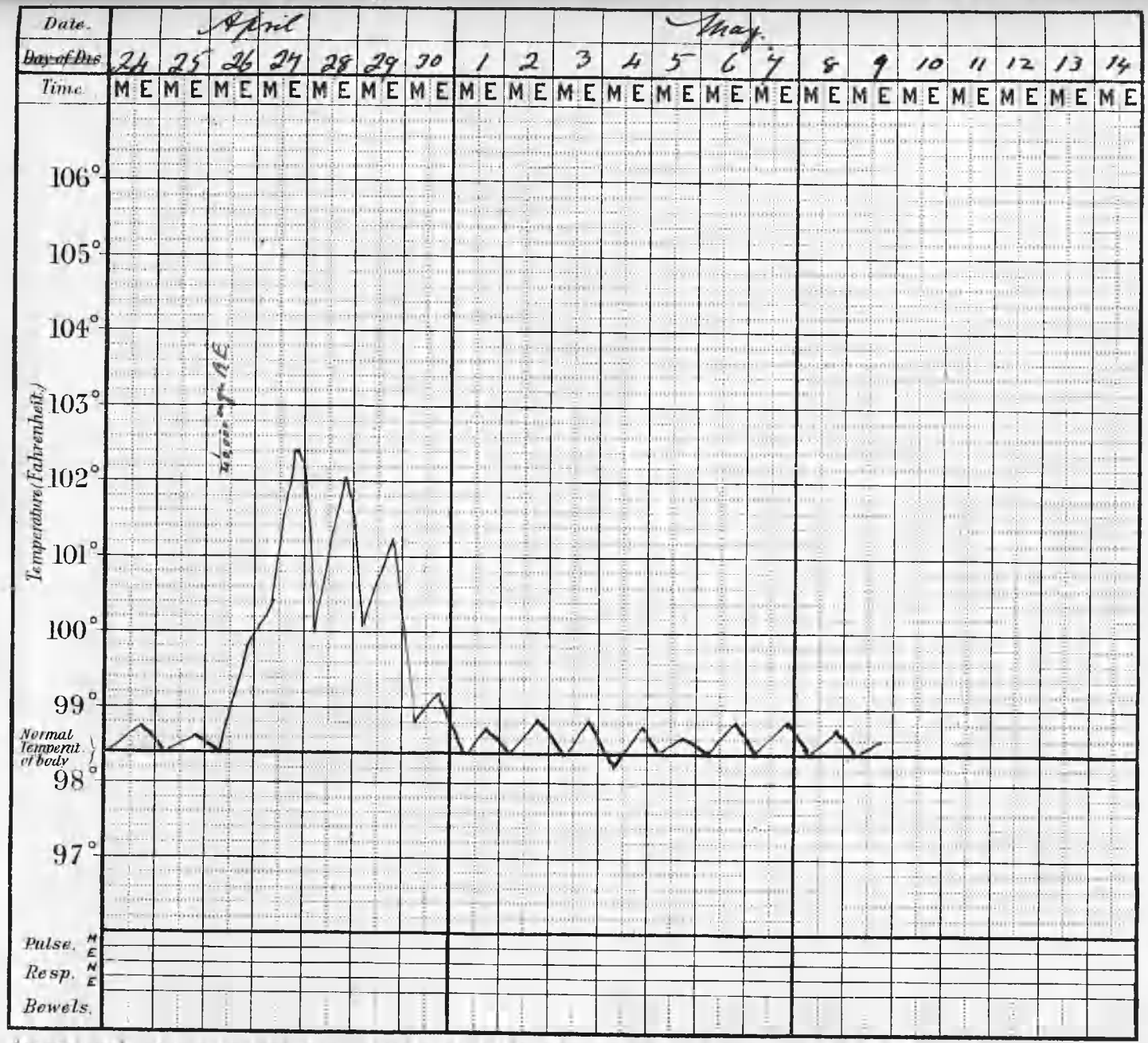
Notes of Case.

Diet, etc.



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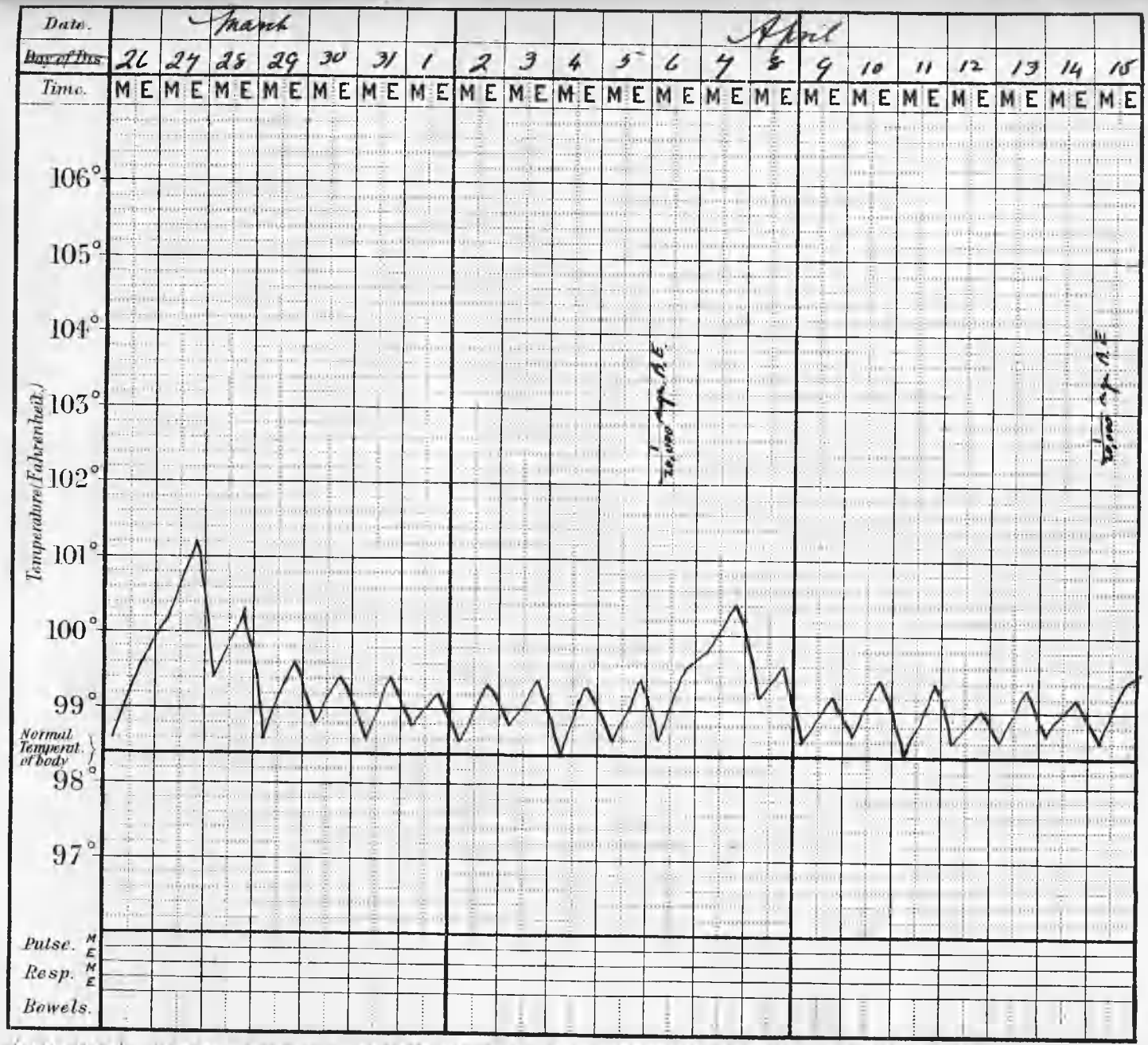
Notes of Case.

Diet, etc.



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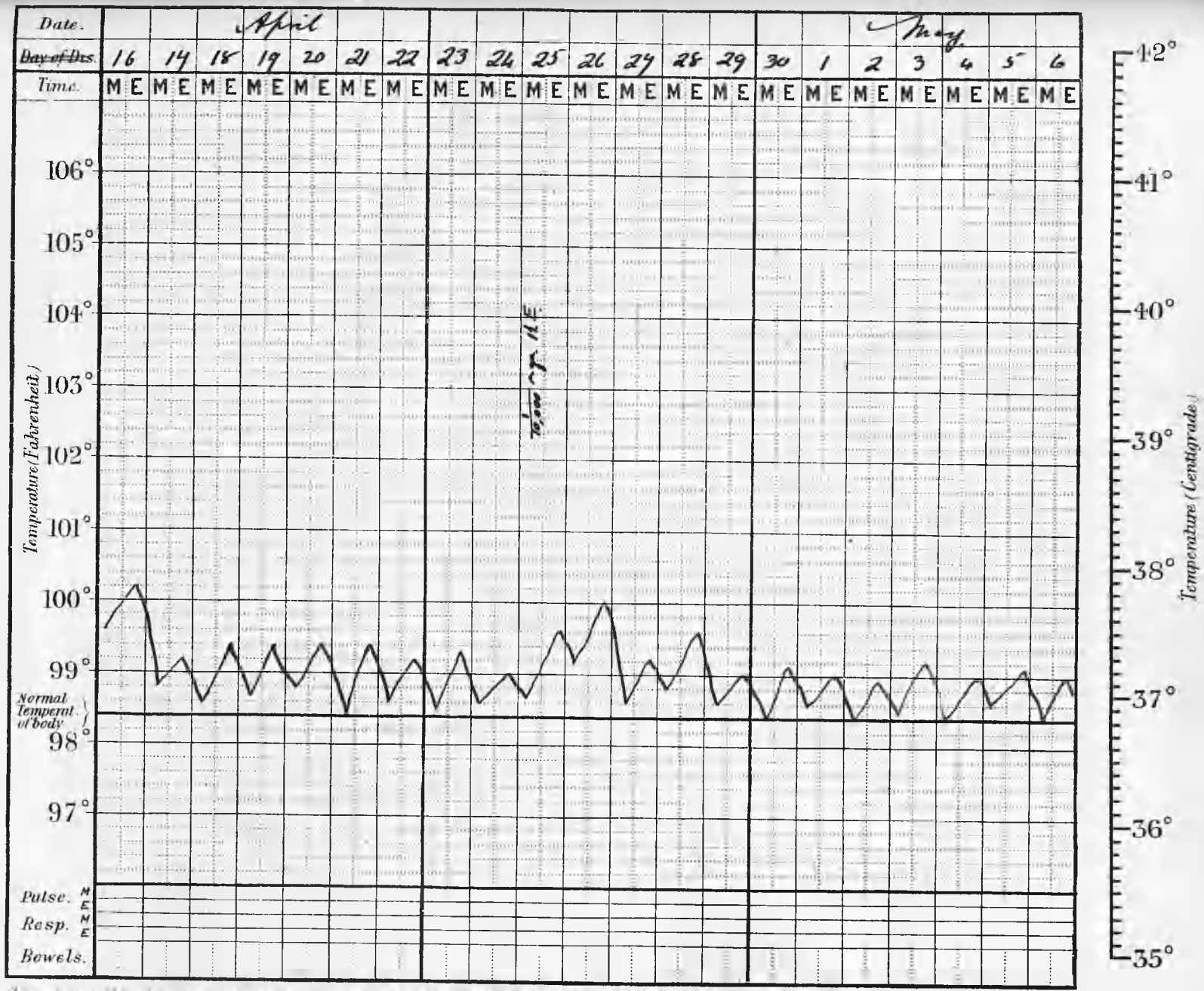
Notes of Case.

Diet, etc.



Result .....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE

Notes of Case.

Diet, etc.

Date.																									
~~Day of Dis.~~	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27				
Time.	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperat. of body

Pulse. M E N E

Resp. M E N E

Bowels.

42° 41° 40° 39° 38° 37° 36° 35°

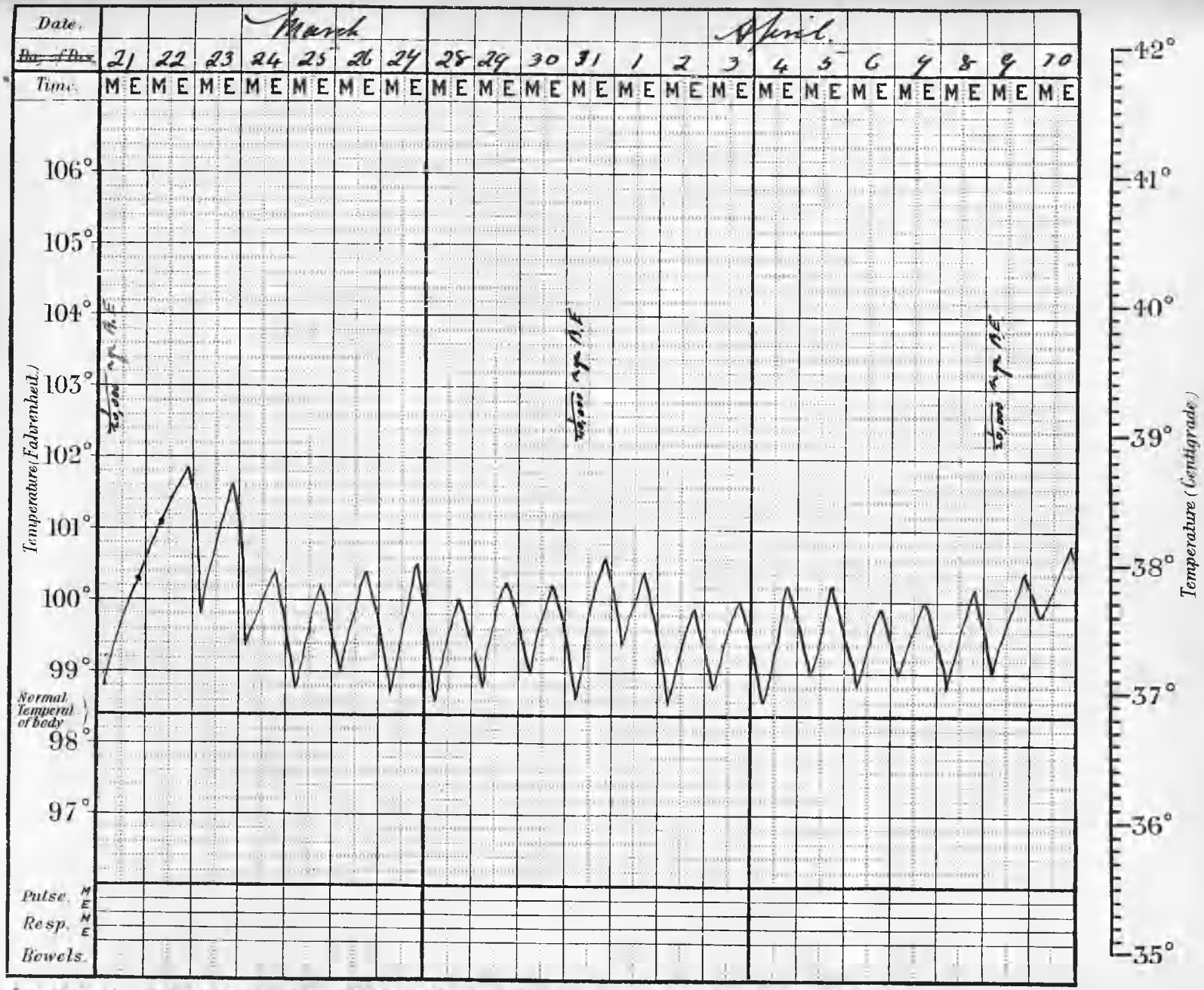
Temperature (Centigrade.)

Result .....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE

Notes of Case.

Diet, etc.



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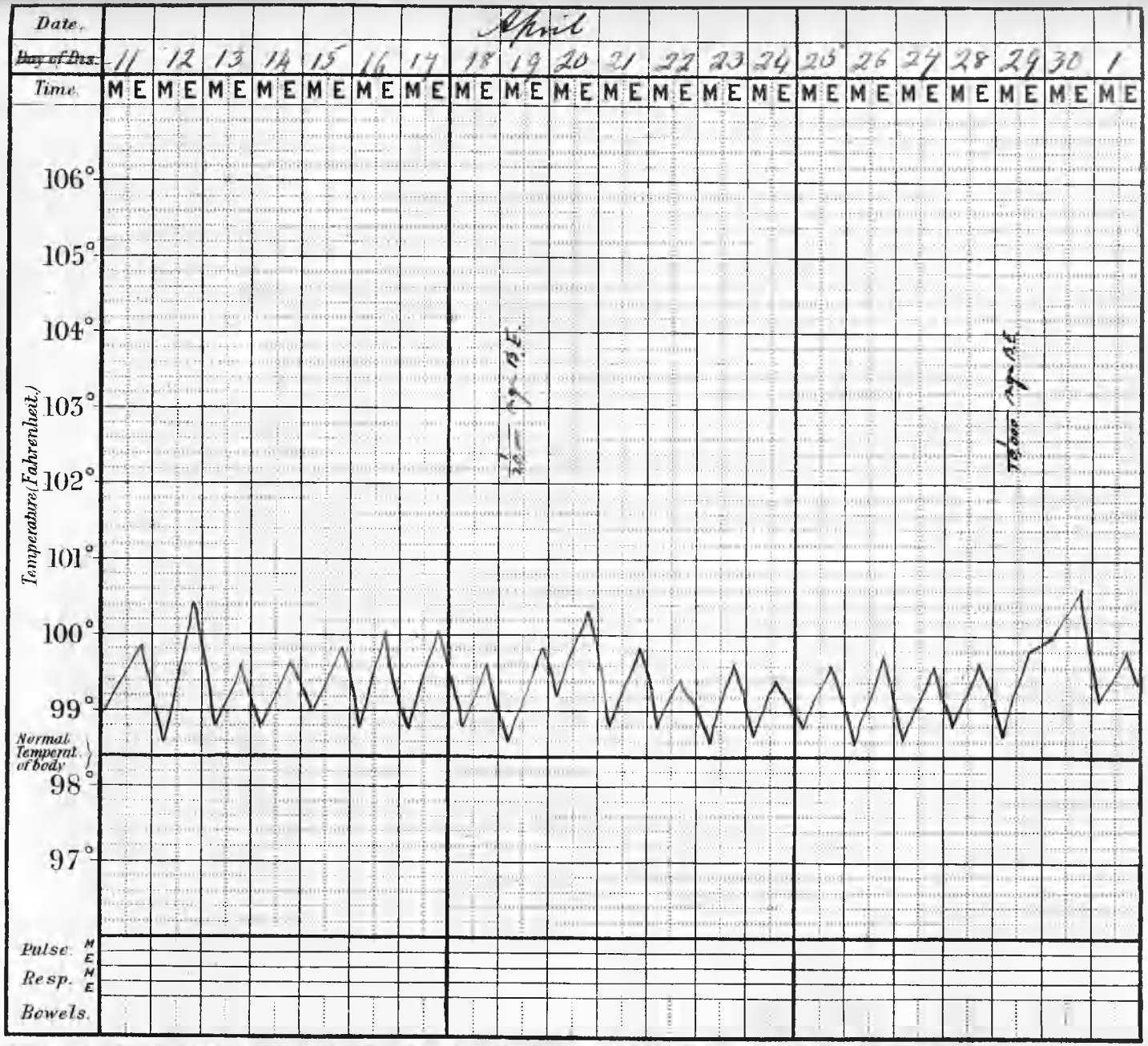
Notes of Case.

Diet, etc.



Result

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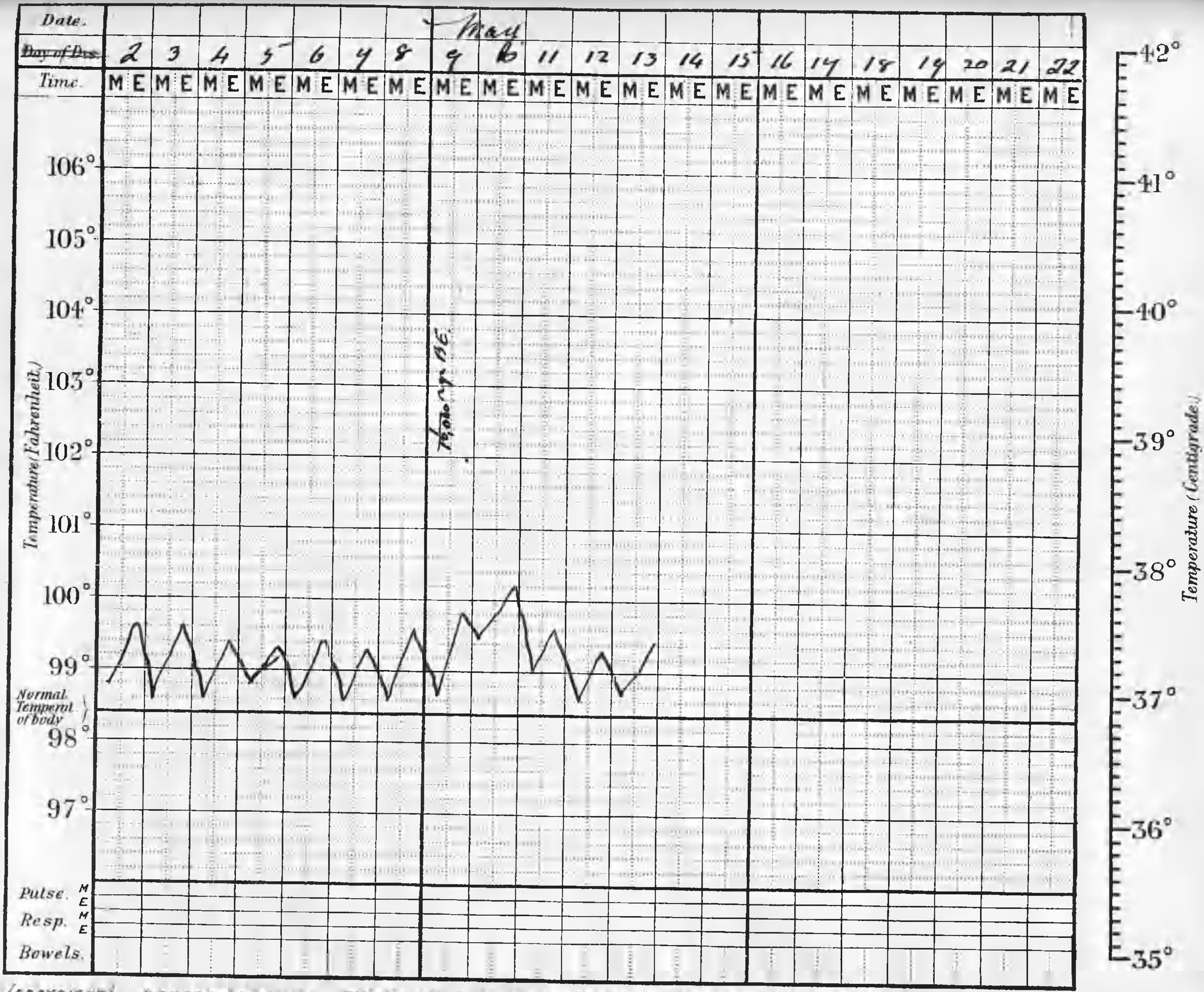
Notes of Case.

Diet, etc.



Result ....

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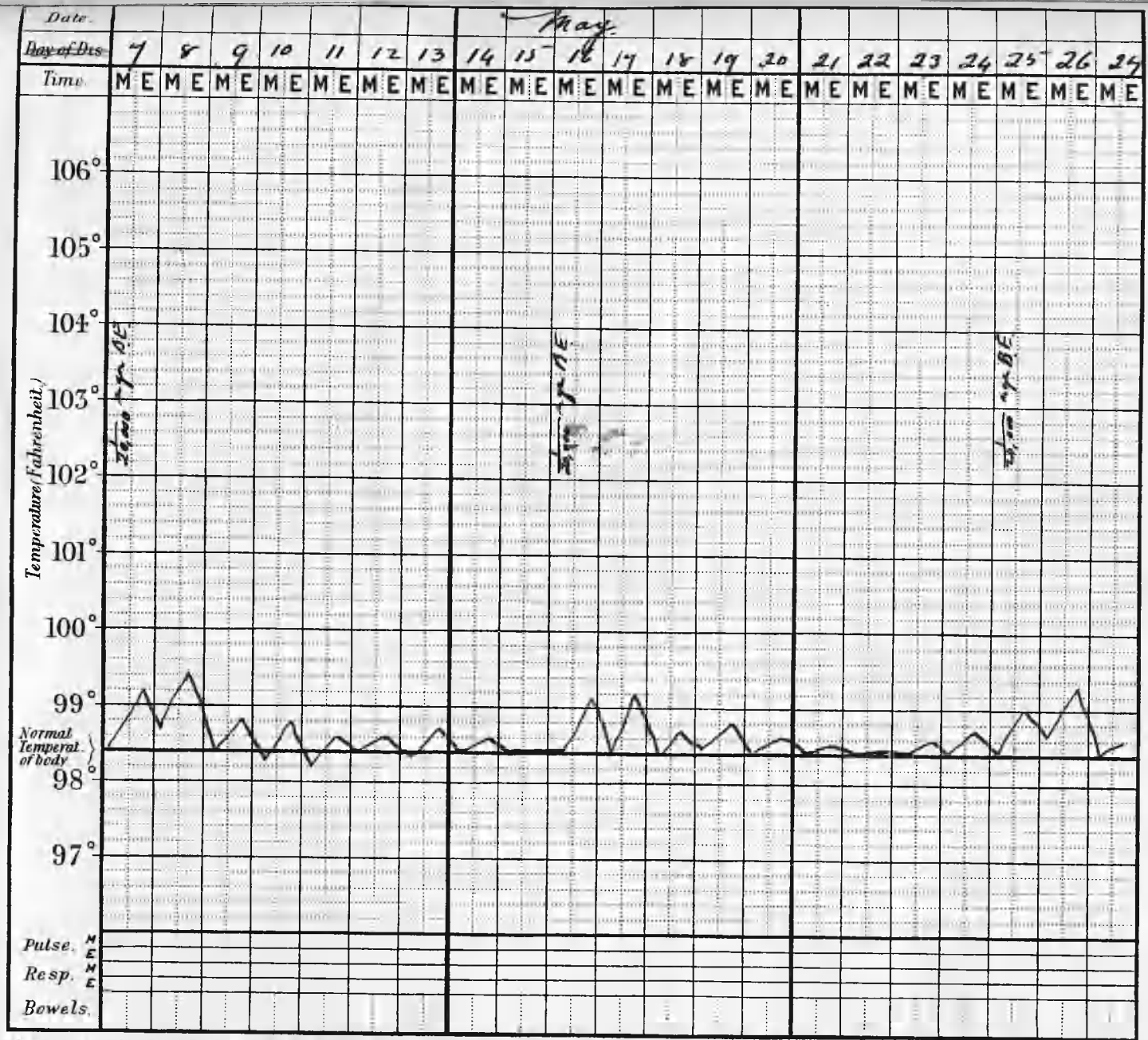
Notes of Case.

Diet, etc.

Result



 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Date.	March																	April			
Day of Dis.	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5
Time.	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

Temperature (Fahrenheit.)

106° 105° 104° 103° 102° 101° 100° 99° *Normal Temperat. of body* 98° 97°

Temperature (Centigrade.)

42° 41° 40° 39° 38° 37° 36° 35°

Pulse. M E N E

Resp. M E N E

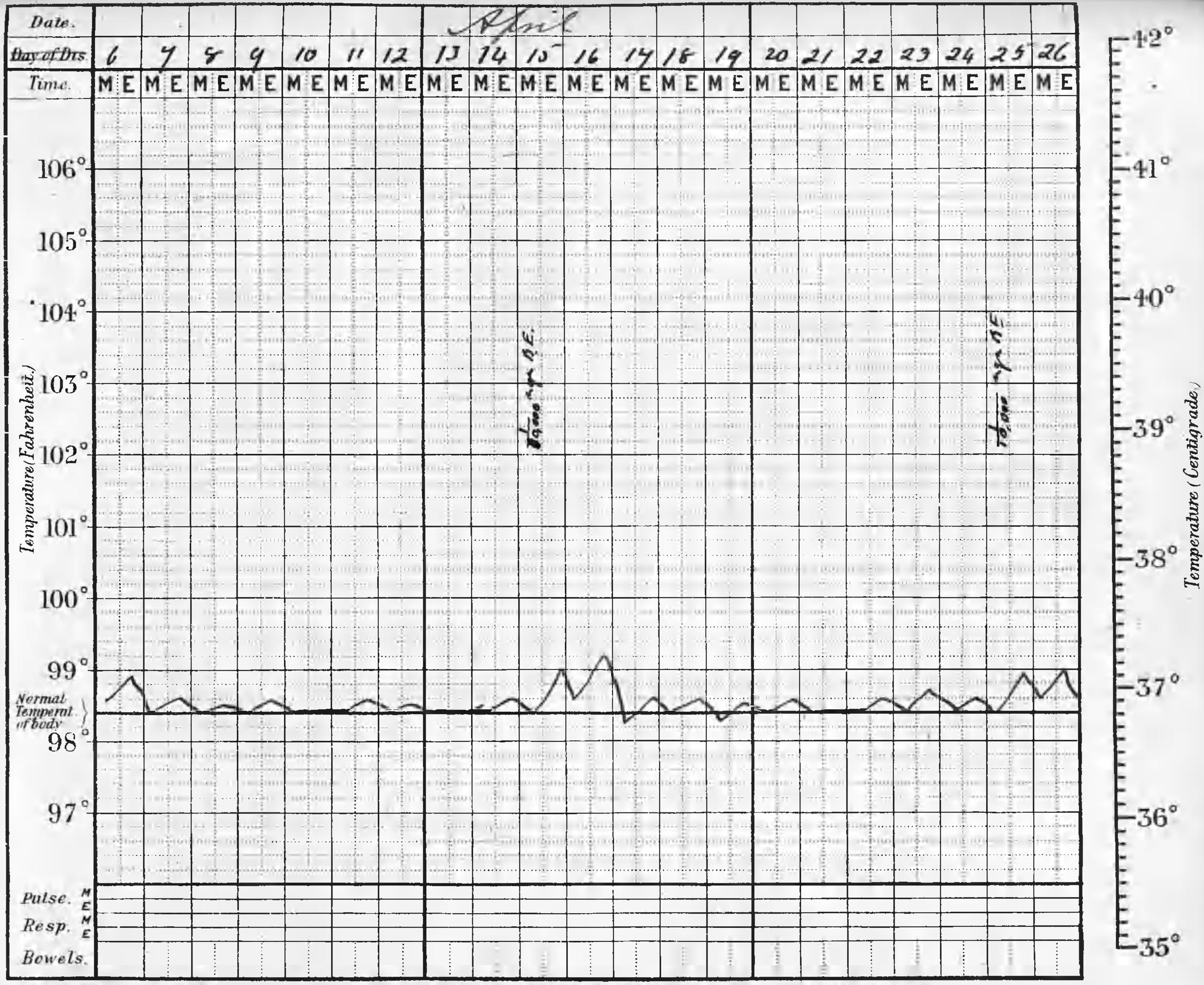
Bewels. M E N E

Result

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE

Notes of Case.

Diet, etc.



Result ....

 RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE.

Notes of Case.

Diet, etc.

Date																									
Day of Dis:	24		25		29		30		1		2		3		4		5		6		7		8		9
Time	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E

Temperature (Fahrenheit.)	Temperature (Centigrade)
106°	41°
105°	
104°	40°
103°	
102°	39°
101°	
100°	38°
99°	
Normal Temperat. of body 98°	37°
97°	36°
	35°

Date																									
Day of Dis:	10		11		12		13		14		15		16		17										
Time	M	E	M	E	M	E	M	E	M	E	M	E	M	E	M	E									

Pulse. M E
Resp. M E
Bowels.

Result .....

RULED ON BACK FOR RECORDING OBSERVATIONS ON URINE