THE RECENT WORK ON SCARLET FEVER

by

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PREFACE.

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It is very doubtful if even the most brilliant workers are completely independant. Ever so much more so must I acknowledge my indebtedness, and primarily to Dr.William Dow, the Medical Superintendent of Knightswood Hospital. His wide clinical knowledge was at my disposal and his never-failing interest was a source of enthusiasm when one's own became damped. I tender my thanks to the nursing staff for the necessary preparation and for their patience which at times must have been sorely tried; to Dr Buchanan of the Glasgow Public Health Laboratory for permission to consult his library and to Mr William Ogilvie, Chief technician, for the reproduction of the photographs and microphotographs; to Miss Grillo of the Glasgow School of Art for the water colours and lastly but by no means least, to Annie, our laboratory maid for the performance of a huge amount of extra work uncomplainingly, the number of tubes requiring cleaning reaching a gross or more a day for weeks on end.

W.A.H.

Sept., 1927.

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INTRODUCTION.

The work on which the following thesis is based was carried out at Knightswood Hospital, Anniesland, during the period 1924-27. The results are divided into three parts; firstly the resumé of the recent work on scarlet fever with the arguments for and against the different theories; secondly the original investigations which I myself have performed, comprising a study of several methods of identifying the so-called scarlatinal streptococcus, an account of the uses of the Dick toxin and a record of my experience with the antitoxin; and lastly the bibliography composed of all the references on the subject obtainable. With regard to this last section, some of the articles are out of reach owing to my linguistic limitations and others by reason of inaccessibility and therefore I have endeavoured to make good the deficiency by using the abstracts to be found in the more every-day periodicals. Part I is dependent, of course, on Part III as are many of the comparisons drawn in Part II. Each of the subsections of Part II is prefaced by a short index giving the sequence of subjects considered in the section. Appended are facsimiles of cards and other records to show the method of accumulating the data and also the temperature and pulse rate charts relating to the antitoxin section of Part II.

PART I.

SURVEY OF THE RECENT WORK ON SCARLET FEVER.

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SURVEY OF THE RECENT WORK ON SCARLET FEVER.

The etiology of Scarlet Fever is one of those subjects where the answer seems to be apparent but the proof is very difficult. Loeffler in 1884 noted the abundance of haemolytic streptococci in the throat in Scarlet Fever but it was Klein who put forward the theory that they were the cause of the disease. While investigating an epidemic of scarlatina that had been traced to a dairy farm, he found streptococci associated with a constitutional disease in the cows used. Others argued that the disease from which the cows really suffered was cowpox. In 1891 Kurth isolated a streptococcus which later Baginsky and Mervyn Gordon also held to be the causative agent. The last worker carried out a large series of sugar reactions and along with certain cultural peculiarities decided that together they were sufficient evidence for identifying the streptococcus isolated as being peculiar to scarlet fever. The claims of a diplococcus were supported first by Class in 1900 and later by Mair. They rest on their recovery from the throat in 87% of 1st week scarlet fever cases and the production of a disturbance resembling scarlet fever when cultures of them are injected into monkeys. Recently Italian workers describe a minute diplococcus found in the blood, urine and throats in the early days of the infection. Di Christina and Caronia are the two most associated with the work. They have gone the length of producing a vaccine which they claim gives immunity to scarlet fever. Endeavours to confirm the work of Di Christina and Caronia have been made more in Europe than elsewhere with very contradictory results. Some uphold their findings and detect uniformity with the Dick work/

work while others fail to discover any such organism. Döhle and later Arnato have described inclusion bodies in the polymorphonuclear leucocytes but their specificity has been denied by others.

To return to the claim of the haemolytic streptococcus, Moser in 1902 produced an antitoxin by injecting into a horse living streptococci and their broth arguing that if streptococci were the cause of scarlet fever, then one should be able to produce a curative serum. The strains he isolated were from cases of toxic scarlet fever. This serum was and still is, used with curative effect but its universal adoption dropped through owing to the variability of its potency. It was shown lately that such variability did occur but as no method of gauging the strength of the antitoxin was available, the potent batches of sera could not be separated off from the weak. Later Saochenko, a Russian investigator, in 1905 proved that Moser's serum contained both antitoxin and anti-bacterial substances and also that a potent toxin could be separated off from broth cultures of streptococci by filtration. Finally Gabritschewsky in 1907 produced a vaccine for preventive inoculation . A certain percentage of children inoculated with this vaccine developed an exanthem indistinguishable from scarlet fever but without desquemation, others had a sore throat while a few vomited. Those children who already had had scarlet fever showed very slight, if any, reactions. Second and later injections did not induce such severe reactions. Gabritschewsky considered that he had proved that the streptococcus was the cause of scarlet fever. All along the difficulty had been/

been to reproduce the disease in animals but Saochenko realised that negative results with animals did not negative the proof of the causal relationship. Gabritschewsky's vaccine is still used in Russia and workers maintain that it materially reduces the incidence of the disease during epidemics.

The more modern work on the subject dates from the discovery of Schultz and Charlton in 1918 that the intradermal injection of convalescent scarlet fever serum, into a scarlet fever rash, produced an area of blanching. They were under the impression that such blanching was the property of normal serum and that this property was lost when the person took scarlet fever but returned later in convalescence. It remained for Mair, 1923, in a masterly article on the subject, to formulate a theory which has been fully substantiated by later workers. He argued that the reaction was one between toxin and antitoxin and pointed out that the failure of the serum of a patient in the acute stage of scarlet fever to blanch a rash was not a change occurring at the onset of the disease but had been present previously. He also proved that the presence of such blanching power almost invariably followed on an attack of scarlet fever and postulated that where it was present without the person having had scarlet fever, it was probably an index of natural immunity. The credit of actually proving the causal relationship of the haemolytic streptococcus to scarlet fever must be given to the Dicks. They isolated from the septic finger of a nurse, a haemolytic streptococcus. In Oct. 1923, they swabbed the throats of five volunteers with pure cultures of the organism grown for four days in sheep's blood agar. Three remained well; one had a sore throat with a slight

rise/

rise of temperature but no rash, while the fifth developed definite scarlet fever. The filtrate from a broth culture, filtered through a Berkefeld candle, was sterile and had no effect on five volunteers. Four of those volunteers were inoculated with the unfiltered culture and one had malaise, sore throat, but no rash, one had a sore throat for one day, while two remained quite well. A fifth volunteer developed definite scarlet fever two days after inoculation. Here we have two cases of experimental scarlet fever probably caused by a haemolytic streptococcus or some closely allied organism which does not pass through a filter.

The next point was to elucidate why only two out of the ten volunteers developed scarlet fever. They supposed that it was due to a varying susceptibility and began to look about for a suitable index of susceptibility. This they found in what is now known as the Dick test. A small amount, .1 cc. of a diluted sterile filtrate 1-1000 in saline is injected into the skin of people with no history of having had scarlet fever gave inflammatory reactions in some. These reactions appeared in about 4-6 hours and reached their maximum size in 24 hours. In convalescent scarlet fever patients 96% gave a negative reaction while in those with no history of scarlet fever 50% gave a positive reaction. They also found that in two instances, people with positive reactions took scarlet fever after which their reaction became negative. The first strain of haemolytic streptococcus was a mannite-fermenter. The Dicks found that there were other scarlatinal streptococci which did not ferment mannite. On the inoculation of three volunteers, one negative to the intradermal test and two positive, with a culture of the non-mannite-fermenting strain, both positive test volunteers developed scarlet fever. The organisms, both in the case of the Mannite-fermenter and the non-mannite fermenter were recovered/

recovered in pure culture from the throats of the experimental cases. The Dicks then claimed that they had elucidated the etiology of Scarlet Fever.

Their further work consisted in the production of a method of preventive inoculation and of an antitoxin. The former they achieved by injecting small doses of toxin into susceptible individuals. Some developed all the signs and symptoms of Scarlet Fever but they quickly settled. (A similar state of affairs we have seen happened with Gabritschewsky's vaccine). The Dick test in those cases became negative or less positive within ten days. The antitoxin was produced by injecting subcutaneously into horses, gradually increasing doses of the toxic filtrate. The serum was withdrawn and tested, by the neutralization of a skin test dose of Dick toxin, for potency. Before being used curatively, it was concentrated. This concentrated antitoxin produced a beneficial effect on the course of severe scarlet fever and particularly so in toxic scarlatina. It also diminished the incidence of complications.

Besides the Dicks, many other workers were investigating the possibility of the haemolytic streptococci being the cause of Scarlet Fever. Dochez, Avery and Lancefield in 1919 considered that the streptococci found in the throat in scarlet fever formed one biological group. A similar result was arrived at by Bliss, Tunnicliff, Gordon and Stevens, all much about the same time. The methods used were those of agglutination, agglutinin absorption and opsonification. Dochez in 1921 maintained that he had produced a disease resembling scarlet fever in guinea-pigs by inoculation with the streptococcus isolated by him. He further produced an antitoxin which

he tested for potency by determining its capacity to blanch the rash in scarlet fever, i.e. to give the Schultz-Charlton phenomenon. Given therapeutically this antitoxin caused a rapid defervescence of the disease. He immunized horses by injecting subcutaneously melted agar and allowing it to solidify. Then he inoculated the central part of the agar with the streptococcus so that the toxins produced would filter through into the surrounding tissue. The idea was not quite successful as the bacteria grew to the surface and caused an abscess to form with subsequent sloughing.

There are, then, three sections to the modern investigation of scarlet fever (1) methods of recognising the scarlatinal streptococcus, (2) the value and uses of the Dick Toxin, and (3) the titration and value of the antitoxin.

Several names have already been mentioned with regard to the agglutination and agglutinin absorption tests. Further work on the subject by Smith, James, Griffith and others, tend to show that the scarlatinal streptococci cannot be clumped together into one biological group. There are several types although the majority are included in two. There is also, to a slight extent, some serological relationship between the scarlatinal streptococci and those found in other diseases. The opsonic method of identifying the streptococcus is associated with the name of Ruth Tunnicliff. She uses concentrated human convalescent serum,and serum from sheep and from rabbits. She has found in the immunization of animals, a tendency for the serum to lose its specificity if too frequent or too big immunizing doses are given. She also found some batches of serum to lose their agglutinating power rapidly on standing. Rosenow has

elaborated/

elaborated a precipitin reaction for scarlet fever streptococci similar to the one advocated by him for meningococci and other organisms. At first he used the serum produced by a horse that had had very heavy inoculations of streptococci. Later he found that equally good results were to be had with the antitoxin used curatively. The Dicks suggested that the production of toxin could be applied as a means of identifying the causal organism and recommend the testing of the organism for its capacity to produce a toxin capable of giving a reaction in high dilutions in Dick positives and also of being completely neutralized by the specific antitoxin. McLachlan found that all the streptococci isolated by him from scarlet fever throats produced a toxin giving the characteristic reaction in high dilution in Dick positive reactors. Most of these toxins were neutralised by the specific antitoxin but not all of them. He also found streptococci from other sources could produce a toxin but the reactions in a susceptible person were seldom so strong as with the toxin of the true organism. Lastly some of the non-scarlatinal strains produced reactions in Dick's negatives as well as in Dick's positives.

The use of animals has been extensively tried with little success. Goats and pigs sometimes give a reaction to Dick toxin but the results are not constant. Mackie and McLachlan endeavoured to sensitize guineapigs to culture filtrates by injecting living scarlatinal organisms. The results were not promising. The reactions to the toxic filtrates were only elicited in high concentration and often there was no neutralisation when mixed with the specific antitoxin. Some non-scarlatinal strains gave as good reactions as the specific organism.

The Dick toxin has two main uses, for testing for susceptibility and for the active immunization

of susceptibles. It is now practically accepted that a negative Dick reaction denotes in susceptibility to the exanthem produced by the scarlatinal streptococcus. But it does not denote freedom from possibility of a throat infection with that organism. In other words it shows antitoxic immunity but not antibacterial immunity. It has been argued that the Dick toxin is not a true toxin and that the Dick reaction is a protein reaction. On the other hand there is evidence that it is not an anaphylactic reaction. The highest percentage of positives in human beings with no history of scarlet fever is found between the second and fourth years of life. This percentage is higher in the middle and upper classes than in the poorer class. The answer to this is said to be the chance of an attack of mild scarlet fever being missed among the poor. The percentage is higher among those who live in the country than in those who live in towns. The curve of age susceptibility follows closely that of the age incidence. In the testing of scarlet fever patients, it has been found that between 80 to 96% of all cases, if tested within the first three days of the disease, give a positive reaction. After this time, the percentage positive rapidly drops until in the fourth week of convalescence it has reached 18% and in the later days may drop to 4%. Why some should remain positive after having had a definite attack of scarlet fever is debatable. Perhaps the particular strain with which they are infected is different from that producing the test toxin or the immunity which they gained was quickly lost.

In the active immunization of susceptibles, it is usual to speak of the dosage in terms of skin test doses, one skin test dose being the amount of toxin giving a positive reaction in the early days of scarlet fever and a negative in convalescence. A thousand skin test doses of toxin injected into a susceptible person will produce the "scarlatinoid syndrome", the punctuate rash. headache, vomiting and perhaps sore/

sore throat. To prevent such an eventuality, the first dose should be less than the 1000, e.g. 250 and the doses given in increasing order 500, 1000, 2500, 5000 at weekly intervals. Some give 500, 5000 and 30,000 without finding very much general disturbance. Others use detoxicated toxins as anatoxin, toxin altered by formalin or as toxin diluted in 2% sodium ricinoleate. One writer advises one dose of 3000 skin test doses of detoxicated toxin in cases of emergency as in an epidemic. He claims that 70% of the Dick reactions were subsequently negative when retested eight days after injection and 97% negative twenty one days after injection. In active immunization, it is usual to find that strongly positive reactors are difficult to immunize and if a negative reaction is obtained it is of comparatively short duration. If larger immunizing doses are given, the immunity is likely to last longer. Active immunity lasts from eight months to six years varying with the individual.

The assessing the potency of the antitoxin is one of the most important items. It is on this score that Moser's serum failed. There are three methods used, (1) the ability of the antitoxin to produce the Schultz-Charlton reaction, (2) the neutralisation of the Dick's test toxin and (3) the reversal of a Dick positive result when antitoxin is injected into a susceptible person, i.e. the production of passive immunity. The first method was adopted by Dochez, the other two by the Dicks. The injection of 5 c.c. of a good antitoxin should change a Dick positive to a Dick negative reaction in 24 hours. Another method has been elaborated by Parish and Okell. They use a rabbit and find the protective value of the antitoxin against a lethal dose of streptococci injected intravenously. The results give promise of becoming a preliminary method at least, although the method is a little rough.

The antitoxin is used prophylactically and curatively./

curatively. For protection it is generally accepted that enough antitoxin to neutralize 125,000 skin test doses of toxin is necessary. The immunity develops within 24 hours and lasts from seven to ten days. Curatively, enough to neutralize 500,000 skin test doses is required, repeated in 24 hours if necessary. It usually brings down the temperature, diminishes the rash, and in some instances diminishes the incidence of complications. It gives most striking results in toxic cases when given early but has little or no effect on septic scarlatina. The third use of the antitoxin is for diagnosis - the Schultz-Charlton test. Blanching is obtained in the majority of early scarlet fever rashes but not in all. The exceptions are still inexplicable. The blanching appears within eight hours of injection but the maximum effect is not seen until the twenty-fourth hour. Normal horse serum does not cause this effect and scarlatinal serum does not blanch any other type of rash.

The modern conception of scarlet fever is one analogous to diphtheria. The seat of the infection is in the throat and a toxin is elaborated that causes most of the symptoms. It is rare for streptococci to be found in the bloodstream of scarlet fever patients except when almost moribund. The toxin causes the rash, headache, sickness and vomiting but the organic lesions, the ulceration of the throat, the otitis media and the septic complications are due to the organism. It is still possible that the streptococcus isolated is not the causal organism and that the disease is similar to swine erysipelas as suggested by R.A.O'Brian. But the case for the haemolytic streptococcus is very strong.

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PART II.

Streptococcus Scarlatinae.

The Dick Toxin.

The Antitoxin.

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STREPTOCOCCUS SCARLATINAE.

Culture media and methods used.

The results of the cultural and biological tests.

Toxin testing and neutralization.

The results of the serological tests.

Discussion.

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Streptococcus Scarlatinae.

Any investigation into the subject of the pathogenic streptococci impresses one with the complexity of the subject and the paucity of one's knowledge. Here an endeavour was made to narrow down the work to an inquiry into the possibility of identifying the streptococcus scarlatinae by its toxigenic properties and its behaviour towards specific agglutinating sera.

The medium used was almost wholly Hartley's modification of Douglas's trypsinised broth. This medium was selected as it was expected to give a high toxin production and to be suitable for the growth of streptococci. The medium was originally devised for the production of a high grade diphtheria toxin as it was found that the raising of the H-ion concentration during the first days of growth was reduced to a minimum. Cole and Onslow's pancreatic extract is necessary as Allen and Hanbury's liquor Trypsin Co. contains glycerol. The authors remark that the filtration of extracts is a slow process. It is a very slow process. It took over a week to filter 28 ozs. The subsequent addition of concentrated hydrochloric acid causes a cloudy precipitate to form which can be filtered off but even then further precipitation occurred in the fluid prepared.

Several points were noted in the making of the media. 1500 cc. of broth were made up at the one time requiring a 2-litre flask. In the preliminary heating of the infusion to 80°C it required an hour in the steamer at 90°C to bring the temperature of fluid uniformly to the same height. The length of time and the degree of heat used both here and subsequently in the process determined the exact tint of the medium, from a pale yellow to a definite brown. The broth after filtration and adjusting is seldom clear and on heating it in the steamer for 1 hour a brown flocculent precipitate/

precipitate forms. If this is filtered through sterile filter paper in a sterile funnel into a sterile receiver, the fluid can be kept for weeks without the growth of moulds. It was found convenient to make the broth in bulk and retain it so after the second filtration. When required it was distributed into sterile tubes or flasks and autoclaved by raising the steam pressure slowly until 10 lbs. per sq. inch was reached when the heat was turned off and the steriliser allowed to cool. The pH was adjusted by using phenol red as an indicator after the fashion advised in the Medical Research Council's pamphlet on the subject. The result was checked by using a Universal indicator. In the sterilization of the media, it was found that heating to 100°C, even for an hour, did not make any appreciable change in the pH, but that the small amount of pressure used in the autoclaving reduced the pH from 8 to 7.8. When the pressure was raised higher and continued for a longer period the reaction dropped from pH8 to pH 7.6. When the final reaction required was pH8, the allowance had to be made for the change on autoclaving.

The solid media used was Hartley's broth with the addition of 2% agar and adjusted to pH 7.8. This was found to give an excellent growth of almost all the strains of streptococci isolated. This medium is hereafter called solid Hartley. It was here that it was noticed that the longer the heat was applied the darker became the media. In one batch of solid media for some unknown reason no growth whatever was obtained. When transferred on to fluid media, all strains grew abundantly and the only abnormality detected was that the reaction of the solid media was pH8 instead of pH7.8. But this error caused the death of almost half the cultures as solid media was the media used for carrying them on. A subsequent batch of solid Hartley adjusted/

adjusted to pH 7.8 and made from the same broth as the former, gave excellent growths. But thenceforth the cultures were carried on in broth tubes. Another calamity of the same nature occurred later but fortunately at the end of the experiments. About 4½ litres of Hartley's broth was made up at the one time. It was distributed into tubes and sterilized. After inoculation and incubation, not the slightest sign of growth was apparent in any of the three dozen tubes used. On the supposition that the stock cultures had died out another set of tubes was inoculated; but again no growth although three tubes of the old media which were used as controls showed abundant growth. Something had gone wrong with the Hartley's broth. The reaction was tested and checked and found to be still pH8 and the only physical difference between the old and the new media was that the former had a specific gravity of 1.0126 while that of the latter was 1.009 using a Westphal balance. In using this instrument it was found that even a slight change of temperature of the fluid to be examined from the standard 15°C made a difference in the last two figures of the result. The horseflesh used first came under suspicion as it had been procured early in the week and might not have been fresh. Media made with a second supply of horseflesh and a batch made from cow's flesh both gave negative results on inoculation. On the possibility that the pancreatic extract had lost its action, as the Biuret reaction for the old media showed a more complete digestion than the new, media was made with Allen & Hanbury's Liq.Trypsin Co. But again no growth and it was not until New N/I NaOH solution was made that anything like the former growth of streptococci was obtained. What had happened to the stock solution of caustic soda can only be a matter for conjecture. That the new medium had an inhibitory effect on the organisms was proved/

proved by making up mixtures in varying proportions, of the old and new broth. Growth was only obtained when at least a half of the medium was from the old batch.

Blood plates were made in the style recommended by Gordon. About 7 cc. of plain agar was first poured into the plate and allowed to solidify. Then the same amount of blood agar was added, so that a thin layer of the latter was obtained on a basis of plain agar. Here the blood agar was made by adding one cubic centimetre of defibrinated rabbit's blood to 14 c.c. of melted solid Hartley. This was sufficient for two bloodagar layers. To conserve the amount of rabbit's blood required, the same idea was developed in regard to tubes. A rather wide tube was used, 6" x $\frac{3}{4}$",and only a short slope of plain agar formed. A 17 c.c. tube of solid Hartley was melted and the temperature brought down to 50^{0}C. The agar slopes were arranged in batches of eight. The difficulty was to insert 2 c.c. of blood agar on to each plain agar slope with the least risk of contamination and without the pipette becoming blocked. The former disappeared with practice and it was rare to find a tube contaminated among the later batches. Washing out the pipette with boiling water, a fish kettle sterilizer being used, eliminated the latter. The sterilizer was half-filled with water and kept boiling, with the lid off, all the time. The melted "solid" Hartley was placed in a beaker of water at 50^{0}C at the left hand while the agar slopes were at the right. One cubic centimetre of defibrinated blood was blown into the melted agar and intimately mixed. A 2 c.c. pipette, to which a short piece of rubber tubing and a glass mouth-piece were attached, was sterilized by boiling in the fish-kettle for five minutes. The pipette was raised half out of the boiling water and the rubber tubing and mouth-piece allowed to hang over the side until cool.

Then/

Then, while the pipette was still hot, two cubic centimetres of blood agar were withdrawn from the left hand tube and as quickly as possible transferred to one of the sloped agar tubes. The cotton wool stoppers were replaced and the pipette rinsed out three times with boiling water, then allowed to lie in the sterilizer. The sloped agar tube was now inclined so that the blood agar formed a thin layer on the surface. When solid, the tubes were incubated for 24 hours to make sure of their sterility. The process was first tried with one cubic centimetre of blood agar but that was found insufficient to give a satisfactory layer. The supply of blood agar requires to be kept at a higher temperature than usual to give one time to carry out the necessary manoeuvres. It makes no difference to the colour of the media although the tubes do not keep so well as plates made with blood agar at 45°C. It is advisable to pour off any condensation water in the plain agar slopes as it is liable to prevent the formation of a perfectly solid blood agar layer. Washing out the pipette thrice with boiling water is sufficient to clear out any blood agar left clinging to the inside. An assistant is unnecessary. One can obtain eight blood tubes from one cubic centimetre of defibrinated blood, a material saving in the testing for haemolysis. These tubes were used to find out if a culture still retained its haemolytic property after frequent subculturing. They can also be used for the separation of haemolytic organisms from a throat swab but all the primary isolations in the subsequent work were carried out on blood plates.

Swabs were taken from the throats of the selected cases, mostly definite scarlet fever patients in the early days of the disease, but a few non-scarlatinal patients. The tonsils and peritonsillar areas were the sites rubbed. The cotton wool tip was inserted into a small sterile test-tube (3" x ½") with 2 c.c. of saline and the wool massaged against the side of the tube to procure as thorough a washing as possible. The resulting emulsion varied in density according to the amount of exudate on the swab. The necessary quantity, one, two or three loopfuls as the case might be, were transferred to a blood agar plate and spread evenly over the surface with a spreader.

After 18 to 24 hours incubation at 37°C, the plates were examined for haemolytic colonies and a sample of each was stained by Gram's method and its nature determined. It was usual to take four of the colonies with the clearest haemolytic rings at the first search and if none were streptococcal, another four were sampled. When all of the first four colonies were found to be streptococci, that one giving the most typical picture, morphologically and by staining, was selected as the stock strain. It probably would have been better if two at least of the streptococcal colonies were subcultured from each plate as done by other workers. It would have, to a certain extent, eliminated the accusation that the particular colony selected was not that of the causative organism.

A tube of Hartley's broth was inoculated from the selected colony and incubated overnight. The growth was examined microscopically for purity and subcultured on to a blood tube. One of the resultant haemolytic colonies was again put through Hartley's broth, this time the incubation being for four days. After the first twenty four hours, the growth was examined microscopically and a tube of solid Hartley inoculated. This tube, on incubation, gave the stock culture. The biggest problem was keeping the different/

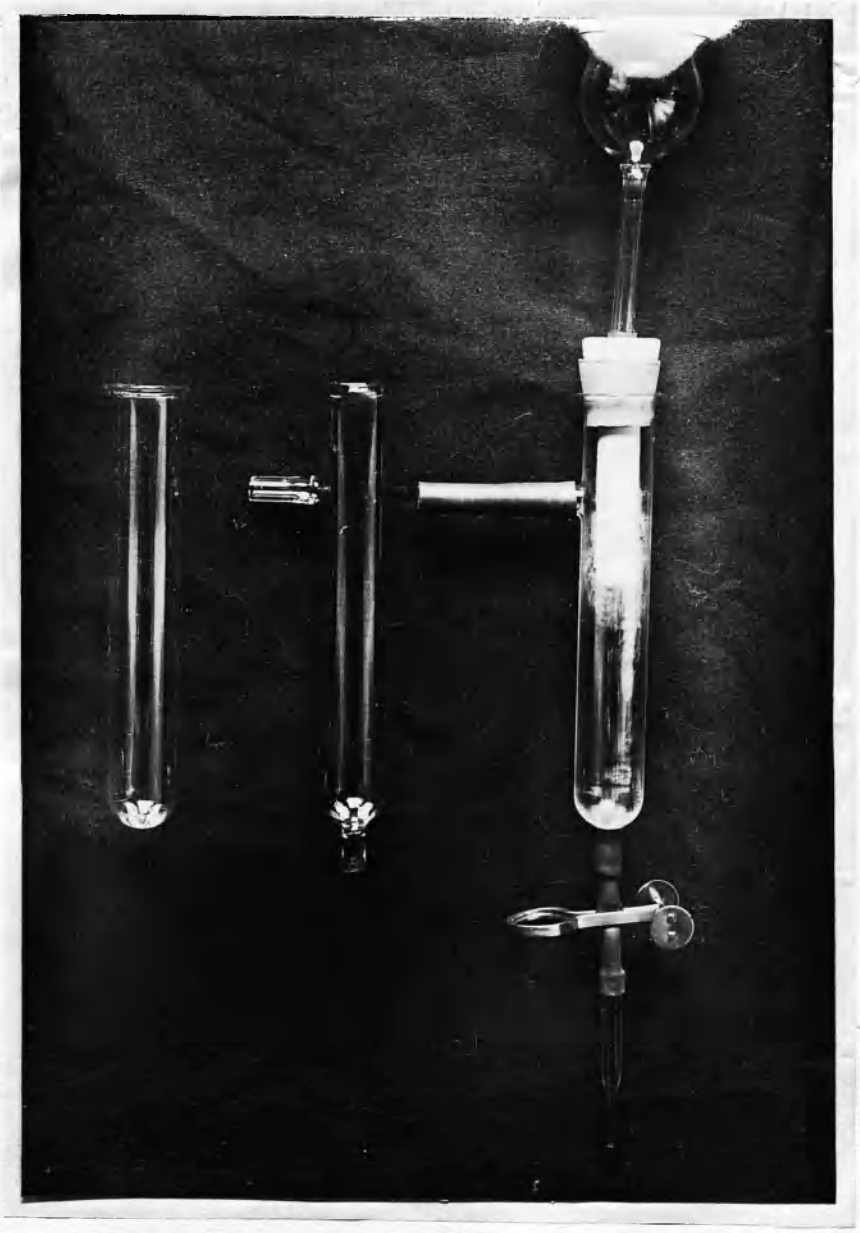
PHOTOGRAPH I.

The stages in the manufacture of the filtration apparatus.

(a) The test-tube.

(b) with side and end stems added.

(c) the completed filter.



different stock strains alive. No easy method was discovered. The growth on solidified serum was too scanty to trust. Our ice chest was reliable between 4 and 8°C but such temperatures as used by Smith of Aberdeen were quite beyond our reach. Repeated subculturing was required and it is not to be wondered at that sooner or later some would "fall by the wayside." At first solid Hartley was the media used as it showed up the characters of the colonies and it was easy to spot any contamination. But when this media went wrong, all future subcultures were made in Hartley's broth with occasional subculturing on to solid Hartley to show up the character of the growth. When solid Hartley was used, subculturing was required every seven to ten days and even then it was not always easy to keep them alive. With Hartley's broth, on the other hand, the cultures remained alive for fourteen days at least and in many instances for twenty-one days. In both instances, the inoculated tubes were incubated for 24 hours, then left the rest of the time in a cool place, out of the bright light.

To return to the broth culture that has been incubated for four days, this culture was allowed to stand for two days and then filtered through a Maasen filter. Allowing the culture to stand gives time for the growth to sediment and if only the supernatant fluid is filtered, there is much less clogging up of the pores of the filter. The type of apparatus used is illustrated in photograph No.1. It is a modification of Macleod's apparatus and has cheapness and simplicity to recommend it. Two short glass stems are added to a thick walled 5" x $\frac{3}{4}$" test tube. To the lower stem is attached a piece of thin-walled rubber tubing with

a/

a short piece of glass tube drawn to a point as in a pipette. To the upper stem is attached two inches of rubber tubing somewhat thicker than that for the lower stem. A 70 x 15 m.m. Maasen filter is selected and fitted with a rubber collar so that it fits the neck of the converted test-tube. A 5/8" rubber cork with a sufficient aperture bored in it is all that is necessary. The thistle funnel was a later addition. It was added to obviate the difficulty of filling the filter without some of the fluid running over the top. At the same time, the small capacity of the filter meant that only the first charge was likely to be clear as when the supply tube reassumed the upright position, the sediment was stirred up. The funnel is attached to the filter by fitting the end with a narrow band of thin rubber tubing and screwing it into the aperture of the filter. It will be found to fit exactly and make a tight joint.

Sterilization is effected by placing the whole apparatus upright in a 600 c.c. Erlenmeyer flask in the autoclave. The side stem prevents the tube slipping into the flask. The funnel should be stoppered with cotton wool and the filter loosened before the steam is turned on. Exposure to steam at 20 lbs. pressure for fifteen minutes suffices. Immediately on removing from the autoclave, both rubber connections should be occluded by spring clips similar to that illustrated in the photo as applied to the lower tube. From time to time it was necessary to heat the filters to redness to burn away organic matter filling up the pores. Only once did a filter break and then it was almost certain that it had been cracked as the filtrates from that particular filter were not sterile. The suction was supplied by a water pump. Glass connections were used instead of thick walled tubing and only two rubber joints were necessary, one at the side stem of the filter (illustrated) and one

connecting/

connecting the glass tubing to the pump. In this way there was no difficulty due to collapse of the system. Several of these filters were used at the one time. It was possible to fill up the thistle funnel with the supernatant fluid from a broth culture, exhaust all the air from the receiver, clip off the side tube and allow filtration to proceed without further suction being necessary. A few minutes' suction from each apparatus set them all agoing. The amount of broth to be filtered, about 8 c.c.will occupy just one third the capacity of the receiver and can be run off when the process is finished. Thin walled tubing is best in connecting the lower stem to the glass pipette as in filtration, it collapses and forms an additional help in making the apparatus air tight.

Each filtrate, which will be called toxin, although some did not contain toxin, as it was prepared, was incubated at 37°C. for 24 hours as a test of sterility. In fluids with a known toxin content, this procedure did not influence the amount in the slightest. If sterile, the toxins were stored in the ice-chest until an opportunity arose for testing them. At first on the assumption that they would behave as the standard (streptococcus scarlatinae Sherman procured from the National Collection of Type Cultures) the toxins were prepared by incubation of the inoculated broth for twenty-four hours only. But it was found that when one came to test them, the toxin content was very small and the first dozen had to be made anew by inoculation of broth tubes from the stock cultures (in most of them, more than a month after isolation) and incubation for four days. In the last five strains, the toxin was prepared according to the method of Mackie. He argued that as heating for an hour at 56°C did not in any way destroy the toxin present in a broth, one might sterilize a fluid by exposure to a temperature of 56°C for/

for an hour without diminishing the amount of toxin. In that way, the tedious business of filtration is avoided. The last five broth cultures, then, were heated in a water bath at 56°C. for an hour, the fluid centrifuged in sterile tubes and the resultant supernatant fluid preserved as the toxin. No disinfectant was added to any of the toxins prepared.

Each strain was tested for the solubility and action on mannite and raffinose. The bile solubility test was carried out by the exposure of a fixed film of the culture to the action of a two per cent. solution of sodium taurocholate for fifteen minutes. The bile solution was then washed off, the films stained by Gram's method and examined microscopically. The sugar media was a 2% peptone broth with 1% of the sugar and 5% of ascitic fluid or sterile horse serum added, using acid fuchsin as the indicator. The tubes were read after two days incubation and again after seven days.

As regards the agglutination and agglutinin absorption experiments, the methods of Gordon and of Smith of Aberdeen were followed closely with very slight modification. The type organism was the streptococcus scarlatinae Sherman, a culture of which was obtained from the National Collection, Lister Institute. This organism is referred to as SIII in the results as it was with the third sample that most of the work was done. Rabbits were the animals used. Intravenous injection of at first dead organisms and later of living organisms was carried out over a period of three months with weekly intervals between the injections except the last four which were at fortnightly intervals. The initial dose was 500 millions particles and it was gradually increased to 2000 millions. Then living organisms were used starting with 50 millions and rising to 1000 millions. By such gradual dosage and wide spacing a titre of 1-1600 was obtained. In the case of the second type serum 81-3 (exact history referred to later) the time at one's disposal was limited and the immunization was more rapid with a consequently lower

titre/

titre . The doses were given every second day for the first fortnight and every three days for the second fortnight, the dosage being the same as in the other type. The titre of this serum was only 1-400. Difficulty was experienced at first in the intravenous injection of rabbits but as time went on, one became expert in striking the vein. Following the first two injections, the veins used became thrombosed but that was probably due to injury of the vessel wall by the point of the needle.

In both methods of serological testing, a heavy growth of streptococci is required. In all cases Hartley's broth was used but in tubes containing 17 c.c. of media and not in flasks as recommended by one author or on plates as recommended by the other. Using flasks containing 50 c.c. of broth only a scanty growth was obtained while the same organism in the same broth but distributed in tubes grew abundantly. This phenomenon has been encountered by other workers in the instance of pneumococci. The absorption tests in both methods had to be repeated again and again before the results were uniform.

Gordon's method is one of absorption of agglutinin only. An emulsion of the unknown coccus is made in .85% saline and adjusted so that each c.c. contains 50,000 million particles. It is heated to 65°C. for one hour. The titre of the agglutinating serum is found and a dilution in saline, one thirty-second of the full titre formed. One cubic centimetre of the diluted serum is added to one cubic centimetre of the unknown coccus suspension (50,000 millions) and the mixture incubated for 2 hours in a water bath at 37°C. The tubes should be shaken from time to time to disperse throughout the fluid any sediment formed. The mixture is now centrifugalised and the supernatant fluid pipetted off and put up against equal quantities of emulsion of the type coccus. The racks are placed in an incubator at 55°C overnight and/

and read the next morning. The emulsion of the type coccus contains 2000 million particles per cubic centimetre and should not show any sedimentation in 24 hours. If the emulsion of type coccus is made up in saline in a cylindrical vessel and left to stand for several hours the heavier particles fall to the bottom and leave a homogeneous opacity. In subsequent series of absorption tests the concentration of type coccus was reduced to 500 million per cubic centimetre, to reduce to a minimum any spontaneous agglutination which may take place in a Dreyer tube, although in bulk it appears perfectly stable. The length of time allowed for absorption was also altered. It was found that if given three hours in the water bath at 37°C, the absorption of agglutinin was more complete than if left only two hours. In the final series, the supernatant fluid after centrifugalising was pipetted into the sterilized sediment from two broth cultures (roughly 50,000 million organisms) and the incubation repeated. This was found necessary as only a few of the streptococci tested fully absorbed the agglutinins at one incubation. The results are considered later.

Smith's method makes use of the facts governing agglutination and includes agglutination as well as absorption tests. The agglutination test is as follows. The growth from a salt-free broth culture is washed twice with distilled water and suspended in .001N NaOH and adjusted to 500 million particles per cubic centimetre. The immune serum is diluted with M/25 NaCL and equal quantities of varying dilutions of immune serum are added to a similar amount of the coccal emulsion and incubated for two hours at 55°C and read. The only modification made here was that the strains were grown in Hartley's broth instead of the special fluid medium recommended.

In the absorption test, the deposit from 50 c.c. of a broth culture of each strain is washed twice with distilled water/

water and suspended in 1.2 c.c. M/25 NaCl. .98 c.c. of the emulsion is added to .02 c.c. of immune serum and incubated for 2 hours at 55°C. The mixture is then centrifugalised and the clear fluid made up in varying dilutions and added to equal amounts of the homologous strain in .001 N NaOH so that each c.c. contains 500 million organisms. The tubes are incubated in the water bath for 2 hours at 57°C and read. Here as in Gordon's method, the cultures were grown in a small amount of fluid instead of in 50 c.c. flasks. Two cultures in 17 c.c. of Hartley's broth in tubes were used instead of the way recommended. In both Gordon's and Smith's methods a number of controls are necessary. In the agglutination tests, the index coccus is tested against saline and against normal serum; in the absorption tests the type serum is put up against the index coccus when unsaturated, saturated with the homologous coccus and with a heterologous coccus. The way in which the records were kept may be of interest. For each strain which it was decided to investigate, a filing card was made out giving the source with name of patient, ward, disease and day, date of swabbing. On the left hand top corner was placed the serial number and the number of the colony selected, e.g. 54-3. The former number is that in the order of sequence, the latter the number of the colony selected. A record of each subculture was kept, giving the media used, the date, and from what culture transferred. The latter fact was denoted by the letter of that particular culture, e.g.

29.3.27.
E Solid Hartley D. E is the letter denoting the particular subculture quoted while D is that of a former culture, a note of which was made previously on the card. A comment was made on the macroscopic and microscopic characters of each subculture. A facsimile card is appended which will more clearly illustrate the method.

In all some 91 throats were swabbed. Of these 79 were from definite scarlet fever patients, five were from cases of doubtful scarlatina, one from a patient in contact with scarlet fever, one from a supposed scarlet fever carrier, three taken post mortem from an empyema in a fatal case of scarlatina, one from the throat in an acute bronchitis patient and one in a case of acute leucaemia. Haemolytic streptococci were found in 67 of the scarlet fever throats examined and in six of the other sources. Four of the doubtful scarlet fever cases showed no haemolytic colonies and a similar result was found with one of the post-mortem specimens, and the case of acute bronchitis. On the other hand haemolytic streptococci were discovered in the throats of one of the doubtful scarlet fever patients, of both the supposed carrier and the contact, of the acute leucaemia and in the cultures from two of the post mortem specimens. Of the twelve scarlet fever patients showing no haemolytic streptococci on their throat swabs, one was in his forty-second and one in her fortieth day of disease, but all the others were within eight days of the onset of the disease. Owing to the catastrophe overtaking the solid media only 36 strains were fully investigated, 33 being from scarlet fever throats, 2 being post-mortem specimens and one from the throat of a contact.

The appearance of the primary growths on blood agar plates varied considerably. In some the number of haemolytic colonies were few, in others very numerous. Among the latter were the plates from swabs from the throats of secondary scarlet fever patients, those patients who had recovered from the first attack to fall a victim a second time. In those instances, almost 99% of the colonies were of haemolytic streptococci while in the others about 50% or less were due to haemolytic streptococci. The degree of haemolysis/

haemolysis was much about the same, the diameter of the halo being about 3 m.m., varying with the size of the colony. The colonies themselves were pin-head or slightly larger than pin-head size and opaque, appearing 9-12 hours after incubation. In most instances the streptococci were found in long chains but in some they appeared in places as diplococci, in others as ovoid cocci or sometimes in chains of ovoid bodies. Subculturing proved that all these forms were streptococci morphologically. Colonies indistinguishable from those of haemolytic streptococci were produced by a Gram negative bacillus resembling the coli-typhoid group.

The growth in broth was in all cases granular with sedimentation of the particles. In two of the thirty-six there was some opacity as well as granule formation, but in the rest the supernatant fluid was clear. In some the sediment was flocculent and at times little greyish yellow masses were found floating through the media or clinging to the sides of the tube. Later, after frequent subculturing in fluid media, all strains grew, at first, uniformly throughout the broth but there was a tendency to relapse into the granular condition. In some there was a certain amount of growth in the fluid part of the medium but the greater part had sedimented. Where growth did occur in the broth which went wrong, referred to already, it was distinctly granular but differed from the ordinary growth in that the particles were more compact and the granules appeared like grains of sand. Of course, the mass of the growth was only a fraction of that found in a suitable batch. Curious changes in the shape of the organisms took place during subculturing. Where the units of a strain were found at first to tend to become ovoid, later cultures showed the same feature but not constantly. The changes

did/

did not seem to be influenced by the medium used or the length of time incubated as they were present in 18 hours' cultures whether in solid or fluid media and might be absent in cultures examined a week after incubation. If anything, they were more common in broth cultures and where the units of the streptococci were big. In fact it was only where the individual cocci were rather larger than usual that one met ovoid shapes. Some approached almost bacillary forms but close examination of cultures on solid media failed to reveal any abnormal colony, macroscopically or microscopically. Such pleomorphism appeared late in the series of subcultures in strains that had not previously shown it but might only be found in one culture. The growth in fluid medium was in the form of long chains. Where the individual units of the chain were small, the chains were sometimes made up of as many as sixty cocci. At times cocci that were small in size on primary isolation became larger as the subculturing proceeded. In no instance was there visible sign of contamination in any of the cultures.

On solid media the growth was that characteristic of streptococci, small grey white colonies remaining discrete. With solid Hartley, one of its advantages is its transparency, and the colonies stood out clearly by transmitted light. The growth in this media when suitably prepared was excellent even when the strains were first isolated. Now and again one came across a curious abnormality. An inoculated slope of solid Hartley would show two sets of colonies, one the usual streptococcal type, if anything slightly larger than ordinarily, the other microscopic in size. Both showed streptococci on microscopic examination but those from the tiny colonies tended to loose the stain in Gram's method. Subculturing each type of colony separately produced in the/

the case of the larger colonies, Others to all appearances the same although nearer the usual size. In the case of the tiny colonies there was either no growth or the colonies were the same as in the instance of the other type, more often the former. It would appear that the tiny colonies were those produced by the weaklings of the original culture, whereas the larger ones were the growths of the more robust units. Similar changes were found in the first subculture of the standard type SIII. Only two of the strains isolated had any effect on the sugars. None fermented raffinose but two produced acid in mannite. The organisms used were about the fourth or fifth subculture, that is about a month from primary isolation and the results were read after two days' incubation and after seven. No change was found between the two readings. Both mannite fermenters were tested two months afterwards and still produced acid. It is possible that if all the strains had been tested sooner more mannite fermenters would have been found but this number is about the same proportion as found by other investigators.

All organisms were insoluble in bile salt solution. True pneumococci used as controls showed only the ghosts of the bacteria after exposure to 2% sodium taurocholate.

The toxin produced by each strain of streptococcus was tested on Dick positive reactors. For the identification of the toxin, a companion test of neutralisation by the standard antitoxin must be performed. A series of tests was carried out to determine the amount of antitoxin necessary to neutralize one skin test dose of Dick toxin. Parke Davis & Co's concentrated scarlet fever antitoxin was used, issued as containing enough in one cubic centimetre to neutralize 50,000 skin test doses of toxin. The toxin used was Burroughs, Wellcome & Co's brand. The testing of Dick toxin is totally

different to that of diphtheria toxins. In the case of the latter, the animal used, the guineapig, reacts to the tiniest amount of free toxin. But with Dick toxin, we require human beings, and they react only to a definite amount of toxin. With increasingly smaller doses the reaction rapidly disappears. For this reason only double plus (++) positive Dick reactors are of much use in neutralization experiments. To be strictly accurate, it would have been necessary to carry out the tests all on the one person. The number of tests required negatived such an idea.

The three varying factors are the amount of antitoxin, the length of time of interaction before injection and the temperature at which such interaction takes place. The amount of toxin remains constant. This amount of toxin, .2 c.c. was measured by a .1 cc. pipette into a Dreyer tube and the requisite amount of diluted antitoxin added. The mixture was then left to interact for the chosen time and at the chosen temperature then injected into a Dick positive reactor. The dilutions of antitoxin were arranged so that the bulk of the completed mixture was not more than .3 cc. It was soon found that the difference in the amount of antitoxin required for neutralization at room temperature and at 37°C was so small that the rest of the experiment was carried out at room temperature only. It was also found that to neutralize one skin test dose of Burroughs Wellcome toxin required two and a half times the amount stated on Parke Davis & Co's serum. This merely confirmed the view already held that the brands of Dick Test Toxin available commercially were anything but uniform.

When a skin test dose is exactly neutralized no reaction is visible 24 hours after injection. But if examined at 48 hours after injection it will be found that a small area of redness has appeared. At 72 hours this area will have reached its maximum but it will be neither as big or as intense as an unneutralized reaction. Where the dose of toxin/

GRAPH I.

Neutralization of the skin test dose.

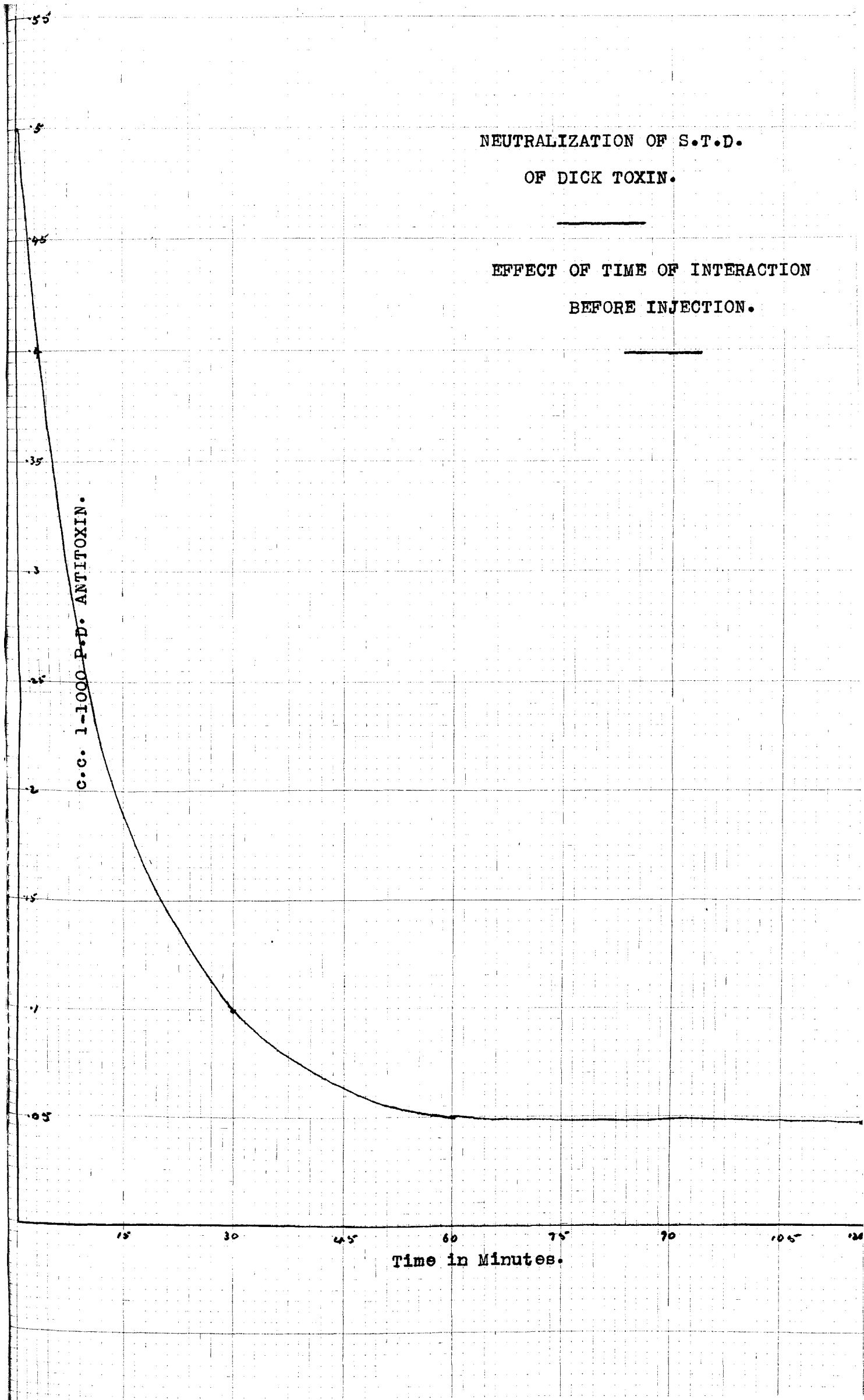
Relationship of amount of antitoxin required to length of time of interaction before injection.

NEUTRALIZATION OF S.T.D.

OF DICK TOXIN.

EFFECT OF TIME OF INTERACTION

BEFORE INJECTION.



toxin is not quite neutralized, a small area of redness, about 10 x 10 m.m. appears by the 24th hour. This increases in size, becoming bigger than the corresponding reaction of the exactly neutralized mixture but as it grows the central area becomes paler and of a greyish white colour. The whole reaction is likely to fade more quickly than the previous one so that there may be a brown area over the site of the reaction to the "not quite neutralized" mixture while that of the exactly neutralized mixture is still pale. Where the dose of Dick test toxin is more than neutralized there is seldom any reaction whatever.

The following is one example of the reactions found:-

9.5.27.	.2 cc. B.W.Toxin + .01 cc.1/1000 P.D. Antitoxin.	.2 cc.B.W. + .02 cc.1/1000 P.D.	.2 cc. B.W. + .05 cc. 1/1000 P.D.

Allow to interact for one hour at room temperature.

Reactions on

10.5.27	25 x 14 P.	18 x 15 P.	-
11.5.27	25 x 15 P white centre.	28 x 15 P. white centre.	15 x 12 P.
12.5.27	Brown	Brown	20 x 15 F.P.
13.5.27	-	-	-

The sizes are in millimetres, the axis in a line with the axis of the arm coming first. The letter following denotes the particular shade of the reaction, P = pink. F.P. = faint pink. Graph 1 shows the relationship of time of interaction to amount of antitoxin required, the union taking place at room temperature. The antitoxin is stated in fractions of a cubic centimetre of a 1-1000 dilution in saline, the time in minutes. It will be seen that ten times the amount of antitoxin is necessary to neutralize a skin test dose of Dick toxin when the mixture is injected immediately, than when they are left to interact for an hour. After the latter period, no increase in length of time of interaction makes any appreciable change in the amount of antitoxin required. The neutral point was taken/

taken as that point where the mixture gave a negative reaction in a very susceptible individual when read 24 hours after injection. The subsequent appearance of the reaction shows the very loose nature of the combination but why a central pale area should appear in "not quite neutralised" mixtures is problematical. It may be that there is produced an area of skin immunity starting at the needle puncture and that the antitoxin injected in the mixture has been washed away by the blood stream from the peripheral areas or that it is merely the sign of vasoconstrictor action of the mixture.

The foregoing part of the work along with most of the toxin testing was carried out in diphtheria patients, the patients giving the biggest percentage of strong positives. These patients had had horse serum in the form of diphtheria antitoxin and were susceptible to that protein so it is not to be wondered at that the neutralisation mixtures' produced serum reactions. This fact did not influence the results of the neutralisations in the slightest as tests on patients who had not had antitoxin showed no variation in the curve illustrated. Also in one diphtheria patient one might have at the same time all the types of toxin reactions and reactions to neutralisation tabulated later. The serum reactions to the neutralisation mixtures usually showed up within fifteen minutes of injection as a morbilliform eruption extending to about two inches around the site of puncture. They lasted for about an hour then disappeared completely before the toxin reaction, if any, appeared. In some it was more an erythema of the same size rather than a definite rash. In my own case, the eruption was morbilliform and appeared five minutes after injection and disappeared in forty-five minutes. This reaction to tiny doses of serum injected intradermally has been recommended for use as a routine test of protein susceptibility. In the subsequent table the sign + stands for a reaction of about 10 x 10 m.m. while ++ is one

of/

of 20 x 20 m.m. When there is a negative that means that the toxin gave no reaction whatever. When a fluid contained no toxin whatever there was not the vestige of a reaction. This latter fact reminds one of what is found clinically. Patients are admitted, usually as diphtheria, with intense inflammation of the throat and tonsils, perhaps with purulent discharge from the nose and later from the ears, but there is no sign whatever of an eruption, not even a flushed face. Cultures are all negative for diphtheria and show only streptococci. These are probably infections with a non-scarlatinal strain, the toxin if any, having no effect on the skin. Where the neutralisation mixture gave a reaction the patient was tested with a control fluid, the diluted toxin being placed in boiling water for two hours. In all instances, the controls were negative so they are not included in the table. The strength of toxin used was 1-250 in normal saline, the dose being .2 c.c. This was found necessary to bring out the reactions. Other investigators have used much more dilute solutions and obtained good reactions but such was not the case here. It might have been that the media they used was more suitable for toxin production but in that case streptococcal toxin does not fall into line with diphtheria toxin. The neutralisation was by the addition of .1 c.c. of 1/100 dilution in saline of P.D. & Co. concentrated scarlet fever antitoxin and allowing the mixture to stand for 1 hour. In the results it will be found that eight toxins gave no reaction whatever, that is to say the filtrates from both cultures of the organisms contained no toxin detectable by the method used. Sixteen toxins produced a reaction in Dick positive patients and were completely neutralised by the specific antitoxin. Six solutions produced a reaction but was not neutralised by the antitoxin, while in the last six toxins, the reaction to the mixture of toxin and antitoxin was worse than that to the toxin alone.

agglutinin/ The results tabulated for the absorption of

agglutinin and agglutination tests are the results of many repeat tests. In only a very few did the original result appear complete. In the agglutination test it was often the difficulty of avoiding spontaneous agglutination even with the improved technique of Smith. With the absorption test it was the incomplete absorption of agglutinin. Even in the end results there were some that did not completely absorb the agglutinin but the absorption went far enough to class them in the group they have been placed.

The Gordon method was carried out first and it was found that 81-3 strain had no effect whatever on the agglutinins. This strain was a mannite fermenter and had been isolated from the throat of a scarlet fever contact. It produced a good toxin which was completely neutralised by the specific antitoxin. All these facts combined to make it a second type serum antigen. The Smith method confirmed the points already differentiating it from SIII (the standard) but the time available did not allow of a higher titre than 1-400 being obtained. All strains not agglutinating with serum SIII or absorbing the specific agglutinin were tested with serum 81.3 for agglutination. In Gordon's absorption method there are some strains that absorbed all but the highest concentrations of antiserum while there are others that could only remove a very small amount of agglutinin. The results with Smith's method, while the agglutination and agglutinin absorption tests of the same organism were more or less in sympathy, the agglutinin absorption test of Gordon did not always tally with that of the Smith. The difference was rather one of degree than of kind. Strain 46.3 illustrates the point. In the agglutination tests, some of the strains only agglutinated in the stronger dilutions, the others being indefinite or negative, as in strain 37.1. Arranging them in groups by their agglutination and agglutinin absorption reactions we

find/

find that twenty-six strains are homologous with the standard Sherman strain SIII, only four are homologous with strain 81-3 and the rest fall into neither group. With strain SIII, it reacted consistently throughout, produced a good grade toxin which was neutralised by the specific antitoxin. The agglutinating sera kept their power well. Some batches of SIII serum remained at full potency for three months being stored during the time in a cool place although not in the ice chest. This is contrary to what other observers have found with some of their sera.

If we arrange the strains according to toxin production then only sixteen are streptococci scarlatinae. Also the toxin production had no relation to their behaviour with agglutinating sera. By serological tests I have been able to separate out the haemolytic streptococci found in scarlet fever patients' throats into three groups, the majority being in that group homologous with the streptococcus scarlatinae of Sherman. This result is similar to those of others who found that the majority of scarlatinal streptococci fell into one serological group while the others were in a smaller group or unclassifiable. But the result of the toxin production is quite at variance with that found by others. The majority found that no matter what serological group the strains fell into or their biochemical reactions, more than 80% produced one toxin neutralised by the specific antitoxin. Here, by toxin production, one could divide the strains into four groups, one producing no toxin. one forming a toxin not neutralised by the scarlatinal antitoxin, one where neutralisation was possible and one where the addition of antitoxin made the skin more susceptible to the toxin thereby giving a larger reaction. But certain fallacies are possible. Firstly with regard to the strains isolated, as only one colony was picked off it is possible that it was not that of the causal organism./

organism. But Smith taking two colonies found no variation between any pair out of a series of 209 throat swabs. Then the toxin production might be hindered by unsuitable media. Other workers use a serum phosphate broth pH 7.6 or a serum rabbit glucose broth pH 7.6. Hartley's broth with a pH8 was chosen owing to the proof of its suitability for diphtheria toxin production. Against this argument is that fact that the broth cultures of strains with varying toxin content were made from the same batch of media. In one batch of toxins, one might find a culture producing abundant toxin and another with none. The last fallacy is in the possibility of the toxin not producing a reaction in that particular person. Owing to the number of Dick positives available each toxin and neutralisation could be tested on only one patient. This is the weak point in the results. But even then, supposing it could produce a reaction in one Dick positive and not in another then that toxin is of a different type to the standard toxin.

The investigation reveals the fact that one need not expect an easy method of identifying the streptococcus scarlatinae by toxin production or serological reactions. The number of times the latter reactions had to be repeated negatived any hope of a quick result. Undoubtedly the lesson learnt is that quoted in the first sentence of this section.

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RESULT OF STREPTOCOCCAL TEST.

Bile solubility - = Insoluble.

Sugar reaction + = Acid produced.

\- = No change.

Agglutination and absorption reactions

++ = Marked agglutination.

\+ = Definite result.

± = Sedimentation but supernatant fluid still somewhat opaque.

Grouping according to agglutination and agglutinin absorption reactions.

No. of strain.	Bile Solubility.	Sugar Reactions. Raffine.	Mannite.	Absorption Test. Gordon's method. Serum SIII. Titre 1-1600 1-200	1-400	1-500	1-1600	C
SII	-	-	-	-	-	-	-	-
16-2	-	-	-	±	-	-	-	-
17-2	-	-	-	++	++	+	+	-
20-3	-	-	-	+	+	+	±	-
21-1	-	-	-	+	-	-	-	-
25-2	-	-	-	±	-	-	-	-
28-2	-	-	-	-	-	-	-	-
29-1	-	-	-	-	-	-	-	-
34-1	-	-	-	-	-	-	-	-
37-1	-	-	-	-	-	-	-	-
40-2	-	-	-	++	++	+	+	-
44-2	-	-	-	-	-	-	-	-
46-3	-	-	-	-	-	-	-	-
54-3	-	-	++	+	-	-	-	-
56-1	-	-	-	+	+	+	±	-
58-2	-	-	-	-	-	-	-	-
66-3	-	-	-	-	-	-	-	-
69-3	-	-	-	±	-	-	-	-
70-3	-	-	-	-	-	-	-	-
71-3	-	-	-	+	+	±	-	-
72-2	-	-	-	-	-	-	-	-
73-1	-	-	-	-	-	-	-	-
75-1	-	-	-	+	±	-	-	-
77-3	-	-	-	+	+	-	-	-
79-2	-	-	-	+	+	±	-	-
81-3	-	-	++	+	+	+	±	-
83-1	-	-	-	±	+	±	±	-
84-2	-	-	-	+	+	±	±	-
85-1	-	-	-	+	+	±	±	-
86-1	-	-	-	+	+	+	-	-
88-1	-	-	-	+	±	-	-	-
90-6	-	-	-	+	±	-	-	-
92-4	-	-	-	±	±	-	-	-
96-2	-	-	-	±	-	-	-	-
97-1	-	-	-	+	±	-	-	-
98-2	-	-	-	±	-	-	-	-
103-5	-	-	-	±	+	-	-	-

No. of strain.	Agglutination Test. Smith's method. Serum SIII. Titre 1-1000							Absorption Test. Smith's method. Serum SIII. Titre 1-1000			
	1-25	1-50	1-100	1-200	1-250	1-500	1-1000	1-125	1-250	1-500	1-1000
SIII	+++	+++	+++	+++	+++	++	++	-	-	-	-
16-2	+	++	++	++	+	±	-	±	±	-	-
17-2	+	+	-	-	-	-	-	++	+	+	-
20-3	++	++	++	+	+	+	-	++	+	+	+
21-1	++	++	++	+	+	+	±	+	±	-	-
25-2	++	++	++	++	+	+	+	±	-	-	-
28-2	++	++	+	+	+	±	±	-	-	-	-
29-1	+	+	+	+	±	±	-	±	-	-	-
34-1	++	++	++	++	+	+	+	-	-	-	-
37-1	+	+	+	+	±	±	-	±	±	±	-
40-2	-	-	-	-	-	-	-	++	++	+	+
44-2	++	++	++	+	+	+	+	+	±	-	-
46-3	+	+	+	±	±	-	-	+	-	-	-
54-3	+	+	+	±	±	-	-	+	-	-	-
56-1	+	±	-	-	-	-	-	++	+	+	+
58-2	+	+	+	+	+	+	+	±	-	-	-
66-3	++	++	++	++	+	+	+	+	+	-	-
69-3	+	+	+	+	±	±	-	±	-	-	-
70-3	+	+	+	+	+	+	±	±	±	-	-
71-3	-	-	-	-	-	-	-	+	+	+	±
72-2	++	++	++	+	+	+	+	±	±	-	-
73-1	+	+	+	+	+	+	±	±	-	-	-
75-1	++	++	++	++	++	+	+	-	-	-	-
77-3	+	+	+	+	+	+	±	-	-	-	-
79-2	±	±	-	-	-	-	-	+	+	+	±
81-3	-	-	-	-	-	-	-	+	+	+	+
83-1	-	-	-	-	-	-	-	+	+	+	±
84-2	±	-	-	-	-	-	-	+	+	+	±
85-1	-	-	-	-	-	-	-	+	+	+	+
86-1	+	+	+	+	+	+	±	-	-	-	-
88-1	+	+	+	+	+	+	±	±	-	-	-
90-6	+	+	+	+	+	+	±	±	-	-	-
92-4	++	++	++	++	++	+	+	-	-	-	-
96-2	+	+	+	+	+	+	+	±	-	-	-
97-1	++	++	+	+	+	+	±	±	-	-	-
98-6	+	+	+	+	+	+	+	±	-	-	-
103-5	++	++	++	++	+	+	+	+	+	-	-

No. of Strain.	Agglutination. Smith's method. Serum 81-3 Titre 1-400				
	1-50	1-100	1-200	1-400	6
17-2	-	-	-	-	-
20-3	-	-	-	-	-
40-2	-	-	-	-	-
56-1	+	+	+	±	-
71-3	+	+	+	+	-
79-2	+	+	+	+	-
81-3	+	+	+	+	-
83-1	-	-	-	-	-
84-2	-	-	-	-	-
85-1	-	-	-	-	-

No. of strain.	Toxin Testing.		Grouping.
	Test.	Neutralisation.	
SIII	+	-	
16-2	+	++	SIII
17-2	+	++	3
20-3	+	-	3
21-1	+	+	SIII
25-2	-	-	SIII
28-2	-	-	SIII
29-1	-	-	SIII
34-1	-	-	SIII
37-1	+	+	SIII
40-2	+	+	3
44-2	+	-	SIII
46-3	+	+	SIII
54-3	+	-	SIII
56-1	+	-	81-3
58-2	+	-	SIII
66-3	+	-	SIII
69-3	+	+	SIII
70-3	+	++	SIII
71-3	+	+	81-3
72-2	+	-	SIII
73-1	+	-	SIII
75-1	-	-	SIII
77-3	+	-	SIII
79-2	-	-	81-3
81-3	+	-	81-3
83-1	+	++	3
84-2	+	++	3
85-1	+	-	3
86-1	+	-	SIII
88-1	+	-	SIII
90-6	+	-	SIII
92-4	-	-	SIII
96-2	+	-	SIII
97-1	+	-	SIII
98-2	-	-	SIII
103-5	+	++	SIII

THE DICK TOXIN.

The Dick Toxin.

Material and Method.

The test.

The reaction.

Variations from the normal.

Results in (a) Pneumonia.
Measles,
Whooping Cough.
(b) Diphtheria.
(c) Scarlet Fever.

Variations in a person taking scarlet fever and in those treated with antitoxin.

Evaluation.

Active Immunization.

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THE DICK TOXIN.

The Dick test is the intradermal injection of a small amount of diluted Dick toxin, the toxin produced by the streptococcus scarlatinae isolated by the Dicks and by Dochez and Sherman. Such an amount of toxin is called a skin test dose and is said to be that amount of toxin which will give positive reactions in patients in the early days of scarlet fever and negative reactions in convalescents. We have found that 1 c.c. "Agla" syringes are the best, provided it is proved that the piston fits the barrel exceptionally well. Not all "Agla" syringes are suitable as some are ground much more loosely than others. The syringe can be tested by fitting it together and, after filling and emptying it several times with water, pulling back the piston until lower end of the latter is at the first mark. Now close tightly the nozzle of the syringe with the ball of the finger and press down the piston as far as it is possible and keep it down for two seconds. If on releasing the pressure on the piston, it does not spring back to the .8 c.c. mark, it is not suitable. Usually in an unsuitable syringe, as the piston is pressed home the air can be seen escaping between the piston and the barrel wall. An ordinary hypodermic syringe is quite useless for accurate work. Two such "Agla" syringes are necessary and it has been the practice to mark, with a diamond, the end of the piston either T or C "test" or "Control", the "test" syringe being used for the test solution only and the "control" for the control fluid. If any mistake takes place, the syringes must be boiled before being used again. Ordinarily the syringes are sterilized by immersion in 1-20 carbolic acid solution, the syringe being taken to pieces. Boiling is not advisable and unnecessary when two syringes are kept for this work alone as besides destroying the colouring in the graduations, it/

the
it makes the piston work loose in the barrel. In the previous section, the testing of the different toxins necessitated the frequent boiling of the syringes with subsequent destruction as the pistons worked loose in the barrels. The graduations can be made to stand out clearly by rubbing into them a saturated alcoholic solution of brilliant green or other aniline dye. But these latter marks, while standing carbolic acid lotion, are also destroyed by boiling. The ideal syringe, of course, would have a coloured plunger but 1 c.c. "Agla" syringes are not made with such refinements. A 1 c.c. "Agla" tuberculin syringe with a coloured plunger is procurable but the cost is prohibitive for everyday work.

The needles used were No.214 rustless steel needles, specially made for intradermal work and supplied by Burroughs, Wellcome & Co.. The bevel in these needles is flat and at an angle of 30° to the stem. This is most certainly the ideal angle. To have a shorter point is to have difficulty in penetration while a longer one is liable to favour leakage. The point itself must be sharp but the edge must be blunt, otherwise the skin is cut and there is bleeding with liability to lose some of the test fluid. The needles are sterilized by boiling and after use are syringed through with methylated spirit and dried by ether. Such a procedure is necessary with fine-bored needles, although the chance of the stillettes being rusted in is less with rustless than with ordinary steel needles. The needles can be stored in methylated ether in an air-tight jar. The repeated boiling destroys the point of the needles and they require frequent re-sharpening. Blunt needles make the work unnecessarily distasteful to the patients, especially when the majority are young children. The pain is and should be negligible. All that is felt is a tiny prick with a slight burning sensation/

sensation as the fluid is injected. One finds even very small children coming up smiling for re-testing. Their behaviour often depends on that of the others, rather than their personal feelings in the matter. If a hardy patient in a ward is taken first, it is possible to perform 20 or 30 tests in that ward without a single child crying. On the other hand, if a mistake is made and a tearful child selected first, the ward thereafter becomes a Vale of Tears. The children, even quite small ones, take an intelligent interest in the test and recount with gusto the size and colour of their reactions with subsequent changes. In one instance a mother returned and wanted to know what the Dick test was as her children with some of the others in the same street (who had been in this hospital) had been playing at Dick tests complete down to the reading of the reaction.

The performance of a large number of Dick tests produces a technique peculiar to the operator. The following method was found to be the quickest and most accurate. The syringes are taken out of the carbolic acid lotion and fitted together, making certain that ends are screwed home. They are washed free of carbolic acid by pulling in and forcing out sterile water several times. The needle, taken out of sterile water, is fitted to the end and also screwed home. The requisite amount of test fluid is pulled into the syringe and all extraneous air got rid of. It is an advantage to prepare both test and control syringes at the same time. The skin of the flexor surface of the forearm is cleaned with spirit, the forearm is held by the left hand of the operator in such a way that the extensor surface is against the palm of the hand while the thumb and fingers of the operator stretch the skin of the flexor surface. The syringe is held in the right hand so that the thumb and forefinger grip that portion of the syringe where the end and the barrel meet and the head of the piston rests against the/

PHOTOGRAPH II.

Method of holding the syringe.

the palm of the hand. The last manoeuvre is illustrated in photograph II. The needle, with the bevel upwards, is now inserted into the skin, just under the epidermis and at right angles to the long axis of the forearm, and the fluid injected by pressure on the piston by the palm of the hand. The control is carried out in exactly the same way. If the right arm is always used for the test and the left for the control, no mistake can ever be made in the reading. This is particularly so where no control is used.

The weak points, those where leakage is likely to take place, are between the needle and the skin, the needle hub and the nozzle and the end of the syringe and the barrel. The last two can be excluded if precaution is taken to screw home the parts. As regards the first one, some maintain that the slow withdrawal of the needle will prevent leakage, but if the needle has been inserted far enough, about ½", there is unlikely to be any loss. Tilting of the needle is not advised. The peculiar hold of the syringe is the only one that can be maintained for long periods without much chance of cramp and also the one with which the necessary force can be exerted. The amount of force required is considerable and if the connections are not tight it is possible to have beads of fluid appearing at the needle hub or to force out the end of the syringe. In an ill-fitting syringe the fluid will be found to be leaking from between the piston and the barrel, forming a little pool in the hollow of one's hand.

As long as the needle point is in the skin, the exact depth is unimportant. If one takes a section of the skin, it will be seen that the cutis vera occupies almost the whole depth of, and it is into the cutis vera that the fluid is injected. While skill in the technique was being developed, these tests where the fluid seemed to have gone too deep were repeated. It was invariably found that the/

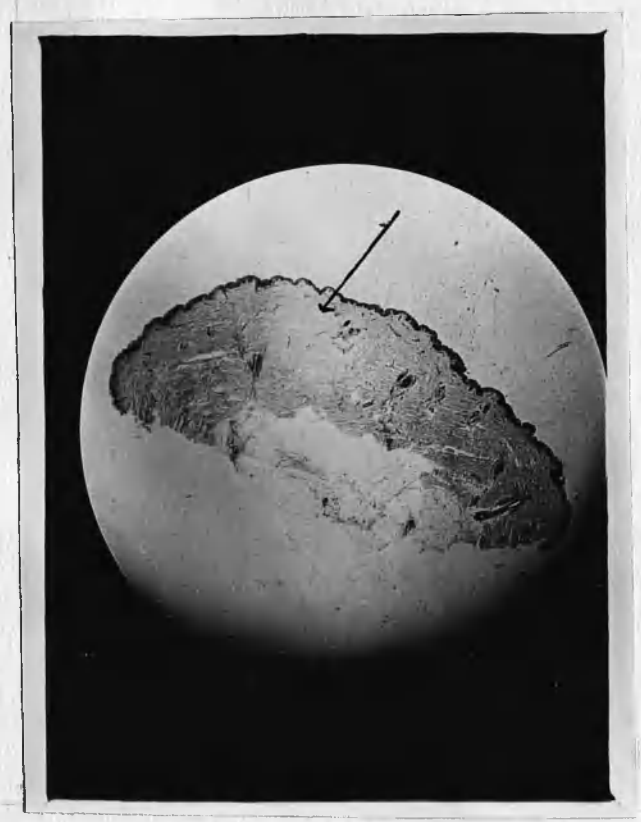
PHOTOMICROGRAPHS.

A. With agar just under the epidermis.

B. With agar in the centre of the cutis vera.

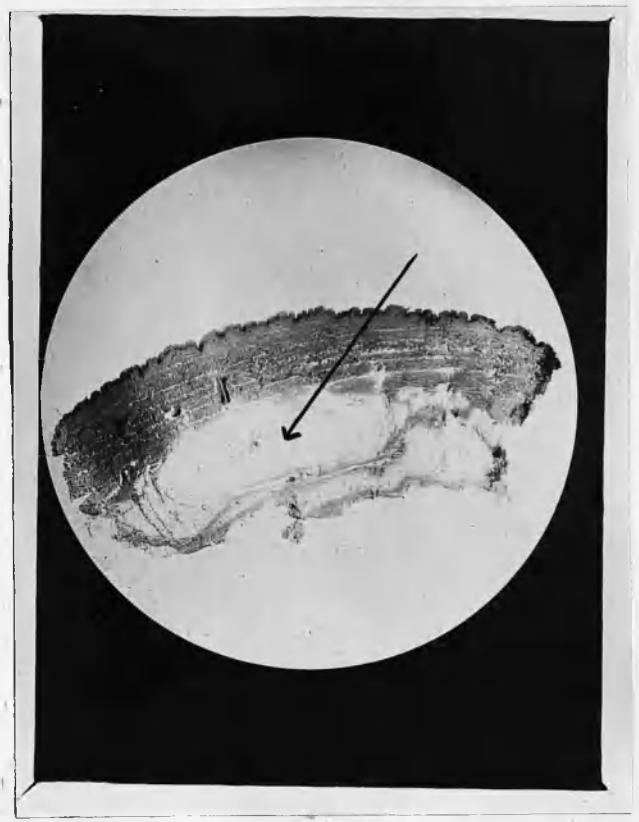
C. Agar in the lower part of the cutis vera.

The arrow points to the location of the agar.



A

B



C

the first and supposed inaccurate test was as good as the later correctly performed one. This was even better demonstrated in the case of the Schultz-Charlton test, where the abdominal skin does not lend itself to uniformly accurate injection and where repetition was more often necessary. Photomicrographs A, B and C are from an experiment to illustrate the point. A small amount of 2 per cent. agar solution (ordinary agar medium) was melted and the temperature maintained at 50°C. An intradermal syringe and needle were fixed together and heated by boiling water being forced in and out. When the syringe was hot, melted agar was pulled up to the .1 c.c. mark and injected into the skin of a cadaver so that the needle was just under the surface of the skin and was visible throughout its whole length. The syringe and needle were cleaned immediately with boiling water and the manoeuvre repeated. This time the needle was inserted deeper into the skin but still superficial enough for the exit of the bore of the needle to be visible as a dark dot. Lastly the operation was performed with the needle buried completely in the skin. The areas of skin were excised, fixed in Zenker's solution, imbedded in paraffin and sections cut. The section from which the photomicrographs were taken are from the centre of the injected areas, i.e. from half way through the blocks. It will be seen that the agar has distended the cutis vera in all these situations. In A and B the more superficial injections, it is more in the nature of an infiltration, while in C, the deepest, there is distinct cavity formation but still in the cutis vera. It is also noticeable that in spite of an endeavour to get as near the surface as possible in section A, the agar is still under the epidermis and in the cutis vera. Probably the experiment would have shown up better if a small percentage of iron had been added to the agar and the sections stained with a distinctive iron reagent. As it is, it shows that the possibility of error due to faulty/

faulty technique in the performance of intradermal tests, is small.

Although the above view is put forward, it must be understood that all intradermal work has been carried out in the recognised manner. The needle point should be at such a depth that the needle is visible as a dark blue line. A better guide is that mentioned in the second half of the above experiment, namely the exit of the bore of the needle appearing as a dark dot. Even with very thin skin it is possible to produce uniform results and after dexterity has been attained, it is very seldom that a Dick test has to be repeated.

Where the test has been correctly performed, the injection of the fluid produces a raised wheal with several dimples on the surface where the hair follicles have tacked down the skin. Sometimes the wheal appears but the dimples do not stand out clearly. The main point is that a visible swelling should be produced. If no swelling appears then the test should be repeated as, although the fluid may be in the skin, the location is not definite. The swelling disappears in from five to ten minutes, sometimes giving place to an evanescent patch of erythema over the site of the injection.

In the consideration of the reactions to this test, let us go over the changes which occur in a person giving a good positive reaction. Four hours after the test is performed, one may see a faint pink area about 10 m.m. in diameter, not raised above the surface nor tender to touch. At 8 hours the area has become oval with the long axis in the long axis of the forearm. The margin is a little more distinct but it is not raised and it is still faint. At the twelfth hour it has reached 30 m.m. in length and 20 m.m. in breadth; it is of a deeper pink and stands out more prominently. Twenty-four hours after injection

PLATE I.

the size is slightly more than at twelve hours, about 35 m.m. by 25 m.m., it is of a deep red colour, the margin is slightly raised and the reaction is surrounded by a pale halo. There is some tumefaction of the skin and it is only tender to firm pressure. The state of affairs is admirably depicted in Plate I. At the thirty-sixth hour, the reaction has become fainter, the margin and the halo are fast disappearing and, by the forty-eighth hour, only an oval brown area marks the site. This brown area is perceptible to touch as a roughening of the skin. About four days from injection, even this brown area will have gone, but the roughening is still perceptible. Between the 10th and the 14th day, fine powdering is visible, just as if flour had been dusted over the skin and the excess removed. By another seven days, the site of injection is indistinguishable from the surrounding tissue. On the control arm no difference is noted, or at the most, a tiny blanched area, 8 x 8 m.m. This blanching is interesting as it is probably due to vaso-constriction and is found in the test arm in Dick negatives and also in those giving a negative response to the blanching test (considered later).

Many variations from the above description occur but it can be taken as a standard for a "double plus" reaction. Variations occur in shape, in size, in tint and in time of appearance. There are also some abnormalities in times of maximum intensity and of disappearance. The usual shape is oval, the short diameter being two-thirds of the length, but some are almost exact circles while others are long and narrow. In such cases the superficial area would give the truest value. In size one may have reactions of a few millimetres only in diameter or up to several square inches. Any difference, no matter how small, from the control should be noted, excepting, of course, the papule which often follows the needle prick. The size most frequently found is about

30 x 20 m.m. and the longest I have seen was in a child late in the convalescence from septic scarlet fever. There were two elements, an outer oval area pink in colour and measured 80 x 50 m.m. and an inner deeper tinted one 25 x 20 m.m.. Reactions of 40 x 30 m.m. and 50 x 40 m.m. are not uncommon, nor are the smaller ones of 20 x 10 m.m. and 15 x 15 m.m.. The shades of colour obtainable are easily the most pleasing part of the reaction. The range extends from a faint delicate pink to a deep almost purple crimson. In recording the results letters were added to the size to describe the tint but they are most inadequate. V.F., very faint, stands for a just perceptible reaction: F.P., faint pink, for one where the shade is a little deeper and more easily discernible: P, pink, where the area stands out but is not bright: R.P., red pink, one with a tinge of crimson but not so deep as R, red, where the reaction is bright and fiery. On these last two points, size and shade, depends the assessment of the reaction.

Sometimes the reaction is not a uniform erythema but is punctate, exactly as a scarlatinal eruption. In those instances, they were not many, the reaction would be characterised as pink, as they resembled the rash in a case of mild scarlet fever. In one instance the reaction was of the nature of a bright red erythema with flecks of a deeper tint as in a very severe scarlatina. It was not always possible to reproduce them. At times when an example was required for copying, a child, who formerly had a punctate reaction, now gave a uniform blush with the same toxin. It may be due to the accidental entrance of the toxin into the skin capillaries or perhaps some peculiarity of the skin itself. It certainly supports the theory that the rash in scarlet fever is the reaction of the skin to the toxin and not the result of toxin acting through the nervous system.

The swelling of skin is present in only about a half

of the"double plus" reactions and very seldom in the weaker ones. When the swelling and redness disappear, one can sometimes feel a thickening of the skin about the site of injection but this is by no means constant. The halo around the reaction appears to be due to vaso-constriction as it is paler than the surrounding normal skin. Like the swelling and the thickening it is present most often along with severe reactions. Even in reactions 48 hours old, where there is still a tinge of pink, the clear border may be detected.

The depth of colour of the subsequent brown patch is proportionate to the intensity of the reaction. In the fainter degrees, there is no staining left while in the more severe ones, the marks appear as bruises. As one might expect, the deeper the staining, the longer it takes to disappear. The average time is about three to four days, but with a few the staining remains until desquamation starts.

Desquamation occurs only in the minority but one can have all degrees from the powdering already described to definite scarlatiniform pin-hole formation. In the really severe types, it may start about the eighth day from injection, but in the rest it is usually later, about the fourteenth day. Between the time of disappearance of the staining and the appearance of the desquamation there is a quite perceptible roughness simulating the sensation one finds on feeling the skin of a scarlet fever patient. That peculiar dryness is a distinctive point in scarlatina and is a strong factor in the diagnosis if the case is seen after the rash has disappeared. The powdering in the milder reactions resembles closely the desquamation in anti-toxin treated cases of scarlatina, a description of which will be found in the next section. One found the pin-hole type of feeling rather more often in early cases

of/

of scarlet fever that had given good reactions. It seemed as if the additional damage of the Dick toxin on the top of that produced by the toxin circulating during the acute phase of the illness caused an earlier and more extensive peeling of the reaction area. This peeling was quite apart from the general desquamation, coming on earlier and standing out clearly. On the whole the degree of desquamation varied directly as the intensity of the primary reaction. In the mild reactions, one might have the staining lasting one day or being absent altogether and no desquamation following. In others the staining would be present but except for a slight roughness of two days' duration, nothing else happened.

The variations in times of appearance and disappearance and of intensity of the reactions, are interesting. The usual time of appearance is between four and twelve hours after injection. In the more intense reactions the result appears early and continues to increase in intensity till the 24th hour. In some, it is the eighth hour before any sign of reaction is apparent while in others it is the twelfth hour. In a few all that is seen at the twelfth hour is a slightly raised wheal, colourless, but occupying an area equal to that of the subsequent reaction. This last abnormality I have seen only thrice in about 1200 tests. It is not uncommon to find a clear circle on the test arm at the twelfth hour similar to that described as sometimes appearing at site of the control injection. In some the reaction is delayed until eighteen hours after injection but still reaching the stage of maximum intensity within the twenty-four hours. The usual time for disappearance is between thirty-six and forty-eight hours after injection. The majority start to fade about the twenty-eighth hour, but in some one finds the reactions becoming again bright about the thirty-sixth, to disappear again within the

next twelve hours. One striking phenomenon found mainly in cases in the early days of scarlet fever but sometimes in others, was the appearance of the reaction at its full development at the twelfth hour but complete disappearance by the twentyfourth or the appearance of a brilliant reaction twelve hours after injection but only a faint pink area at the twenty-fourth. These abnormal reactions may account for the small percentage of positives which I have obtained in the early days of scarlet fever as the results were read at the twenty-fourth hour. If one were to include reactions present at any period within the twenty-four hours, the percentage positive would be somewhat higher.

Before inquiring into the nature of the reaction and its value, let us consider the results obtained in testing children and adults (a) not suffering from scarlet fever, and (b) who have had scarlet fever. The number of diseases treated by this hospital is limited, so that the patients not suffering from scarlet fever were either measles, whooping cough, pneumonia or diphtheria patients. The numbers are too small to be considered in age-groups separately and the percentages are given for the constituents of each disease group or for the combined age-groups of measles, whooping-cough and pneumonia where the numbers are sufficient to warrant such a procedure. In diphtheria the percentage is given for several age periods together and also for the whole group. The numbers in each age period are a good index of the age incidence of each disease. With scarlet fever patients, the results are given according to the day of disease on which they were tested. The numbers here are also too small for each day to be considered separately and several inclusive groups are made (a) 1st to 3rd day, (b) 4th to 6th day, (c) 7th to 10th day, (d) 11th to 20th day, (e) 21st to 30th day, and (f) after the 30th day. In all, some twelve hundred tests were performed. Of these/

these about two hundred were for practice and about a hundred and fifty were in the cause of testing various dilutions and diluents for Dr R.A.O'Brien of the Wellcome Research Laboratory, none of the results of which are included in the following tables. The rest include 145 on cases of pneumonia, 15 in whooping-cough, 54 in measles, and 143 in diphtheria. In scarlet fever 483 tests were carried out on patients at various stages in the disease.

The toxin used was one of three kinds (a) that supplied by Parke Davis & Co. as concentrated toxin with diluent, (b) that obtainable from Burroughs Wellcome in its diluted form, and (c) toxin produced by SIII the strain of streptococcus haemolyticus Sherman received from the National Collection of Type Cultures. At least three fourths of the tests were with toxin "B" which was found to be by far the most reliable. There is a decided lack of uniformity in the strengths of the Dick test toxin obtainable commercially. That supplied by Parke Davis & Co. I find far too weak. The number of negatives procured in a trial series of tests on early scarlet fever patients was too small to be a coincidence. Burroughs Wellcome toxin is more likely to give better results although the fluid is directed and must be used within three weeks of receipt. Such Dick test toxin remains active for months although not up to full strength. As an experiment, a bottle of diluted toxin was left in a cupboard at room temperature for four months. When the fluid was re-tested it was found to be still active but had depreciated to the extent of giving a "single plus" reaction in "double-plus" patients. The SIII toxin was used in such dilution as gave comparable results to those obtained with Burroughs Wellcome toxin as proved by experiment. The volume of the skin test dose varies. With Parke Davis toxin it is .1 c.c., with Burroughs Wellcome it is .2 c.c. while with the home-made toxin .2 c.c. of 1-500 dilution in saline gave the best results.

A/

TABLE I.

RESULTS IN DICK TESTS IN PATIENTS SUFFERING FROM

(a) Pneumonia.

-1		-2		-3		-4		-5		-6		-7		-8		-9		-10		-15		-20		-30		-40		-50		+50		Age groups.
28		35		14		13		11		10		4		2		-		2		7		3		4		7		-		5		Numbers in each group.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
5	23	12	23	7	7	5	8	7	4	1	9	1	3	1	1	—	—	1	1	1	6	0	3	0	4	0	7	—	—	0	5	Number under each sign.

Total 145
28.3% positive.
71.7% negative.

(b) Whooping Cough.

-1		-2		-3		-4		-5		-6		-7		-8		-9		-10		-15		-20		-30		-40		-50		+50		Age groups.
-		4		4		4		-		-		2		1		-		-		-		-		-		-		-		-		Numbers in each group.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
—	—	2	2	0	4	1	3	—	—	—	—	1	1	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Number under each sign.

Total 15
26.7% positive.
73.3% negative.

(c) Measles.

-1		-2		-3		-4		-5		-6		-7		-8		-9		-10		-15		-20		-30		-40		-50		+50		Age groups.
4		8		10		10		2		6		7		3		1		-		3		-		-		-		-		-		Numbers in each age group.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
0	4	2	6	3	7	4	6	0	2	1	5	1	6	0	3	0	1	—	—	0	3	—	—	—	—	—	—	—	—	—	—	Number under each sign.

Total 54
23.7% positive.
76.3% negative.

Combined.

% Reactions in Each Age Group for the added numbers of the above diseases.

5		27		16	31	10		18		10	17	7	6	2		14		3	10	1		5		0	1	1	1	1	9	0	3	0	4	0	7	—	—	0	5	Total numbers.
15.6		84.4		34	66	35.7		64.3		37	63	54	46	12.5		87.5		23	77	16.7		83.3		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	% in each group.

A copy of the sheets used in recording the reactions is attached at the end with a note explaining the signs used. In the following tables, positive reactions are those recorded as ++, +, ±, while negative reactions include ∓ and -. The number of pseudoreactions was very small, about 2% of the total of which a half were positive combined reactions.

Table I shows the results in children suffering from or convalescing from pneumonia, measles and whooping cough. The percentage reactions for the total number in each disease closely approximate one another, 28.3% positive and 71.7% negative in 145 cases of pneumonia; 26.7% positive 73.3% negative in 15 cases of whooping cough and 23.7% positive and 76.3% negative in 54 cases of measles. The similarity is probably due to the fact that the children all come from the same social grade. Their parents are poor, they live in crowded houses and if illness occurs, the patients must be sent to hospital. That the figures for measles patients should fall into line with those of the other two diseases is interesting as other investigators have found that a positive Dick reaction may become negative when the patient takes measles to become again positive later in convalescence. The above figures do not demonstrate any such variation unless the same change is true for pneumonia and whooping cough. If such a variation does occur it may be in the nature of a heterologous response to antigenic stimulus especially so if measles is due to a streptococcus. In that case it would be analogous to the same phenomenon found in the enterica group of diseases. In the section showing the percentage-age-group reactions for the combined numbers of the three diseases, it will be seen that the number of positive reactions in children under one year is few, being only 15.6%, but that in the immediately succeeding years the percentage positive rises to above

the/

TABLE 2.

RESULTS OF DICK TESTS IN DIPHTHERIA.

-1		-2		-3		-4		-5		-6		-7		-8		-9		-10		-15		-20		-30		-40		-50		+50		Age periods.
5		7		10		12		11		22		14		16		5		17		16		6		11		1		---		---		No. in each age group.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
1	4	1	6	4	6	5	7	6	5	11	11	8	6	7	9	4	1	3	4	8	8	1	5	2	9	0	1	----		----		No. under each sign.
20	80	14.3	85.7	40	60	41.7	58.3	54.5	45.5	50	50	57.1	42.9	43.8	56.2	80	20	42.9	57.1	50	50	16.7	83.3	18.2	81.8	0	100	----		----		% for each group.

Total 143
42.7% positive.
57.3% negative.

MODIFIED GROUPING.

Age Groups.	0-3		4-8		9-50	
No. in each group.	22		75		46	
Reaction.	+	-	+	-	+	-
No. in each sign.	6	16	37	38	18	28
% for each group.	27.3	72.7	49.5	50.5	39	61

TABLE 3.

RESULTS OF DICK TESTS IN SCARLET FEVER TABULATED ACCORDING TO DAY OF DISEASE.

1	2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		Day of illness.
3	30		40		28		18		20		14		10		14		9		8		9		12		13		6		15		Number.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
1	2	16	14	21	19	21	7	8	10	8	12	4	10	4	6	8	6	5	6	3	5	2	7	2	10	5	8	2	4	2	13	Number under each sign.

17	18		19		20		21		22		23		24		25		26		27		28		29		30		30+		Day of illness.
13	8		10		7		14		4		5		5		5		2		13		4		6		3		137		Number.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	Reaction.
5	8	3	5	1	9	3	4	5	9	1	3	3	2	1	2	1	4	0	2	7	6	2	2	0	6	1	2	18	119	Number under each sign.

MODIFIED GROUPING.

Grouping of days of disease.	1-3		4-6		7-10		11-20		21-30		30+	
Number in each group	73		66		47		101		59		137	
Reaction.	+	-	+	-	+	-	+	-	+	-	+	-
Number under each sign.	38	35	37	29	19	28	28	73	21	38	18	119
% in each group.	52	48	56	44	40.4	59.6	27.6	72.4	35.6	64.4	13.1	86.9

the average. In the columns for 5th year and onwards the fewness of the numbers does not warrant any deductions being made.

Table 2 shows the results of testing diphtheria patients. These children differ from the measles, whooping-cough and pneumonia patients, in that their parents are in more comfortable circumstances and that their presence in hospital is really for the purpose of preventing the spread of infection rather than for nursing. Here 42.7% are positive and 57.3% negative. Taking the percentage for each age group, it will be found that the number positive for children under two years of age is almost as low as the corresponding number in the preceding table. But after that age the percentage rises higher and remains higher until adolescence. But here again the numbers are too small to give a true average and to increase the possibility of truth the ages have been divided into groups with the ages 4 to 8 years as the central period. We now find that the numbers in the first period, 0-3 years, give percentages approximating those in the preceding table, those of the second period 4-8 years give a high figure 49.5% positive while the last group, 9-50 years give a number less than the average for the disease. The tables bear out the well known fact that children who take diphtheria are also very liable to take scarlet fever while the children of the poorer classes are not so susceptible. The latter table also shows that the age period with the greatest incidence of diphtheria, 4-8 years, is also the period where the greatest number are susceptible to scarlatina.

Table 3 gives the reactions in patients with scarlet fever divided according to the day of disease on which they were tested. To obtain workable percentages, the tables have been divided into "days ill" groups. It will be seen that these in the first six days of scarlet fever gave over

50% positive reactions while after that period the percentage positive declines until it reaches 13.1% for a large number over thirty days ill. These figures are at variance with those of other workers. I have been quite unable, even taking smallbatches of early cases to obtain the 80% and 90% positive reactions that others have obtained. The percentage in the days of late convalescence is probably true and even at that time 13.1% are still positive. This is quite in keeping with the fact that second attacks of scarlatina are not rare.

Of the positives in all three Tables, seven have taken scarlet fever, of negatives, two have had symptoms which resembled very closely "scarlatina sine eruptione" or at the most with a slight evanescent blush on the chest. One of the positives who took scarlet fever was a child admitted to a scarlet fever ward and who gave a very weak reaction when two days in. On his third day the test area became much brighter and larger and by the sixth day he had all the signs of a severe scarlatina. This fact emphasised the importance of considering minute reactions. One of the Dick positives was in a whooping cough ward in which there was no cross-infection or any connection whatever with scarlatina and still three days after Dick testing he developed a scarlatinal eruption without fever and without sore throat. The diagnosis was clinched only by the rash giving a positive blanching reaction to the Schultz-Charlton test. Here again the Dick area became brighter on the onset of the infection. The other five cases occurred in a diphtheria ward. They were at various times after testing from three days to nine months. When the infection occurred within three days of testing, the test area became bright again uniformly with no excessive redness at the margin. In the one case where the second disease occurred 7-10 days after testing, the child had had 2½ c.c. of scarlatinal antitoxin on admission. On the first day of scarlet fever, the test area returned uniformly red, on the second the

the central area was not quite so bright while on the third day the central area was pale and of a bluish tint while the margin was brighter and showed a zone of congestion. The reaction resembled those found in toxin antitoxin neutralisations as described in section one of this paper. With two patients taking scarlet fever about three weeks after testing, no change whatever was found in the test area but unfortunately, their rashes were not intense enough to show any definite immunity of that area. But certainly there was no exacerbation of the test. The last case had scarlet fever three months after testing and here the Dick test became brighter for a few hours then died away again. The times of onset of the scarlet fever in these cases are curiously in keeping with the development of active immunity in immunization with toxin. There the reaction becomes negative in seven to ten days to return to positive after three months. It may be that the Dick test gives a local immunity to the area of skin used, the onset of scarlet fever within three days finds the skin in a state of hypersensitiveness, when it is delayed until 7-10 days, the skin is able to repel the rash within twenty-four hours while the margin, which is not completely immune, reacts excessively, and when the infection is delayed until the third week, the skin-area is fully immune. Later than that, the active immunity is gradually lost. This would explain the differences in the reports of the changes in the Dick test on the subject taking scarlet fever.

The reaction of the test in patients who have had scarlatinal antitoxin is also interesting. One case has already been quoted but in that instance the antitoxin used was a poor one and the onset of scarlet fever was not remarkable. With others passive immunity induced by the injection of 2½ c.c. of antitoxin, if gauged by the Dick test, comes on in twenty-four hours and lasts between ten and fourteen days. With the curative use of the antitoxin,

some/

some curious changes take place. If the test is performed at the same time as the injection of the antitoxin, the result in the majority of instances will be negative at the twenty-fourth hour. If the reactions are read at twelve hours, it will be found that about one third of them have come to the size of a "single plus" about 20 x 15 m.m. and pink in colour. Here again we have that premature fading mentioned previously with regard to untreated cases of scarlet fever. Between the tenth and the fourteenth day after injection the Dick test starts to become positive again but only in the minority and only a few are definitely positive at the twenty-first day. I do not find any disproportion between the number of positives in the convalescence of antitoxin treated and non-serum treated cases of scarlatina.

In the blood of antitoxin-treated cases of scarlatina, one would expect to find a gradually increasing amount of antitoxin from the time of injection and such antitoxin would have the same effect on a Dick test as it would have on a scarlatinal eruption. But the Dick toxin appears to lay hold of the skin quicker than the antitoxin can get into the blood stream and therefore gives a reaction at twelve hours. The increasing amount of antitoxin is able to blot out such a reaction before the time for reading is complete. With a similar phenomenon in the Dick test reaction in untreated scarlet fever one may, with justice, deduce that the same state of affairs is present. In other words, the production of active immunity is by means of the rapid accumulation or formation of antitoxin, so rapid, in fact, that the change in the Dick reaction in a second or third day scarlatina is the same as one would find if one had given 10 c.c. of concentrated antitoxin. This is probably the explanation of the low percentage of positives in the early days of scarlet fever in the foregoing table. The susceptibility of antitoxin treated cases of scarlatina to a second attack is a debatable point./

point. On the one hand, we have the development of passive immunity, which it is argued, removes the stimulus for the production of active immunity and is supported by the fact that a few give a Dick positive reaction in convalescence. Some fear that the use of antitoxin will make scarlet fever more prevalent as the risk of second attacks will be greater. But I consider that they look at the question from a wrong angle. The percentage of positive reactions in the late days of convalescence I have found to be the same for treated and untreated cases of scarlatina. I think they have overlooked the fact that the passive immunity disappears gradually and that these patients are in an admirable position to develop active immunity pari passu with the loss of the passive. It is well known that the nurses who take scarlet fever are those who have just newly come to a scarlet fever ward for the first time. It is seldom those who have been in the ward for any lengthy period. Also in those patients who give a "double plus" reaction in the early days of scarlet fever, those who theoretically are not suffering from scarlet fever, one finds that their Dick reactions are negative by the twenty eighth day. They have developed active immunity. All these points tend to prove that the fear of increased incidence of scarlet fever in antitoxin treated cases is quite unfounded.

To my mind, the Dick reaction is a small piece of skin affected with a scarlatinal eruption. The typical punctation, although appearing only in a few, the brownish discolouration, as one finds following scarlet fever and clearly brought out by the blanching test, the pin-hole desquamation coming on eight to fourteen days after the reaction all point to a response to a specific toxin identical with that found in scarlet fever. It is not comparable to the Schick reaction in that it is never so severe nor the desquamation so extensive. The Schick reaction

appears/

appears later, at last the point of maximum intensity is later, and there is present what amounts to practically tissue destruction. Here the reaction is caused by the dilatation of the capillaries with probably injury to their walls and ecchymosis. In the one case I have had of a child dying when the Dick reaction was at its height after death the area appeared as a bruise. Again one can resuscitate a fading reaction by rubbing it and at times produce bruising. Of course these last two points merely prove that some damage has been done to the skin. The swelling with later the thickening is what one finds in the skin in scarlet fever and the changes in the reaction in a child taking scarlet fever tend to support the belief.

It can be taken as proved that Dick negative reactors are immune from scarlet fever, that is to say from the punctate rash which is pathognemonic of the disease. The two exceptions quoted above where there was present a condition suspiciously like scarlatina in Dick negative patients can easily be explained by the fact that the toxin was not up to strength, it being Parke, Davis & Co's toxin that was used. Since the tests were performed with Burroughs Wellcome & Co's toxin only, no such exceptions have occurred. But a Dick negative does not warrant the assumption that the patient is immune from attack by streptococcus scarlatinae as even in the convalescence from scarlet fever or at some later period he may suffer from tonsillitis or pharyngitis due to that organism. On the other hand a Dick positive reactor is not necessarily going to contract scarlet fever whenever he comes in contact with an infected person. He is undoubtedly susceptible to the infection, but there requires to be present some other factor. Perhaps it is injury to or lowering of the defences of, the naso-pharyngeal mucous membrane as suggested by the large percentage of patients from a Nose and Throat Hospital who take scarlet fever if the disease is brought into their wards or the condition of the throat

throat following diphtheria. Again, infection may be due to the increased virulence of the organism and if such variation occurs, as it must if it follows the character of other pathogenic bacteria, then a person giving a mild positive reaction, as 10 x 10 F.P., would be as liable to infection as those with more definite reactions. The instance already mentioned of the child with the faint positive who contracted the disease points this way and it certainly emphasised the importance of noting even the weakest of the reactions. The chance of a Dick positive escaping the infection is illustrated by the sequence of events in our diphtheria ward which was crossed with scarlatina. All patients in the ward were Dick tested and it was found that more than one third were susceptible. Nothing was done except to remove the first case of scarlet fever and still none of those left contracted the disease. Scarlet fever is not a very infectious complaint and because one passively immunizes the Dick positives in a crossed ward it is not proof that such immunization has cut short the spread of infection. Of course such passive immunization has been of use to us where we did not want to close the diphtheria ward. Each new addition received a protective dose of scarlatinal antitoxin along with their curative diphtheria dose thereby allowing us to carry on without waiting until the incubation period of the disease was up. We have had one failure with this method, the case mentioned previously, but on that occasion the error was in using a poor antitoxin.

The work proves that the test is of very little value as a diagnostic agent in scarlet fever. The percentage of negatives in the early days of the disease and the residual positives in convalescence both prohibit any workable deductions being drawn from the results. One useful fact emerges, namely that one can put, without danger, a Dick negative reactor into a scarlet fever ward. This is the

procedure/

procedure we have carried out with all our cases of doubtful scarlatina that showed no sign of any other infection. It was a great help in relieving the congestion in an observation ward. With a Dick positive reaction in the early days of scarlet fever, one can neither say that the person has nor has not had the disease. Nor is the change in a positive reaction a proof of infection. In some true cases the reaction never became negative, while in others with very doubtful clinical signs, a "double plus" reaction in the first days of the infection became negative by the twenty first day. It is as difficult to explain the negative results in the early days of true scarlatina as to account for the persistent positives. It may be variations in strains of the invading organism or due to the peculiar idiosyncracies of the victims.

One cay say quite definitely that a Dick negative reactor will not take scarlet fever while a Dick positive may, provided a reliable toxin was used in the performance of the tests.

Of active immunization I have had very little experience. Forty of the staff of the hospital were Dick tested with only two positives resulting. This is only 5% in comparison to the 12-20% found in Schick-testing. Those two were actively immunized by increasing doses of toxin starting with 250 skin test doses and going through 500, 1000, 5000 to 10,000 doses with four days between the smaller doses and a fortnight between each of the last three doses. The immunization against scarlet fever was an innovation and such a procedure was adopted to prevent the practice falling into disrepute. Each nurse reacted differently. Both had pain, redness and tenderness about the site of injection after each and all of the doses but except after the first dose, one nurse had also severe headache, but was not sick, while the other had nausea and vomiting/

vomiting but no headache. In neither was there any sore throat or rash. When retested four months after the last injection, one was found to be Dick negative while the other was strongly positive, giving a reaction 40 x 30 m.m. R.F. This confirms what others have noted, the difficulty of making strongly Dick positives permanently immune.

With regard to the samples of toxin tested for Dr O'Brien it was found that a toxin diluted with an isotonic buffered solution was superior to those made up with normal saline or with hypertonic or hypotonic solution. By parallel tests, the toxin diluted 1-1000 with the isotonic fluid was found to give a reaction somewhat larger than that obtainable by using a 1-500 dilution in saline but smaller than that from a 1-250 dilution in saline.

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THE ANTITOXIN.

The Schultz-Charlton reaction.

Types of rashes.

Sites of injection.

Results.

The Antitoxin treatment of Scarlet Fever.

Antitoxin used

Indications for administration.

Changes occurring in a serum-treated case examined in detail.

Complications in the series and comparison with untreated cases.

The fatal cases.

Analysis of the results.

The usefulness of the antitoxin.

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THE SCHULTZ-CHARLTON REACTION.

In 1918 Schultz and Charlton, working in Vienna, found that the serum of a patient comvalescent from scarlet fever would, when injected into the skin of a case of acute scarlatina, blanch the rash while serum taken from a patient in the first days of the disease would not. This reaction is called the obliteration of rash or blanching test and is of use as a means of separating a true scarlet fever rash from those scarlatiniform eruptions found in German measles, in sepsis and after enemas. In passing it may be mentioned that the test has been adapted to the diagnosis of other diseases, eg. the instance of the punctate rash in staphylococcal toxaemia being blanched by anti-staphylococcal serum.

It is more convenient to use the curative antitoxin serum than to depend on an adequate supply of convalescent serum. For this purpose parallel tests were carried out with numerous dilutions, both of concentrated and unconcentrated antitoxin, both Parke Davis and Burroughs Wellcome brand. The results are tabulated according to the dilution used and the age of the rash.

Although the eruption in scarlet fever is characteristic there are many sub-varieties. The typical rash is where it is made up of minute punctations of a pink colour set closely together. On the one hand the punctations may not be distinct and the result is a more or less homogeneous erythema which may be pink or red in pink, while on the other hand they may have grown in size until they are papular with or without a crowning vesicle. Sometimes the rash has a morbilliform appearance especially on the extremities, at other times there are areas which resemble or are part of chafed skin. Very occasionally one comes across a condition of the skin of the hands and feet where there is an appearance like the bramble

marking/

marking on a golf ball. The skin is raised into little rounded papules, set closely together and not necessarily congested. This formation I have seen only in scarlet fever and never in any other disease. It is different both from a sudamina and from a miliary scarlatina. Lastly there is the fading scarlet fever rash, the eruption in its third or fourth day. In this type the punctae are faint and intermingled with the brownish mottling and brown-purple background left by the vanished exanthema. This appearance was recorded as a "fixed rash". Each of these types react differently, some being blanched with very high dilutions of serum, others being very resistant. The third factor, the most important, is the age of the rash. The shorter time the rash has been in existence, the easier it is blanched.

In conducting this series of tests, it was the practice to perform several tests on each person using different dilutions of antitoxin and different sites. The chest and abdomen will be found the most convenient. In those sites the rash is likely to be characteristic and as early as can be expected and besides, if any reaction results, it stands out from the surrounding skin. In exceptional cases where the rash has faded from the body, a test can be performed on the skin of the instep where probably the rash will be found to be fresh. Usually four tests were made with two dilutions of antitoxin, one of each on the chest and one of each on the abdomen unless more suitable places were found.

Suppose .2 c.c. of a 1-100 dilution in normal saline solution of Parke Davis & Co's concentrated scarlet fever antitoxin was injected into a scarlatinal rash of twelve hours' duration, one would find, in about eight hours, that the punctations about the site of injection were not so distinct as previously. Between twelve and twenty hours after injection, the rash would have completely disappeared, leaving a clear oval space about 40 x 25 m.m. in size, free from eruption and perhaps

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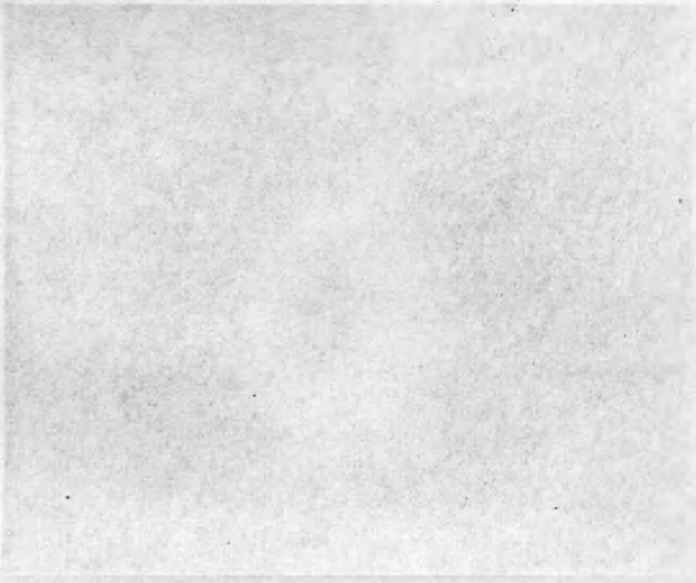

PLATE II.

The Schultz-Charlton Reaction.

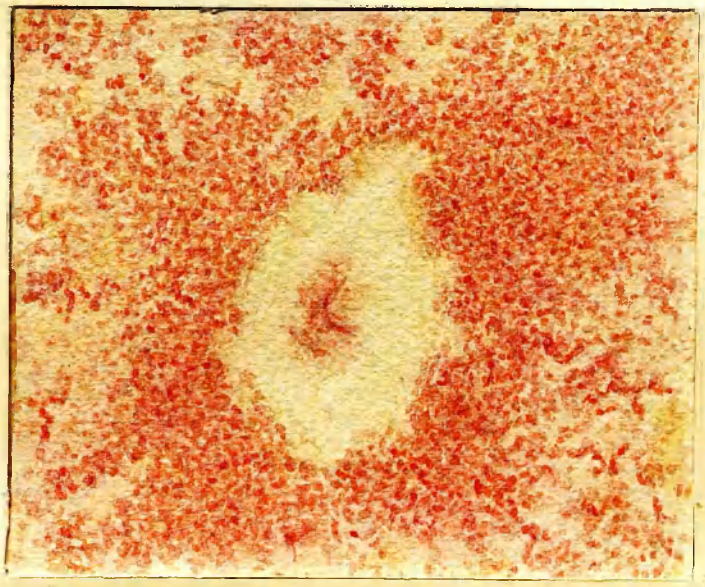

PLATE II.

a slightly pink central spot. The state of affairs would be similar to that depicted in Plate II. This clear space remains free from rash until the eruption has disappeared from the body and even then it stands out as a pale oval piece of skin against the golden brown staining left by the exanthem. It may be distinguishable ninety hours after the performance of the test. This type one would be justified in calling an obliteration of rash test. It has been recorded that such areas do not desquamate but unfortunately I have no definite evidence on this point.

All tests are not so successful as the one described. Sometimes it is merely a diminution in the intensity of the eruption that results with a faint punctation being visible in the pale space, at others the reaction is limited to a circle about 15 m.m. in diameter. In many there is no reaction whatever. I have not seen the return of the eruption in any of my tests. The best results are obtained in rashes of less than forty-eight hours' duration and the greatest percentage of positives is among those of twelve to twenty-four hours old. The exact figures will be found in the table appended. The faintly punctate eruption with an erythematous background is more easily blanched than those that appear bright red or resemble chafed skin. Those containing a papular element do not react at all well, very few showing any lessening in degree of the eruption. This last group includes, the papular and miliary types and also the morbilliform. The fixed rashes, those of several days' duration are very resistant, besides, they sometimes fade away before the time is up for reading the test. The giving of scarlatinal antitoxin I have found, contrary to others, spoils the test as the general effect of the antitoxin starts before the local injection has had time to act. Performing a blanching test on patients who required antitoxin was therefore early discontinued.

Table 4

TABLE 4.

RESULTS OF BLANCHING TEST IN SCARLATINAL RASHES OF VARIOUS AGES WITH DIFFERENT DILUTIONS AND TYPES OF ANTITOXIN.

Dilution	B.W. 1-10			B.W.1-100			B.W.1-250			B.W.1-500			B.W.1-1000			B.W.1-1000c			B.W.1-4000c			P.D.1-100			P.D.1-1000			Analysis of total		
Age of Rash.	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-	No.	+	-
12 Hrs.	4	4	0	---	---	---	---	---	---	---	---	---	2	2	0	---	---	---	---	---	---	12	12	0	10	9	1	28	27	1
1st day.	51	34	17	16	10	6	8	0	8	12	4	8	23	13	9	22	17	5	21	10	11	15	11	4	7	2	5	174	101	73
2nd day.	59	31	28	17	13	4	2	0	2	30	9	21	32	11	21	11	5	6	12	5	7	4	1	3	2	0	2	169	75	94
3rd day.	6	5	1	6	4	2	---	---	---	6	0	6	6	2	4	2	2	0	2	0	2	1	0	1	1	0	1	30	13	17
4th day.	4	1	3	---	---	---	---	---	---	2	0	2	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	6	1	5
5th day.	2	0	2	---	---	---	---	---	---	2	0	2	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	4	0	4

Total 411 tests
217 positive
194 negative.

B.W. 1-10 etc. = Burroughs Wellcome unconcentrated scarlatinal antitoxin diluted with saline 1-10 etc.

B.W. 1-1000 c etc. = Burroughs Wellcome concentrated scarlatinal antitoxin diluted with saline 1-1000 etc.

P.D. 1-100 = Parke Davis & Co., concentrated scarlet fever antitoxin diluted with saline 1-100 etc.

\+ = Rash blanched.

\- = No effect produced.

Table 4 gives the results of some 400 blanching tests on scarlet fever patients with rashes at various stages. The results are extended so as to show the comparative value of the different antitoxins and dilutions used. Latterly the 1-100 dilution of Parke Davis & Co's concentrated antitoxin was the only one used as it gave the most consistently positive results. I have not had good results with pure antitoxin. In some parallel tests the results were much better with a 1-100 dilution than with the same antitoxin used neat. It is probably owing to the greater rapidity with which a saline solution can infiltrate the surrounding tissue. But in all cases the stronger dilution of serum above 1-10 of the unconcentrated type, gave better reactions than the weaker solutions. I have not been able to procure blanching with the very weak dilutions 1-1000 and 1-4000 of unconcentrated antitoxin used by others. It will be seen that the chance of success when the rash has lasted more than 48 hours is very slight. The best time for reading the results is twenty-four hours after injection. Even with a rash which previous experience has shewn to be easily blanched, the chance of a positive result is not definite. Taking the eruptions of twenty-four hours' duration, 73 out of 174 failed to respond. Several other types of rashes were tested, food and septic rashes, and the exanthem of measles and German measles. All, without exception, showed not the slightest response to even the lowest dilutions of serum, even when, as in some of the measles cases, injected within six hours of the onset of the rash.

The reaction seems to be a true local passive immunity, the antitoxin protecting the small area of skin from the toxin. With the report of the rash reappearing one would deduce that the immunity was of very short duration unless a stronger dilution of antitoxin was used. The central pink area in the clear zone I had always regarded as being due to the needle

prick/

prick or perhaps to slight local inflammation (the containers not being hermetically sealed and very liable to be contaminated) but Blake of the M.A.B. considers it to be a definite part in the reaction.

A positive result to the test is of infinite value but a negative is of very little aid. The number of negatives in true scarlatinal rashes makes the occurrence of a negative reaction in a doubtful rash of no help whatever. But where the test does help is in those cases of scarlatina without fever and without a sore throat. Three of our cases, which had been regarded on the appearance of the rash as due to enemas, were diagnosed by means of this reaction. It has most certainly a place in the diagnosis of scarlatina.

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THE ANTITOXIC TREATMENT OF SCARLATINA.

The following account of the serum treatment of scarlet fever is based on work carried out from a clinical standpoint only. No endeavour was made to find out the actual change in the cell content or in the amount of circulating toxin in the blood but merely to note the results of such alterations and to assess the value of the treatment. For this latter reason the standard by which the cases were compared was a composite one conjured up from the appearances and changes in previous untreated subjects.

Any comparison between scarlet fever and diphtheria must allow for the difference which diphtheria antitoxin has made to the death rate in that disease. Therefore while one expects and looks for complications in diphtheria in spite of the antitoxin, one would demand some difference in the incidence of complications in antitoxin treated cases of scarlet fever. Even if such a difference was not remarkable, the action of the antitoxin could still be gauged by the immediate change produced. This latter fact has been taken into account in formulating the conclusions.

The method of collecting the observations on the course of the disease is the same as in the investigation into the types of streptococci found in scarlet fever, by filing card, a facsimile of one being appended. On the front one finds the particulars about the patient along with the record of progress; on the back, the day of disease on which antitoxin was given, the complications and the day of disease on which they occurred and the opinion as to the effect of the antitoxin. At the foot is put the day of disease on dismissal and the number of days residence.

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The serum was in all instances the newer concentrated type, obtained from the two main suppliers for the British Isles. That from Burroughs Wellcome was obtained through the courtesy of Dr O'Brien of the Wellcome Research Laboratories, Beckenham, Kent, while that from Parke Davis & Co. was purchased commercially. Little difference in action was detected between them so that the results are considered together. Both brands of antitoxin are produced by the Dick's method, the gradual immunization of horses to increasing doses of scartinal toxin. I have not had any experience with antitoxin produced by the two other methods, that of Dochez already described in the section on the literature of the subject, and that elaborated by two Chinese investigators in Shanghai. The last antitoxin is more an antibacterial serum as only the washed streptococci are used in its production. The originators claim for it a curative value much in advance of that of the pure antitoxins.

With one exception the serum was administered intramuscularly into the outer side of the right thigh, an initial dose of 10 c.c. being the rule. In this hospital, it has been the practice to desensitize all patients who require serum treatment. Once, we had a fatal case of anaphylaxis and, although it may appear preposterous and quite unnecessary, all subsequent patients with the exception of those of extreme urgency are desensitized by subcutaneous doses of five and ten minims of serum with a half hour interval. Where the child has had serum previously we have given the full dose in small amounts of 5, 10, 20, 40, 80 m. and so on, each dose being double the previous one and again with half hour intervals. The earliest serum rash obtained was 10 minutes after the first desensitizing dose, that is before the second injection was given. This case was exceptional as she

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had had 50 c.c. of unconcentrated serum a month previously. It is a debatable point as to whether this desensitizing decreased the incidence and severity of serum rashes or not. As all our diphtherias are treated likewise, we have no standard of comparison. Usually the areas where the desensitizing doses were given, showed up as red blotches, 4" x 2", within twelve hours of injection and again on the onset of the serum rash. In some the rash was confined to the aforementioned areas.

In one instance, the intravenous method was adopted. In those cases where serum is given intravenously, one must expect a somewhat severe reaction. This takes the form of a rigor starting about one hour after injection. The time of onset can be timed almost to within five minutes and the severity varies with the dose and the age of the patient. We have found that 10 c.c. is as much as one can give safely. More than that produces extreme disturbance and proportionately greater in adults who react very severely. After desensitizing, the serum is given undiluted and very slowly into the median basilic or any other convenient vein.

The type of case treated was dependant on the material available. Scarlet fever is one of those diseases where the virulence is steadily decreasing. There was no suitable toxic case admitted during the two years under review, and the subjects had to be of the moderately severe type or cases where it would be interesting to know their reaction to serum. Some, in fact, would probably have gone on quite as well without serum but it was thought advisable to resort to it on account of one or two outstanding symptoms. Especially was it administered to those with severe naso-pharyngeal involvement in an endeavour to diminish the incidence of otitis media.

The danger in restricting the giving of serum to those scarlet fever patients with moderately severe attacks is that many of those cases going septic have started as mild scarlatina simplex. Charts 4 and 75 are of such patients. There is no way of separating out these exceptions and we have taken the wiser course of sometimes erring on the safe side. Just why they should go septic is a mystery. Perhaps the antitoxin content of the blood is a variable quantity, varying from hour to hour. The invasion of the disease is in the nature of a battle where the lines retreat and advance from time to time and where the defenders are finally victorious would represent the antitoxin being produced in such an abundance as to completely neutralize the invading toxin. On the other hand, when the invader is the stronger, perhaps aided by a near relative, (another type of streptococcus) they completely overrun the defenders, in the case of the disease producing septic scarlet fever. The foregoing theory may be somewhat of a fantasy but there is some support for it from the course of a few isolated cases, e.g. patients with charts 4 and 75 and from the results of the Dick test.

The accusation may be made that these two children quoted never had scarlet fever and Chart 4 is brought up as evidence, it being pointed out that the temperature and pulse rose on the third day after admission, giving her just enough time to contract the disease in the ward. But that argument, in this instance at least, is void as the rise in temperature and pulse was accompanied by rhinorrhoea and a general disturbance but no rash whatever. Again there are cases where the onset of septic complications takes place within twelve hours of admission or where as in the case of Chart 93. the boy is isolated at home, with no opportunity for cross or added infection.

Another help in the giving of serum is the occurrence

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of familiar traits. It was found that, where one member of a family has been admitted with a particular type or a certain degree of severity of scarlet fever and another member contracts the disease, not necessarily from the first member, the last admitted patient has the same type or same degree of severity of the disease. One is able to see those cases in a hospital which drains a particular section of a city. There are two families in the subsequent series, where that trait was demonstrated. It may be that the variety of symptoms and signs of scarlet fever may be more due to individual reaction than to changes in the nature of the invader.

Lastly we have made it a practice to give serum to all adults, particularly females over 30 years of age. Several of the deaths from scarlet fever previous to antitoxin treatment were in women between 30 and 40 years of age, some of them without any detectable cardiac impairment. They died of cardiac failure. Chart A is of such an unfortunate patient, a woman 32 years old, with quite definite but mild scarlet fever; apparently progressing favourably except for a few twinges of pain in the arms and legs. The throat was very congested to begin with and cleared up rapidly but the temperature still remained up and the pulse soft. Quite suddenly she complained of a feeling of sickness and faintness: the pulse became imperceptible and she died within half an hour. There were others of the same type and certainly not those one could label toxic scarlet fever.

To follow clearly the changes in a serum treated case of scarlatina, let us take the picture of a moderately severe instance and mention shortly the transformation. The child is a girl of five years of age and in the second day of disease. She lies in bed drowsy or with periods of restlessness./

restlessness. The face is flushed and puffy, the circum-oral pallor is marked and there is some watery discharge from the nose. The eyes are bright with a tendency to lachrymation and the conjunctivae are tinged pink. The rash of eighteen hours' duration is punctate in character and bright pink in colour, particularly so on the trunk and arms, less so on the legs. It is erythematous on the back and chest and almost blotchy on the arms and the skin is dry and hot to the touch. The tongue is thickly coated with a white fur and is somewhat dry but with clearer areas at the margin. The buccal mucosa is pale in comparison to the much reddened soft palate and the inflamed tonsillar region. The tonsils are big with a few specks of exudate on both and there is some post-nasal discharge on the posterior pharyngeal wall which is inflamed. The cervical glands are palpable at the angles of the jaw and slightly tender to the touch. The puffiness of the face, although not reaching the bloated facies of measles, is undoubtedly present in scarlet fever. It is amazing in the cases of scarlet fever to watch the change in appearance with defervescence. A child, to all purposes well nourished, with fat round face and chubby arms and legs, becomes after a fortnight oval of feature and slim-limbed. The puffiness is really a dermal change as demonstrated by the Dick test. It appears to be an engorgement of the skin capillaries, with one might suppose some oedema or tumefaction. The pink eyes are not an uncommon sight in sharp scarlatina.

With the giving of anti-toxin immediately on admission, one would find the child's condition improving visibly in 24 hours. The temperature would reach the 99°F. line in 36 hours and become sub-normal three days afterwards. The swallowing, which has hitherto been difficult and painful, would become easier and the inflammation would have gone from the throat forty-eight hours after the injection of serum. The rash will have disappeared by

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the thirty-sixth hour and in convalescence the desquamation will be slight and rather late of onset.

Let us examine these points in detail. The change in the serum-treated scarlet fever is more one of symptoms than of signs. (To a certain extent it depends on the time of administration and the following description applies to cases where the serum has been given within three days of the onset of the disease). The earliest effect is in the appearance of the patient. They look better. Although a vague term, it is, at the same time, accurate. The glitter has gone from the eyes; the face is thinner and the expression has altered, the distressed look giving place to one of ease. So characteristic is this change that its absence has been made an indication of a further dose of anti-toxin. It appears within twelve hours of injection and is seldom accompanied by a change in the pulse rate or temperature. Case No.6. illustrates this point. The patient, a girl of fourteen years of age; was admitted with a very sharp attack of scarlet fever in the second day of disease (first of rash). The rash was intense; the face puffy and flushed and she looked and felt miserable. The following morning she was given 10 c.c. A.S.S. (Anti-scarlatinal serum) and in eighteen hours the face had become thinner, although still flushed; the rash had faded and she felt better but there was little alteration in the pulse rate or temperature. Case 19, 23 and 24 are similar. The face remaining flushed, is an interesting point, present in a fair percentage of the series. As in the above cited example, it is possible to have a rash disappearing from the trunk and limbs within eighteen hours without any apparent difference in the colour of the face, although it is the rule to have a lessening of the circum-oral pallor, at least of its sharp outline. The case of which No. 5 is the chart is another instance of the change in appearance. The

patient/

patient, a boy of three, had a moderate attack of scarlet fever but developed in his second week of disease severe cervical adenitis which later became septic. He was given 10 c.c. A.S.S. on his thirteenth day and although it did not alter the course of the disease it had quite a beneficial effect on his appearance. On the other hand Chart No.14 is of a patient who showed a sudden drop in temperature and pulse rate within eighteen hours of injection of anti-toxin without the least appreciable improvement. This again emphasises the importance of appearance in gauging doses.

Where the serum has been administered in the afternoon, it is seldom that it improves the chances of a good night's rest. In fact one often finds that the patients become more restless and at times actually delirious as is frequently the case in untreated scarlatina. Headache is apt to persist for the first twenty-four hours even although there is a feeling of general well-being.

The fall of temperature is more by rapid lysis than by crisis. In about two-fifths of the series the fall is by crisis with a very characteristic sequence. Chart No.82 is a typical example. Until thirty-two hours after injection there is practically no change in the height of the pyrexia; then there comes a sudden drop to 99°F. with a "dancing" about the 98°-99° area for three to four days before it finally settles. Chart No.3. is an even more outstanding example. The drop in temperature takes place at the twentieth hour after injection and the secondary period occupies five days. In Chart No.4. (already referred to in the paragraph on administration) the serum, although given later, on the seventh day, brings about a fall by crisis at the 48th hour but the secondary period lasted for 40 days. This case was one where one felt that without serum, she would have become septic. Chart No.83 is an example of the crisis being delayed for 36 hours, and the

secondary/

secondary period lasting only two days, while Chart No.40 is one where the crisis, with a drop of only 2°F., is at the 24th hour, but the secondary period extends to 5 days, both in moderately early cases of scarlet fever without any detectable abnormality or ensuing complication.

The usual time of onset of the crisis is between 12 and 36 hours after administration. A few are delayed until the 48th hour but none are before the 12th with an average between the 18th and the 24th. The secondary period lasts on an average four to five days in an uncomplicated case. In none was there a fall of temperature to 98°F and it remained there from that time onwards. In Chart No.41. the crisis is at the eighteenth hour with a drop to 99°F. and in another twelve hours to 98, about which it remains for four days. But as these temperatures were taken in the axilla, one would expest at least a normal morning temperature of between 97 and 98°F., and therefore this case also falls into line with the others.

In more than half the series, the fall in temperature was by rapid lysis, usually with rather a steep slope to start and then tailing away. Charts Nos.11 and 107 are excellent demonstrations of this type. Of course in a morning and evening chart, this would appear as a fall by crisis but the four hourly chart shows clearly that it is a true lysis. But here again there is the unsettled temperature for several days. Chart No.89 is probably the most interesting one of the series. It is of a fifth day miliary scarlet fever patient treated by ~~the~~ intravenous injection of antitoxin. It will be seen that except for the sharp rise of temperature following injection there is no apparent difference in the course of the pyrexia. In fact it did not influence it in the slightest.

As regards comparison with the normal charts, B & C are of interest. They are of patients with scarlet fever

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of about equal degrees of severity, the one being given serum as she had some cardiac impairment. It is plain that the difference in the course of the pyrexia took place about twenty-four hours after injection. Up to that time the one chart is a replica of the other. After that time the chart of the serum-treated patients shows a rapid lysis to the normal area although there is that "dancing" between the 98 and 99°F. lines for six days. The gain is exactly two days less pyrexia.

The exceptions falling into neither of these groups are, where the temperature falls slightly, then becomes intermittent or is intermittent from the beginning, the administration of antitoxin having no effect. The majority are of scarlet fever patients with some complication. Chart No.12 is of a moderately severe scarlatina complicated by erysipelas of the face starting simultaneously. Here the temperature which has remained at the same level for three days, drops by crisis forty eight hours after the injection of the serum but becomes remittent almost immediately afterwards. The serum had no effect on the course of the erysipelas. It is remarkable that in spite of the admirable conditions found in scarlet fever patients, the low vitality of the skin, the fissures about the nose and the purulent discharge, erysipelas is comparatively rare. Chart No.15 is one where the temperature remains high until the twelfth day by which time both ears have discharged. Otorrhoea is the commonest cause for continued pyrexia in the first three weeks of scarlet fever. Time and again one finds that a temperature which has been unsettled for almost weeks comes down to normal when otorrhoea appears. Usually no sign whatever is present of any middle ear disease although in a small percentage the glands draining that area are palpable or tender or there is earache without any visible change in the tympanum. Chart No.2. is similar to No.15 except that there is a

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period of apyrexia. But the cause was the same, otitis media. In others there are various possible agents e.g. in Chart No.73 the boy had a septic arthritis of the left ankle and in No. 114 the patient had, at the same time, lobar pneumonia. But in a few the pyrexia remained without obvious cause. It is with this last group that one felt that they were on the point of becoming septic. Nos. 44, 50, 71, and 92, are in this group. In this connection Charts Nos.38 and 38A may be considered here. The patient, a girl of five years of age was admitted with sharp scarlet fever. She was a sister of a patient treated ten months previously without antitoxin who had turned in septic scarlatina. This latter case recovered and was dismissed over nine months after admission, free from all discharges. A fortnight after dismissal her sister (patient 38 under review) was admitted and was given antitoxin in case she should follow the course of the previous patient. A week later their father (No.54) was sent in with the same type of scarlet fever as case 38 and also was given serum. All this time the originator of the trouble was at home showing no sign whatever of any discharge or possible nidus. Finally three weeks from the admission of the first return case the mother (Case 39), the last member of the family, was admitted with scarlatina. As these cases occurred at the beginning of the antitoxin treatment when antitoxin was not plentiful it is possible that they would not have been given serum had the previous family history not been known. But to return to the charts, No.38 is where 10 c.c. A.S.S. were given on the second day of the disease, while No. 38A is the chart of the same case after the development of secondary scarlet fever. It will be seen in Chart No.38 that the temperature comes down by lysis to go up again two days later and to remain intermittent for more than a fortnight. During this period, the child was listless and drowsy but the only discoverable abnormality was the abundance of acetone in the

urine,/

urine, decreasing in amount as the temperature settled. In Chart No.38A, the primary pyrexia is higher, falling on the fourth day, remaining down for three days and then becoming unsettled as in Chart 38 for about fourteen days. No antitoxin was given for the second attack as the symptoms and signs were slight and again no cause was discovered for the secondary rise in temperature.

The effect of serum on the course of the pulse rate is also shown on the charts. The pulse line in the majority of the cases follows very closely the temperature. In a small fraction, the pulse rate drops suddenly between the twenty-fourth and the forty-eighth hour while the temperature comes down by lysis but such is exceptional.. An interesting fact appears from consideration of these pulse rates. In one third of the charts of adults with moderately severe scarlet fever and temperatures from 101° to 103°F, the pulse rate is below a hundred per minute and in one it is eighty. This definitely lessens the value of the pulse rate as a diagnostic aid and in adults as a slow pulse should not be taken as negativing scarlet fever when met with in a patient over sixteen years of age. The change in the character of the pulse is one of lessened tension. The pulse becomes quieter if one may use such an expression.

But both temperature and pulse remain unsettled until all sign of the acute phase of the disease has disappeared. In comparing the observations on the course of the illness and the temperature and pulse charts, one finds that where the patient is reported as "back to normal" the pulse and the temperature are found to be permanently settled. The nose and throat combine the two areas which react the most and the least satisfactorily. It is very pleasing to find a thick purulent discharge or a thin watery excoriating discharge clear up as if by magic in twenty-four hours. Case No.1. shewed such a change. Although the serum was given late in the disease, the mucopurulent discharge stopped completely in twenty-four hours./

hours. Case No.5, where the discharge had been present for some days, also reacted in twenty-four hours although here, the effect was merely a lessening of, and not a complete stoppage. Post-nasal discharge, on the other hand, is not so tractable and one must not expect much improvement before five days.

The changes in the condition of the mouth and throat are rather variable. The average time which elapses before improvement can be seen in the throat is thirty-six hours. Of course, as has been mentioned previously, the pain or discomfort in swallowing disappears very rapidly, in some in under twelve hours, but visible change is seldom present before twenty-four hours after administration. The alteration is a lessening of the inflammation with a more gradual disappearance of any organic injury. Where there has been a dry glazed tongue with brownish white fur, in twenty-four hours, the glazing disappears, the tongue becomes moist and red and the fur quickly lessens. In forty-eight hours, the tongue is probably clean and pink in colour and the papillae stand out clearly. That is to say, in two days time a tongue which was dry and glazed becomes smooth and moist with no vestige of inflammation. At times it appeared that the use of antitoxin accelerated the peeling of the tongue but this was not a uniform result. In a few, one found that a tongue which was thickly coated and red on the day of administration, became clean and pink in twenty-four hours. The change in the soft palate and the throat is the same but occurs later. The redness fades from the palate, the inflammation and tumefaction from the nasopharynx and the exudate disappears from the tonsils. The time taken for these alterations to occur depends on the number of days the patient has been ill before the serum was administered./

administered. Take, for example, Case No.28, a woman of thirty-seven years of age, admitted with severe scarlet fever. On the third day of disease she was given 10 c.c. A.S.S. At that time the throat was intensely inflamed with enlargement of both tonsils which were covered with exudate. The next day, twelve hours from the time of injection, there was no improvement in the throat condition and a second dose of 10 c.c. A.S.S. was given. The next day again, that is thirty-six hours from the time of the first injection, the tongue which had been dry and red became more moist and had lost the intense crimson appearance but the throat was still inflamed, although the exudate was less, and swallowing was still difficult. It was not until the sixth day of disease that the dysphagia disappeared and the throat regained its normal appearance. Case No.43 is one where the serum was administered on the first day of disease when there was intense pharyngeal and tonsillar inflammation with patches of exudate on both tonsils. Eighteen hours afterwards, the inflammation had gone completely from the throat and the tonsils were clean and pale.

In writing the description of throat conditions a slight amount of hyperaemia is considered as congestion and the word inflammation retained for the picture when the mucous membrane is red when the colour becomes a deep crimson or almost purple tint with sometimes a little haemorrhagic spots, the phrase intense inflammation is used. By exudate is meant the soft cheesy or pussy material which collects about the tonsillar or pharyngeal areas and which can be scraped off with a spatula.

The difference in time between the action on the tongue and on the throat is also illustrated in case No.45. The patient, a boy of eight years, with severe although not toxic, scarlet fever, was given 10 cc. A.S.S. on his

third/

third day of disease. The tongue was thickly coated and dry, the throat was intensely inflamed with enlarged and patched tonsils and the cervical glands on both sides were palpable and tender. Twenty-four hours later the tongue was clean, red and moist but the throat condition was quite unchanged. Forty-eight hours later the tongue was less red, the tonsils were clean but the throat was still inflamed although not so intensely as previously. And it was not until the sixth day of disease that the naso-pharyngeal congestion completely disappeared. In some it was noticed that the inflammation had gone completely from the throat before the tonsils were rid of exudate. Case No.41, a girl of three years of age, admitted on her third day with a sharp attack of scarlet fever, is an example. Thirty-six hours after receiving serum, the throat had become pale but the right tonsil was still patched. Case No.18 is another where the inflammatory throat condition disappeared before the tonsil surfaces were clean. The number showing this phenomenon is not great and they must be regarded as exceptions.

Taking the other side of the picture, there were some that showed no throat improvement whatever. In case No.54, a man of 29 years of age, admitted on his first day of disease with a moderate degree of throat inflammation, the dysphagia and hyperaemia did not disappear until after five days residence. The same result is found in Case No.20, a boy of five years of age with a mild attack of scarlet fever but with severe throat involvement. Here it was four days after the administration of serum before the throat was clean and pink. There was no doubt as to the diagnosis in either case.

Only one of the series had sinusitis. This was a woman of forty-seven with moderately severe scarlet fever. The throat condition cleared up rapidly under serum, the temperature coming down by lysis but not settling completely

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until the eleventh day of disease. Frontal headache with tenderness on pressure over the medial region of the left orbital ridge remained for more than a fortnight as did the presence of pus in the left nostril.

A very curious occurrence is the recrudescence of the tonsillitis at some later period in the disease. Twelve of the series had a secondary tonsillitis and one a quinsy quite apart from the primary throat affection. In four of these cases, it occurred about the fourth week of the disease, from the twenty-fourth to the thirty-second day. The others were all previous to their twelfth day of disease and in some as early as the fourth day. Another point is that except for the three, all the patients attacked were adults. This latter fact may be owing to the older patients being able to complain while other instances in the children were missed. But this is improbable as all serum treated patients were examined daily and any pharyngeal congestion or difficulty in swallowing would have been noticed. One example will suffice. Case No.39, when admitted, had intense inflammation of the throat with dysphagia but reacted well to serum, the throat$ clearing up in forty-eight hours. Three days later the throat became again very painful with the return of the inflammation and the dysphagia and the condition yielded very slowly to local treatment. To give a satisfactory explanation is difficult. Unfortunately note of the usual state of the tonsils or of the causal organism was not taken but in none of the cases was there the vestige of a rash or eruption. Supposing streptococci were the invaders, then they must be of a different strain to those causing scarlet fever or the immunity conferred by the antitoxin is very short-lived. But as the Dick test, which we may take as a satisfactory indication of immunity/

immunity, is usually negative until after the fourteenth day, if it does become positive again, we are forced to conclude that these patients are susceptible even in the early days of convalescence to other strains of streptococci or that the immunity to scarlet fever does not protect the pharyngeal and tonsillar mucous membrane even for a short period. It is certainly established that a negative Dick test does not exclude the possibility of a tonsillitis being due to streptococci indistinguishable from those isolated from cases of scarlet fever. That these throat affections were diphtheritic is not the explanation. Although no bacteriological examination was made, the clinical pictures did not suggest diphtheria nor were there any sequelae referable to diphtheria.

The exanthem of scarlet fever reacts very quickly to antitoxin. Few rashes, provided they are not older than thirty-six hours, remain longer than twenty-four hours after the administration of an adequate dose of serum. With the erythematous type, where the tint is bright pink and the punctations are almost indistinguishable from the surrounding redness, the rash is wiped out overnight and within eighteen hours of injection, the skin becomes a delicate golden brown. Where the rash is more intense, the change takes twenty-four hours and is not so complete, the skin becoming a brown colour with darker points where the brighter punctae have been. The effect is best seen on the trunk as the rash on the limbs is not always typical. Case No.9, a second day scarlatina, is one where the rash disappeared quickly. The eruption was profuse, most marked on the trunk and beetroot in colour, with definite punctae. Eighteen hours after receiving serum, the rash was represented by a stippling of the now brownish skin. Case No.7 is rather different. This patient was also in her second day of disease and the rash also disappeared within eighteen hours but a bluish mottling

remained/

remained and there was no sign of any other improvement. Case No.25 is similar to Case No.7 - the disappearance of the rash without any improvement in the condition. It may be argued that the disappearance indicated collapse but in Case No.27 the patient was just as ill as the other two but the rash, although twenty-four hours old, remained. In one case, No.11, the rash disappeared in twenty-four hours but returned brighter than ever at the forty-eighth. The blanching test, which had been carried out before the patient received serum, also stood out more distinctly. This curiosity seems to be comparable to those positive Dick test reactions which return after having faded.

On old rashes, the effect is slight. The erythematous background is removed but the punctae remain. This immobility, of course, is only found frequently when the eruption has been present for forty-eight hours or longer. In case No.42, we have an exception. The rash was less than twenty-four hours old but it was not until the fourth day after injection that the skin was clear.

Where there are papules they remain unaffected as one found in the case of No.31, a girl of eleven years of age admitted on the second day of disease but with a papular although first day rash. It is possible in this particular instance that the rash which was more profuse about the elbows and knees, was more septic in origin than scarlatinal. But the temperature and throat condition reacted to the antitoxin and desquamation was typical.

The action on a miliary rash is best illustrated by case No.89, the patient treated by the intravenous route. This boy had a sharp attack of scarlet fever when admitted on his third day of disease. By the fifth day, the rash had become brighter and in places miliary, the throat was still inflamed and the temperature was slow in settling. In an endeavour to save time, the serum was injected intravenously

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and in eight hours there was a definite appreciable change. The general condition was improved, the rash was less bright and the miliary points were less numerous. Twenty hours later, all the miliary points had disappeared, leaving little flat placques, the size of the head of a pin, slightly raised above the surface. The vesicles had just sunk down and the fluid had been absorbed. Forty eight hours after injection the skin was a dark brown colour with deeper tinted points where the more distinct punctae had been and the placques were still unbroken, contrary to what one would expect to find in an untreated case of miliary scarlet fever. Desquamation did not appear on the trunk until the twelfth day when there appeared, in the place of the brown placques, tiny white points as if little bubbles of air had been imprisoned under the skin. These broke and became typically pinhole in character but the desquamation was not so extensive as one would expect. In some patients with a miliary rash the antitoxin seemed to have no such effect. In Case No.101, where there was an intense miliary eruption, the defervescence and desquamation was exactly the same as in a non serum treated instance. But in spite of these exceptions, for they are exceptions, the vesicles in a miliary scarlet fever rash, when treated by antitoxin, flatten out into tiny placques without immediate rupture.

Flexure staining was quite uninfluenced. There did not seem to be any diminution in the intensity or prevention of its appearance. As antitoxin does not alter the appearance of the skin after the rash has disappeared, one would not expect it to have any influence on the flexure staining.

The degree and time of onset of desquamation varies with the action of the antitoxin on the rash. Seldom does one find the typical pinhole desquamation on the trunk and arms or the skin coming off in sheets. It is more a

powdering/

powdering as if one had dusted flour over the skin and brushed the excess away. The normal markings of the skin are replaced by fine lines of white powder and it gives one the impression that a slight puff of wind would blow it away. In some areas the desquamation is absent altogether and all that can be detected is a dryness of the skin. In other parts, there may be no diminution in degree, the two commonest sites for this latter type, being the neck and face and the feet. The former may be explained by the assumption that the toxin has acted to its fullest extent before the serum was injected and therefore, as in complications already present in diphtheria, the antitoxin is powerless to undo organic destruction. In reference to the latter situation, the feet, it may be argued, that the desquamation in that site is normally the most extensive, and that that part of it due to disuse is not influenced by the antitoxin. Unfortunately for the value of this argument, the desquamation of the feet is often definitely pinhole. Sometimes one finds that there is more than a powdering, more especially on the hands and legs. Then the desquamation is typical in character but much diminished in intensity.

The time of onset of peeling was delayed from seven to fourteen days but in some, once started, it went through the different stages rapidly and it was not uncommon to find the hands starting to desquamate on the eighteenth day of disease and the feet to be completely free of peeling by the thirty-second. Case No.28 is one in point. The serum was given on the first day of the rash, the first sign of desquamation was a dryness of the skin of the neck with powdering of the forearms and by the twenty-third day the hands had peeled and the desquamation was starting on the feet. On the twenty-seventh day, the feet were desquamating typically and on the thirtieth, the day of her dismissal, the peeling was almost imperceptible.

Sometimes/

Sometimes the desquamation starts as a powdering but proceeds to the pinhole stage. In Case No.33, a girl of thirteen with a rash of two days' duration on admission, the peeling showed first as a dryness of the skin at the neck on the tenth day of disease. On the eleventh there was pinholing on the skin of the forearms and by the twenty-second the desquamation on the arms was advanced, the skin of the trunk was dry and that of the feet powdery. On the thirty-eighth day there was no sign of desquamation anywhere except on the feet where it was typically pinhole about the toes. With Case No.32, who was given 10 c.c. A.S.S. on the first day of the rash, the desquamation was reduced to a powdering over the arms and trunk with none elsewhere, at least none up to the time of dismissal on her thirty-fourth day. Case No.110 is an example of a second day rash treated by antitoxin. On the fifth day of disease three days after the administration of antitoxin, while the rash was still perceptible, the skin of the face was desquamating. On the ninth day there was definite powdering of the upper arms; by the twelfth it was present on the trunk and on the twenty-sixth it was pinhole in character on the hands. On the thirty-seventh all that remained was a few flakes to come away from the feet. In Case No.14 where the serum was not administered until the second day of rash, there was not much diminution in the intensity of the desquamation nor delay in the onset. In others one finds that the desquamation started profusely at the neck, then tailed away to a mere powdering on the trunk.

Shortly, one may expect in a case of scarlet fever when the antitoxin has been administered within thirty-six hours of the appearance of the eruption, to find the desquamation starting typically on the face and neck between the fifth and tenth days of disease and devolving into a dryness of the skin of the trunk and limbs with at the most a faint ring-

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TABLE 5.

INCIDENCE OF COMPLICATIONS IN 120 CASES OF SCARLATINA TREATED WITH ANTITOXIN.

Day of Disease.	No. in each group.	Serum Rash.	Albuminuria	Otorrhea	Adenitis	Rhinorrhea	Rheumatism	Secondary Scarlatina	Jaundice	Secondary tonsillitis.	Mastoid operation.	Sinusitis	Death.
1st.	7	2	-	-	-	-	-	-	-	-	-	-	-
2nd.	45	9	7 x	-	7	8	-	1		4	-	1	-
3rd.	37	5	6	5	1	4	3	2	1	6	-	-	1
4th.	22	7	6 x	2	2	4	-	1	1	3	-	-	-
5th.	4	-	1	-	-	1	-	-	-	-	-	-	1
6th.& over.	5	1	2	2	1		-	-	-	-	1	-	1
Total	120	24	22	9	11	17	3	4	2	13	1	1	3
% incidence.		20	18.3 or 9.15	7.5	9.15	14.17	2.5	3.33	1.67	10.8	.83	.83	2.5%
C.B. Ker's figures.		8.2%	10%	7-12%	13%	8%	4%	-1%	-	-	-	-	2-5%

x one case of acute nephritis.
2nd figure in 2nd column on % incidence line gives the number if only late albuminuria are counted.

ringing on the forearms and hands about the twentieth day and reaching the feet about the thirtieth day or fortieth day of disease. Little change can be expected where the rash is disappearing when the serum is given and the best results will be in cases where the case is less than twelve hours old. In this last group, desquamation may be nil.

COMPLICATIONS.

Table 5 gives the incidence of complications in the series, according to the day of disease on which the serum was given. Columns 1. and 2. show the number treated for each day. Comparisons of the percentages of complications for each day-group would be futile with such small numbers, therefore they are all grouped together and the percentage expressed is that of the whole. The standard for comparison is taken from the figures given in the last edition of C.B.Ker's "Infectious Diseases". But those numbers are not quite suitable as they must include many mild cases which would not have had serum. Unless one gave antitoxin alternately to every scarlet fever patient admitted to hospital, i.e. to every second case or selected suitable controls as regards age, sex, severity and day of disease on admission, comparisons must be liable to error. Then again even if such were done, scarlet fever is so variable a disease that it is possible for two apparently identical cases to turn out differently under exactly the same treatment. We have not made it a practice to adopt either method, deeming it more necessary to treat the patients than to collect accurate statistics.

In twenty-four instances, there occurred a serum reaction, in all except one taking the nature of a rash. In the exception, serum sickness was also present. The great majority occurred between the fifth and the sixteenth day after injection. This gives a percentage of 20 which compares unfavourably with the figure of 8.2 for serum-

treated diphtheria cases and especially considering it was concentrated antitoxin that was used.

All albuminurias happening in the series are included in the total, but if one takes count only of the late albuminurias, those after the second week, then the number is reduced by a half,giving a percentage of 9.15, which is not much different from the standard of 10. As the early albuminurias, those present at the same time as the pyrexia, are probably due to the toxins of the disease, they should be taken into account in assessing the value of the treatment. In one case not included in this series, the onset of nephritis was synchronous with the appearance of the primary tonsillitis and was followed in thirty-six hours by a very bright typical scarlatinal rash with numerous miliary points. In this instance, as in the other already quoted, the serum had the effect of causing the little vesicles to collapse, and leave small flat placques slightly raised above the surface. This is the only case I have seen of scarlet fever starting with nephritis although others are recorded in the literature. In this instance, the diagnosis of both conditions was unquestionable.

Of the nine cases of otorrhoea, six occurred on or after the twelfth day but even in some of these there was no settling of the primary pyrexia. Chart No.15 is one in point, the otorrhoea showing on the twelfth day, while Chart No.2. is slightly different, the temperature coming down for one day, then rising again. In an example like Case 51, one could hardly expect the antitoxin to have much effect. This boy had rather a severe attack of scarlet fever, (probably contracted after admission although he had a weak positive Dick test, a point supposed to be in favour of a diagnosis of scarlatina) and was given serum on his sixth day of disease. He was another case where the disease appeared moderately harmless at the beginning. Otorrhoea appeared

on/

on the seventh day. Case No.75 is a replica of No.51, except that this child had clear clinical scarlet fever on admission thirty seven days prior to taking a second attack. On the sixth day of the relapse, the temperature rose again and the picture became one of septic scarlet fever. Serum was injected on the ninth day but that did not prevent double otorrhoea on the eleventh. Chart E is from a case of septic scarlatina (not included in the series) treated by the injection of 50 c.c. of unconcentrated scarlet fever antitoxin. The course of the disease was quite uninfluenced and the child developed double otorrhoea and septic adenitis, the latter requiring several incisions before complete recovery. The temperature took fifty-three days to settle. There was only one case of septic adenitis among the eleven occurring. This boy (Chart No.5.) came in with mild scarlet fever. On the tenth day of his illness, the temperature rose again and the cervical chain of glands enlarged but his tongue and throat remained clean and uncongested. By the fifteenth day he was very much worse and the adenitis had assumed a collar formation. Ten cubic centimetres of scarlatinal antitoxin were administered onthat day but it was the twenty-second day before the temperature settled and the swellings lessened. On the twenty-ninth day, the temperature again rose, the right side of the neck was again swollen and on incision pus was obtained. Others have reported a similar state of affairs as above, the temporary recession of a septic complication under antitoxin.

The 14.17% of rhinorrhoea is hardly comparable to the 8% of C.B.Ker, as the former number includes all types of rhinorrhoea which would detain a patient in hospital while the latter is only of purulent rhinitis although including those occurring in septic scarlatina. As already noted, the effect of the antitoxin on primary rhinorrhoea/

rhinorrhoea is very rapid in action and practically consistent in all cases.

The 3.33% of secondary attacks is interesting, compared with under 1 per cent. in Edinburgh in untreated cases. It has been put forward that the use of antitoxin in scarlet fever will lead to an increase in the number of relapses and this series seems to uphold that view. The arguments for and against have already quoted in the section on the Dick test.

The other complications require very little comment. The three cases of rheumatism were of slight degree and early in the course of the disease while the two cases of jaundice occurred late in the convalescence and perhaps were unconnected with the disease. The one instance of mastoid empyema necessitating operation was in Case No.75 already noted, a septic scarlatina. The conservative operation was performed with good recovery. The single case of sinusitis has also been mentioned, Case No.87, where the serum had no preventive effect.

Three fatal cases occurred in serum-treated patients. Of these, one, at least, must be ruled out as the child was moribund on admission. The boy, case No.93, was admitted on his eighth day of disease. He had started, to all appearances, as a moderately severe case of scarlet fever but on his sixth day his temperature, which had not quite settled, rose higher, his throat became very dirty and his condition much worse. He was given 10 c.c. A.S.S. before admission on his eighth day of disease and another 10 c.c. when admitted. His disease was really of the septic type but he was extremely toxic. The tongue was dirty and the throat intensely inflamed with extensive patching on the tonsillar and peritonsillar areas and there was a coarse papular rash on the knees and elbows. His culture was negative for b.diphtheriae. He went from bad to worse

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and died thirteen hours after admission. Here we have a case which had gone septic and died in spite of the antitoxin. It is difficult to be dogmatic as to whether this was a septic or a toxic case. He showed signs of both and the probable explanation is that he was septic but died of toxaemia.

The second fatality, Case No.95, was a man of forty-four, admitted on his third day of disease. He had had a slight operation on his nose three days previously and had apparently contracted the disease from contact with a definite scarlatina occurring in the same ward. The clinical picture was of a moderately severe case of scarlet fever with congestion of the throat and some greenish pharyngeal secretion. Two days after admission to hospital he seemed to be slightly delirious and complained of vague pains in the arms. There was a copious purulent nasal discharge and the urine was loaded with albumen. He was given 20 c.c. A.S.S. but his condition during the next twenty-four hours became worse, the delirium increased and although his temperature came down by lysis, he died twelve hours after it reached normal. This case was also septic scarlatina. There is no doubt but that for his nose operation he would not have taken scarlet fever and that having taken scarlet fever the antitoxin did not help him in the least. It is difficult to say whether it would have helped him if it had been given him on admission or not. The third case tends to answer that question in the negative.

The patient, a baby of 1 1/12 years, was admitted on her third day of disease with signs pointing to scarlet fever but not diagnostic. The face was blotchy, the tongue coated but not red, the throat congested but clean, and a purulent discharge was present from the nose. A few scarlatiniform punctations were found on the hands and legs. The temperature was 102°F. and the pulse 136. Later on in the day, she became more restless and fretful and the nasal

discharge/

discharge increased and she was given 10 c.c. A.S.S. that night. But there was little or no improvement by the following morning. The rash had disappeared but the throat was still congested and the nasal discharge was as profuse as ever. A second dose of 10 c.c. A.S.S. was administered twelve hours after the first and in twenty-four hours there was a decided improvement in her condition. The pulse and temperature were lower although not back to normal,and the discharge was less. The temperature remained between 98° and 99°F. from the eighth day onwards till the fifteenth, when it shot up again. During this period the pulse remained quick even for this age until the twelfth day, when the left ear discharged without warning. On the sixteenth day the child appeared very ill, the temperature was high and the pulse and respiration rate rapid and all the physical signs of lobar pneumonia were present at the left base. The temperature went higher, the pulse became more rapid until it was uncountable and the child died on the nineteenth day. A post-mortem examination was made and it was found that the whole of the left lung was consolidated with a shaggy appearance of the pleura of the lower lobe and a small quantity of pus in the left pleural cavity. Haemolytic streptococci were recovered in pure culture from the pus. The older writers taught that the more vulnerable points in the body in scarlet fever were the serous membranes, the pleura, the pericardium and the peritoneum. This was the first case I had seen of empyema as a complication and later I saw one instance of pericarditis but I have still to see the peritoneal complication.

The question of dosage has now to be considered. The rule laid down for the treatment of diphtheria also holds good here. The dose given should be of such size as to neutralise the toxaemia. It has been made a practice to give an initial dose of 10 c.c. of antitoxin intramuscularly

to all except those extremely ill. If there is no appreciable change in the patient's condition in eighteen hours a second dose of 10 c.c. is given. In scarlet fever every hour is of importance, even more so than in diphtheria. To wait thirty-six hours before giving a second dose is to waste precious time. It has been shown in the case of diphtheria antitoxin that the maximum concentration in the blood, with the subcutaneous method of administration, does not occur till the third day after injection. With the intramuscular route it is in twelve hours and, of course, with the intravenous method, immediately. There is no reason to disbelieve that the same holds good in the case of scarlet fever antitoxin and it is probable that by thirty-six hours after administration, let us say to a case in the third day of disease, the patient would be recovering naturally. This opinion is given after the consideration of the series and there are several members of the series to whom one would now give a second dose of serum if they had to be treated again but who had only one dose the first time. The patient's appearance is the best index of the degree of toxaemia. As long as there is any unneutralised toxin present, the person looks uncomfortable. Case No.32 is an illustration. This child was admitted in her second day of disease with signs of severe scarlatina. A first dose of 10 c.c. A.S.S. was administered and in twelve hours, althoughthe temperature and pulse remained the same, she looked much easier, but twenty-four hours after injection, the restlessness returned, delirium was present and the temperature and pulse rate went higher. All the antitoxin had become fixed. A second dose of 10 c.c. A.S.S. was given and the following morning there was marked improvement in both the appearance and the symptoms.

As regards nursing, the same care should be taken of treated/

TABLE 6.

Assessment of Antitoxin Treatment.

Day.	No.	S.	M.S.	F.S.	?	-	Out.
1.	7	3	2	1	1	-	-
2	45	18	18	3	**4	1	1
3	37	*11	*14	7	*4	*1	-
4	22	*4	*7	4	*5	1	1
5	4	1	-	1	1	*1	-
6 7	5	-	-	4	-	*1	-
Total	120	37	41	20	15	5	2

Column 1. - Day of disease on administration.

2. - No. of cases in each group.

3. S = Successful.

4. M.S. = Moderately successful.

5. F.S. = Fairly successful.

6. ? = Doubtful effect.

7. - = No effect.

8. "out" = Not suitable for assessment.

* = Second dose of antitoxin.

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treated as of untreated patients. The number of complications occurring after the third week militates against the proposal to dismiss serum-treated cases before the twenty-first day of disease. Seven of the twenty-two cases of albuminuria occurred after the twenty-first day, one being a nephritis, while three of the nine instances of otorrhoea also were in the last days of convalescence. It is probably safe to dismiss serum-treated patients on or about the thirtieth day of residence but as to lesser periods of isolation, the fact of toxigenic streptococci being present in the throat until after the third week of disease must be taken into account.

It is extremely difficult to accurately assess the value of the antitoxin in such a small series of patients. It can only be done by the consideration of all its effects, both early and late. The temperature chart by itself is not a sufficient guide as there may be disappearance of the pyrexia without any change in the patient's condition, or, conversely, the patient may make a complete recovery without any change in the course of the temperature from what it would be in an untreated case. Rapid disappearance of the rash is quite a good index, but that only indicates the presence of skin immunity, and as for the extent of desquamation, it is proportional to the effect of the antitoxin on the rash. Again the incidence of complications would be insufficient, as it would leave out of account the action on the acute phase of the disease.

Table 6 gives a rough estimate of the results according to one's personal opinion of each patient and, if anything, it is on the conservative side. The weak point is that there are no purely toxic cases in the series, those cases which would react completely to a pure antitoxin. A result is considered "successful" when the patient's condition improves immediately, when the temperature and

pulse/

pulse rate come down rapidly and when there are no complications and the desquamation is diminished. "Moderately successful" is where the change is not so dramatic or where some of the above points are absent. Under "Fairly successful" one would class those that did not react well primarily to the antitoxin or developed some serious complication afterwards. Those put down as "doubtful" are where it was very probable that the serum did not influence the course of the disease. In the "negative" column are the fatal cases and those that were definitely unaffected. The two "Out" are where there was some other serious condition present on admission that prevented any opinion being formed. The numbers are divided up into the days ill on administration and an asterisk denotes that one of the cases received a second dose of antitoxin.

It will be seen that in the "first day" group, although the majority are in the "successful" or "moderately successful" columns, there are some where the success was slight. In the "second day" group, where we are dealing with larger numbers, less than a half of the administrations were successful but the majority is still at the left hand side of the table. In the "third day" group the results are not so promising and the number of fully successful cases is less than one third of the total. In the "fourth day" line, the majority has definitely started to move to the right and with the "fifth day" group an with those treated later than the fifth day, the results are still less favourable but the numbers are too small to be of much use.

On the whole, the results are very disappointing. Scarlet fever is still a disease where one must expect a death-rate and complications. It may be that there are several strains of causative organisms and that the antitoxin employed was only successful against one or two of these types/

types or that the exact etiology is still a mystery. That the antitoxin has not made much difference if one compares the results of this series with those of the Edinburgh City Hospital in the pre-serum days is true, but it must be taken into account that the latter figures included many mild cases while those of the present series are all moderately severe or severe examples of the disease. But antitoxin does cut short the primary pyrexial period, it rapidly improves the physical well-being of the patient and it diminishes the severity of the desquamation. It decreases those symptoms and signs due to the toxaemia, the rash, the inflammation and swelling of the throat, and the physical discomfort, but, as in diphtheria, it has no effect on organic changes already present - ulceration of the throat, inflammation of the middle ear - or on septic scarlatina. It might have had a prophylactic influence on the incidence of septic scarlet fever as in the cases referred to where one felt that they were just about to go septic but such occurrences are also found in untreated scarlet fever. As to the effect on complications, if one accepts the statement that the number of cases developing otitis media and adenitis is in proportion to the number of those having severe throat lesions, then the antitoxin will diminish the incidence as it decreases the severity of the throat inflammation and thereby lessens the chance of the spread of infection up the Eustachian tube. But with regard to nephritis, the factors governing its incidence are still a matter for conjecture and the effect of the antitoxin on this complication will be gauged only when a large series of cases are treated with a suitable control for each. It is to be regretted that little change was found in the incidence of albuminuria at the stage of the advance of the disease as this is undoubtedly toxaemic.

But one does not reject diphtheria antitoxin because

it does not save all sufferers and prevent all complications and, further, other investigators have had far more promising results than has been my lot.

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PART III.

BIBLIOGRAPHY.

) Original Articles.

) Abstracts. The first named journal is the one in which the original [illegible] the second [illegible] is which the abstract [illegible] [illegible].

PART III.

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DICK TEST RECORD.

Column. (a) Serial Number.

(b) Brand of toxin and strength with dose.

(c)&(d) Name of patient.

(e) Ward.

(f) Age.

(g) Sex.

(h) Disease from which he is suffering and the particular day of disease.

(j) Any special serum treatment.

(k) The reactions read at various times read in millimetres with added letter denoting brightness as described in texts.

(l) The changes in the control arm.

(m) Hour at which the reaction is brightest.

(n) Sign

++	e.g.	30 x 25 P or 20 x 20 R.
+		20 x 15 P or 30 x 20 F.P.
±		15 x 10 P
∓		10 x 10 F.P. or 8 x 5 R.P.
-		No reaction whatever.

(o) Day, counting from time of injection, when the pink tinge disappears.

(p) Remarks as to further changes in the test area and as to any subsequent relevant history.

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a	b	c	d	e	f	g	h	j	k				l	m	n	o	p.
No. and Letter	Toxin and Dose	Name		Ward	Age	Sex	Disease and Day	Treatment	Test Reactions 4 hrs	8 hrs	12 hrs	24 hrs	Control	Hour of Maximum Intensity	Sign	Day of Disappearance	Remarks
	.2 cc B.W.	Reid	James	8	8	M	S5		18x15 P	Lost in [illegible]	Not Read	Lost	15x8P – 4 hrs	?	+	3rd day	4 hrs. rash increasing
		Searight	George	"	6	M	S49		—	—	"	5x5 V.F.	—	24th	∓	3rd	
		Moran	Annie	"	2	F	S8		10x18 P	16x15 R.P.	"	Flecked 18x15 R	—	24th	++	2nd	? Reinforced 36th hours. Stain - [illegible] late. Deg. -10°
		Moran	Sarah	"	3	F	S10	10 cc A.S.S. – S2	—	R.S.	"	—	—	—	—	—	
		Campbell	Flora	"	12	F	S6		Raised 20x12 R	20x12 P	"	13x4 P.P.	—	4th	+	2nd	
		Kerr	Margaret	"	12	F	S9		R.S.	R.S.	"	R.S.	—	—	—	—	
		Barry	Isabel	"	3	F	S5		—	—	"	—	—	—	—	—	
		Colquhoun	Alexander	"	6	M	S14		—	16x10 D	"	—	—	—	—	—	
		Turkington	Agnes	"	9	F	S7		—	—	"	—	—	—	—	—	
		Cairns	Joseph	"	5	M	S9		—	—	"	—	—	—	—	—	
		Donnelly	Mary	"	7	F	S14		R.S.	8x10 R	"	8x5 P	—	8	∓	2nd	
		Donnelly	Helen	"	5	F	S16		R.S.	R.S.	"	—	—	—	—	—	

etc.

Column h. — S - scarlet fever
P - pneumonia
W - whooping cough
D - diphtheria
m - measles.
" k - R.S. - red spot.

FACSIMILE FILING CARDS.

A = Streptococcal data.

B = Antitoxin result.

A38.2 = Journal reference.

C.80 = No. of chart.

D 4)
R 1) Day of disease and of rash.

54-3 RUSSEL HAMILTON WD9 S2 **A**

4-3-27 THROAT SWAB

4-3-27

A BLOOD PLATE Medium sized pin-head colonies with green haemolysis. Cocci 5-3-27 large and in long chains.

B HARTLEY'S BROTH ⊂ A Uniform turbidity with little sedimentation Streptococci appear typical. Inoculated in bile

6-3-27

C BLOOD TUBE ⊂ B All colonies haemolytic. Typical streptococci

7-3-27

D HARTLEY'S BROTH ⊂ C Uniform turbidity. Cocci in long chains and bold chains well. 18-3-27 — To row 4 54-3

8-3-27

E SOLID HARTLEY ⊂ D Whitish pinhead colonies. Streptococci

18-3-27

F SOLID HARTLEY ⊂ E Uniform whitish colonies. All streptococcal.

28-3-27

G SOLID HARTLEY ⊂ F Fair growth. short chain streptococci.

30-3-27 6-4-27

H RAFFINOSE ⊂ G — No change no change

MANNITE ⊂ G — Acid acid.

I 8-4-27

SOLID HARTLEY ⊂ G Poor growth. Streptococci

J 14-4-27

HARTLEY'S BROTH ⊂ I abundant growth with some sedimentation Typical long chain streptococci etc.

WOODS, Hon F. 9 yrs WD10	A38·2	**B**
ADM 19-5-27 DH R1	⊂ 80	

19-5-27 [4] Rash pink on trunk, bright on lower limbs, throat inflamed tonsils big, tongue dirty 10 cc ASS

20-5-27 [5] 12 hrs later Looks clean. Rash discharging. rash unsightly, tongue coated with pulled areas. throat inflamed with specks of exudate 24 hrs later Restless, temp. up again. throat + tonsils very dirty. Sniffling. 10 cc ASS

21-5-27 [6] 36 hrs later Face clearer, throat inflamed but clean, tongue moist + pink Rash away. Albuminuria 4-5-6-7½ days. Thunderstorm evening

23-5-27 [8] Throat clean + temperature, skin dry. 27-5-27 [12] ♀ Trace albumin.

28-5-27 [13] ♀ ♀ alb. Temp. swinging, glands swollen ++ acute growth.

29-5-27 [14] ♀ ♀ alb. Face puffy, headache. 3-6-27 [19] urine dry, no dysp.

9-6-27 [25] urine + trunk dry, still albuminuria. 13-6-27 [29] Still albumin. Skin of arms dry, none on feet, glands palpable ++.

14-6-27 [34] Urine clear urine foaming, body + legs dry. 20-6-27 [36] Desquamating

30-6-27 [46] Undergoing examination 4-7-27 [47] Examined

CHARTS.

Nos, 1-120 Charts of cases treated with antitoxin, the numbers being in accordance with those in the text (Part II. Section III.)

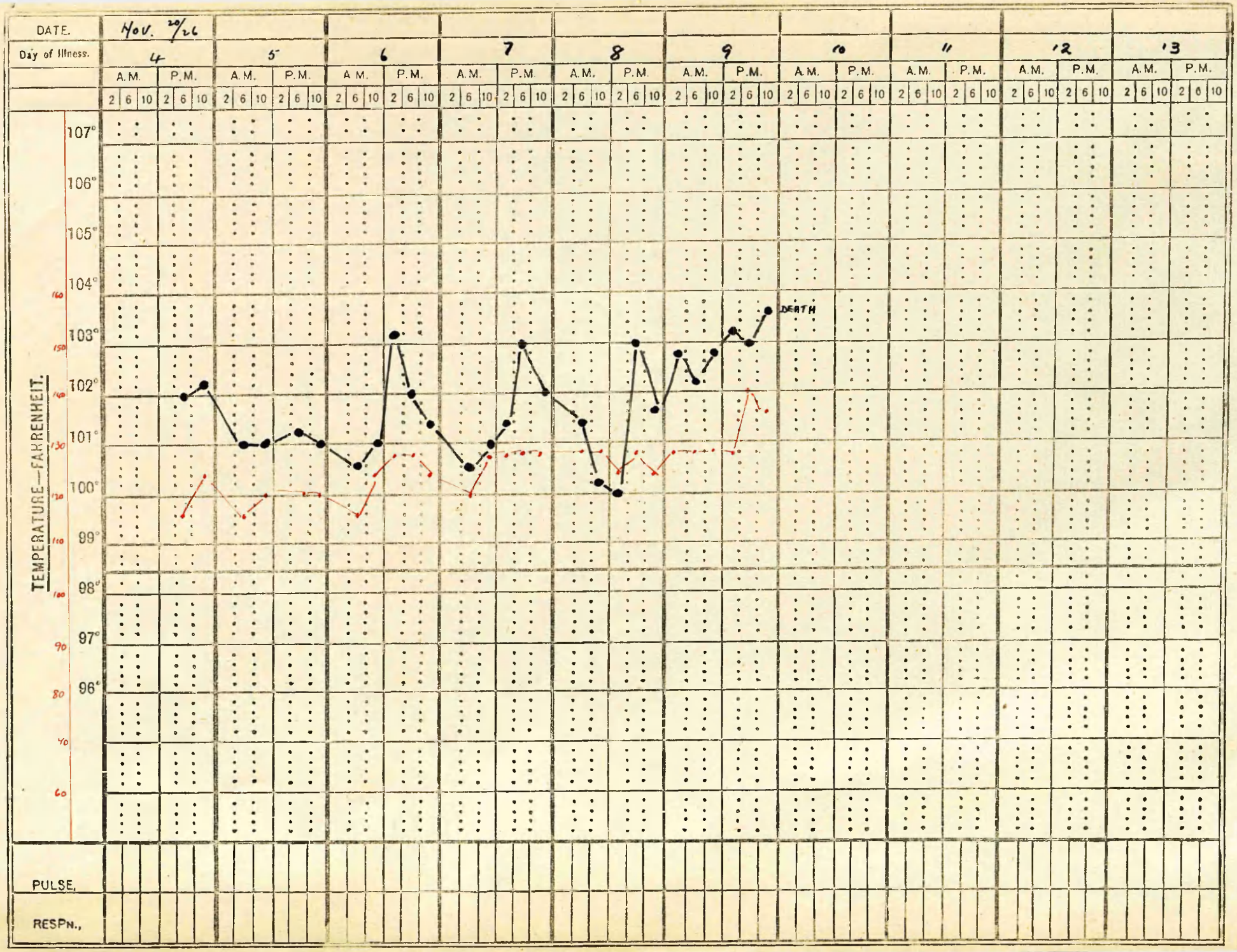
Lettered charts A -E included for comparison or to demonstrate some particular point,

Black line - temperature,

Red line - pulse,

Green line (Chart 8) -respiration,

Two vertical green lines denote the injection of 10 c.c. A.S.S.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Nov. 20/26
Day of Illness.
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A.M.
P.M.
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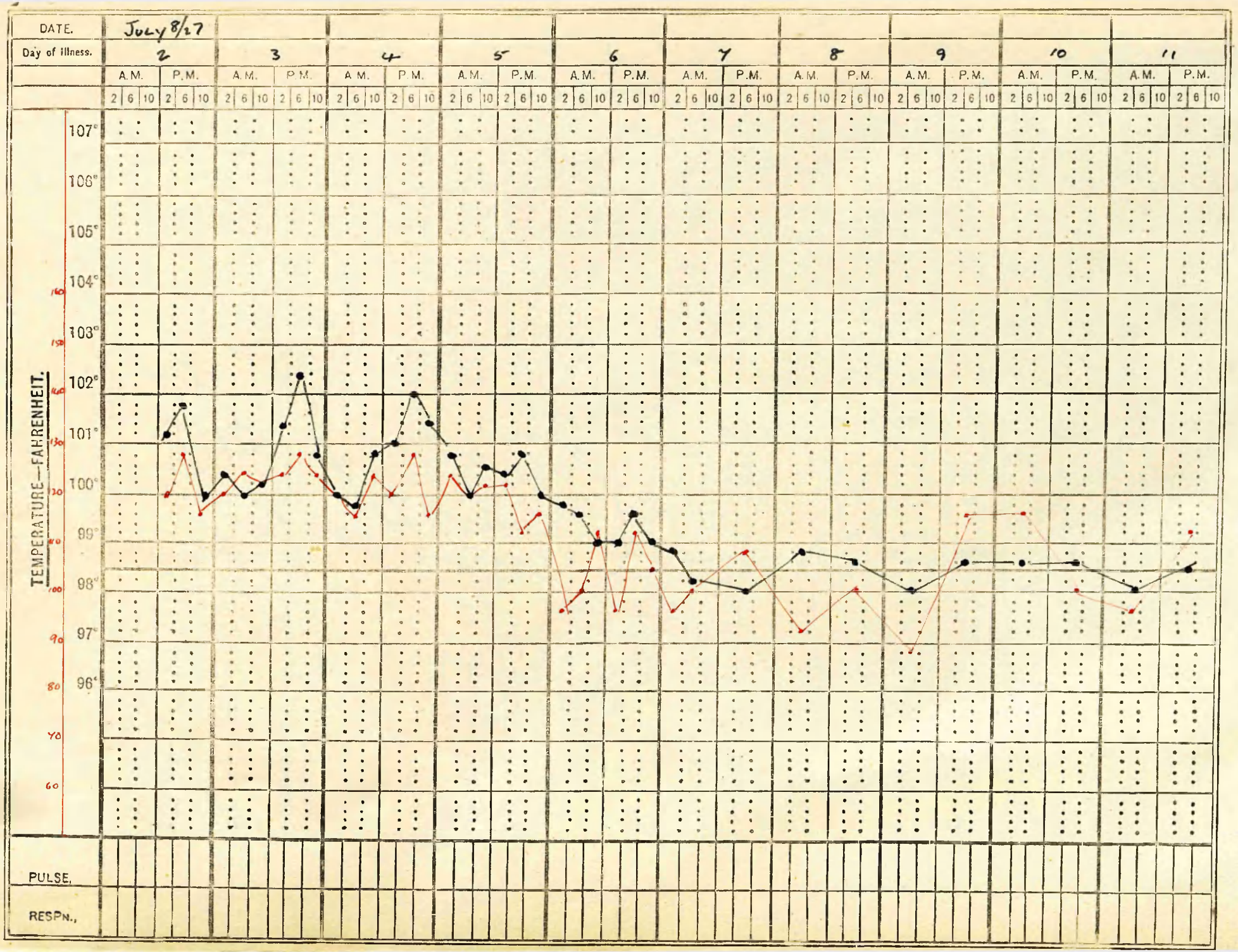
TEMPERATURE—FAHRENHEIT.
DEATH
PULSE.
RESPN.,

A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July 8/27
Day of illness.
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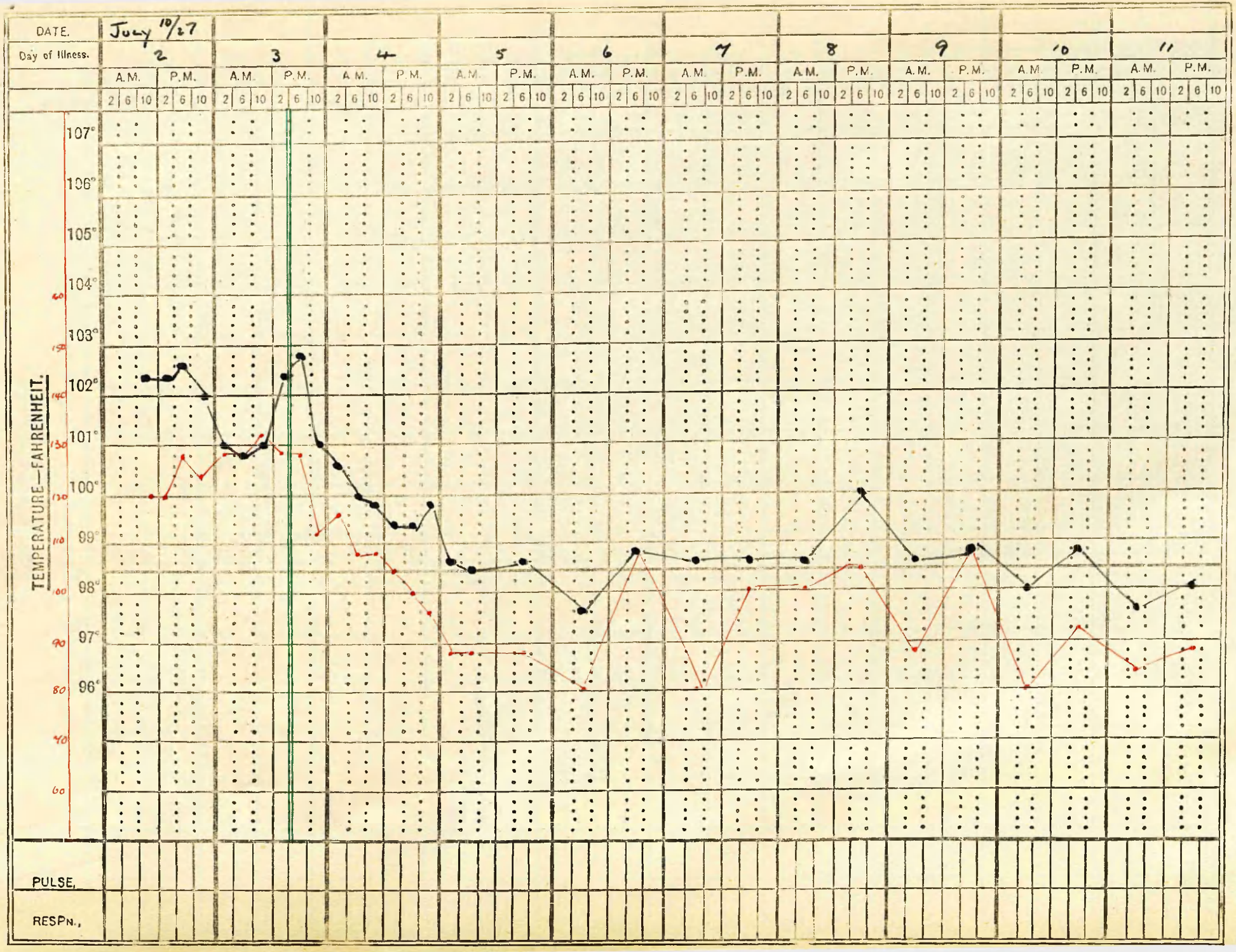
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

[B]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TEMPERATURE—FAHRENHEIT.
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Day of Illness.	2		3		4		5		6		7		8		9		10		11			
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.		
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10		
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PULSE.																						
RESPN.																						

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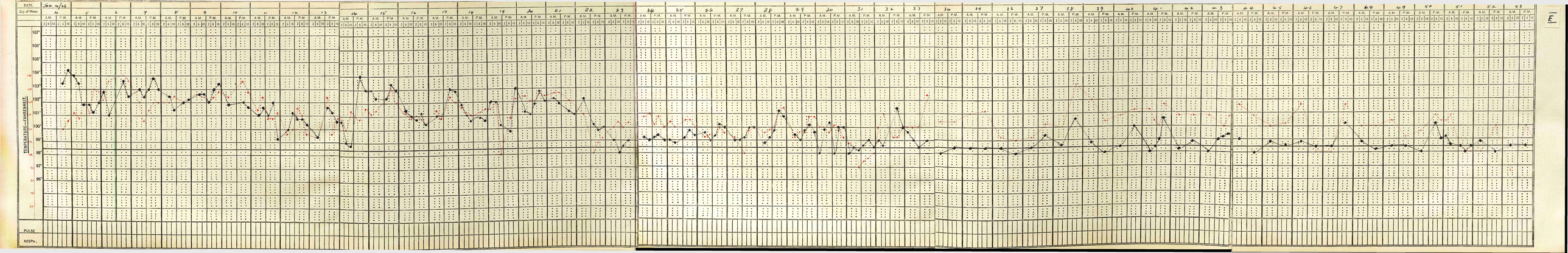
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Jan. 14/26
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PULSE
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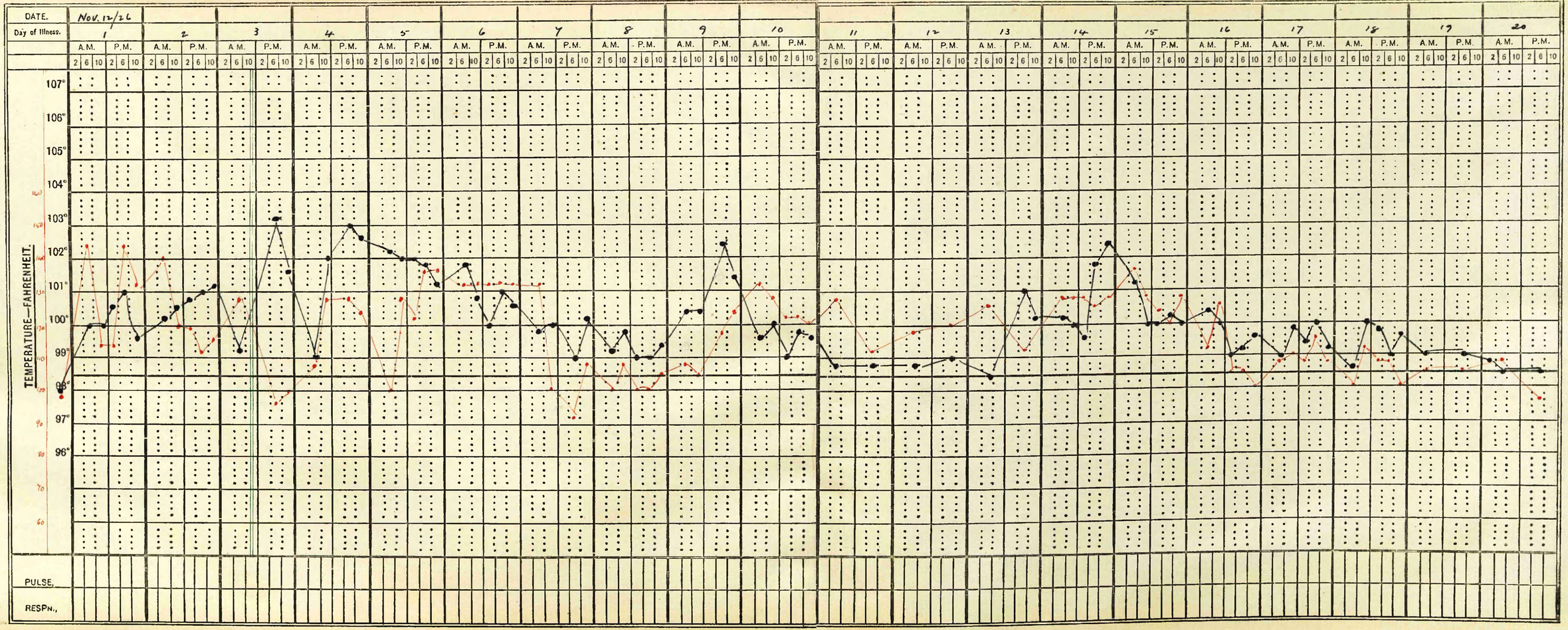
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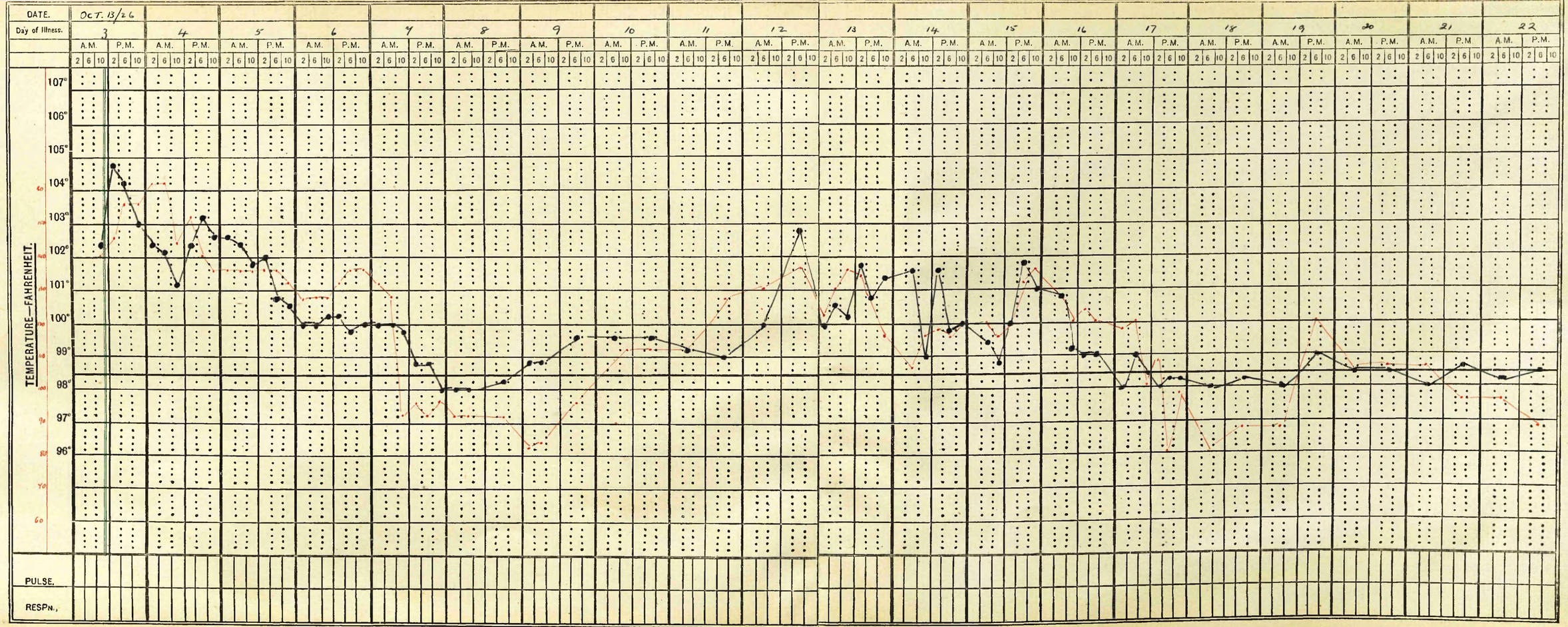
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PULSE.
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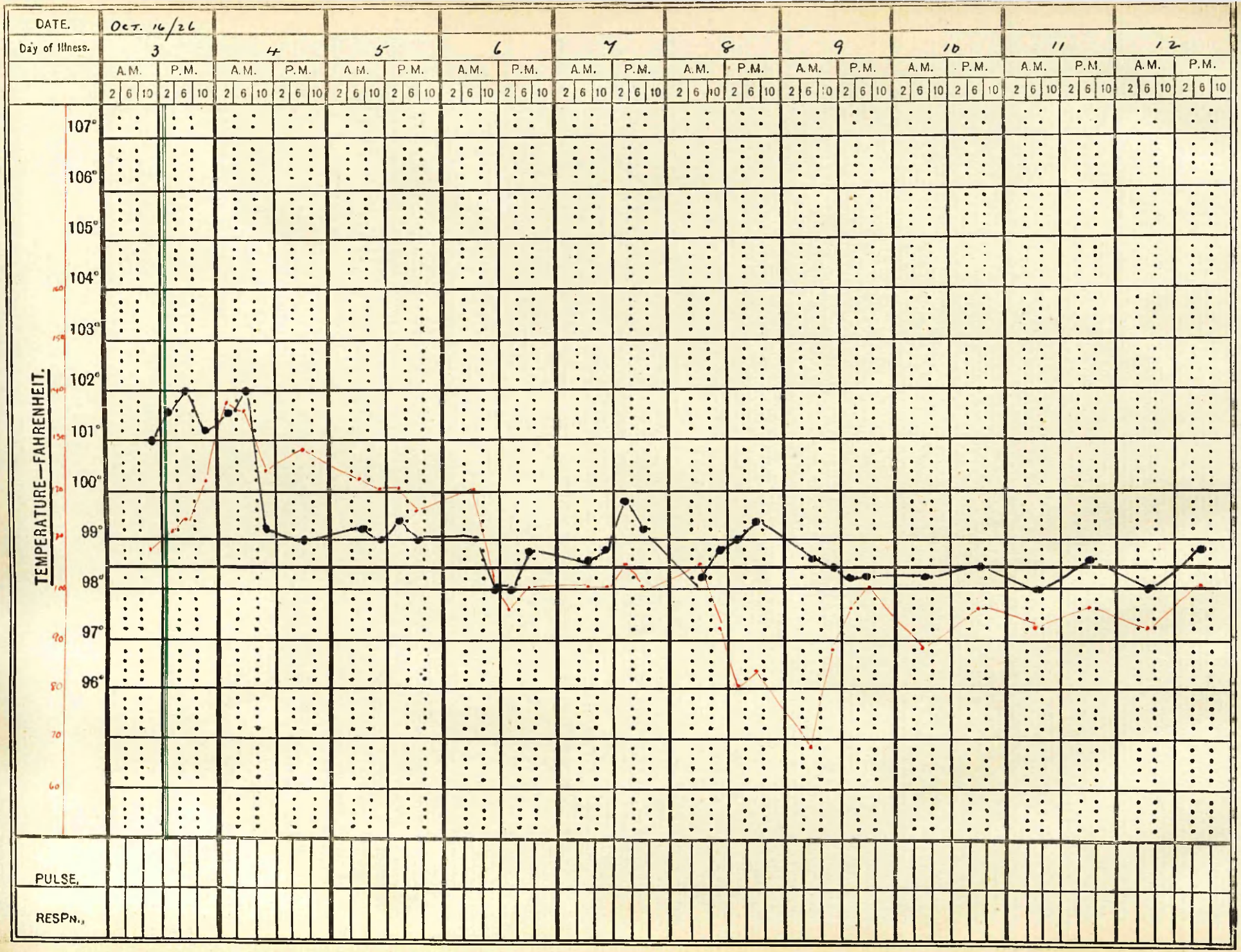
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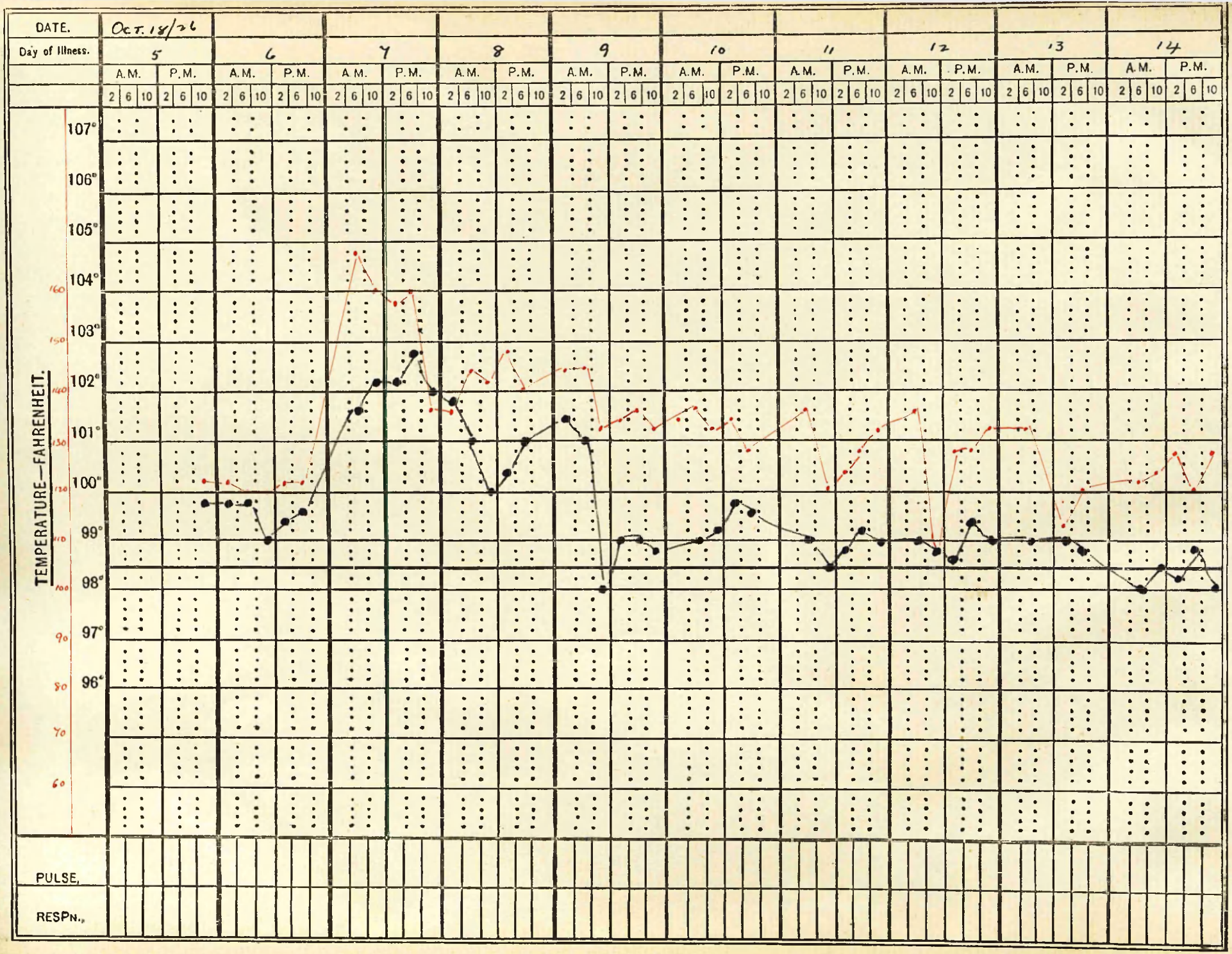
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PULSE.
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DATE. Oct. 20/26

Day of Illness.

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A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.
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TEMPERATURE—FAHRENHEIT.

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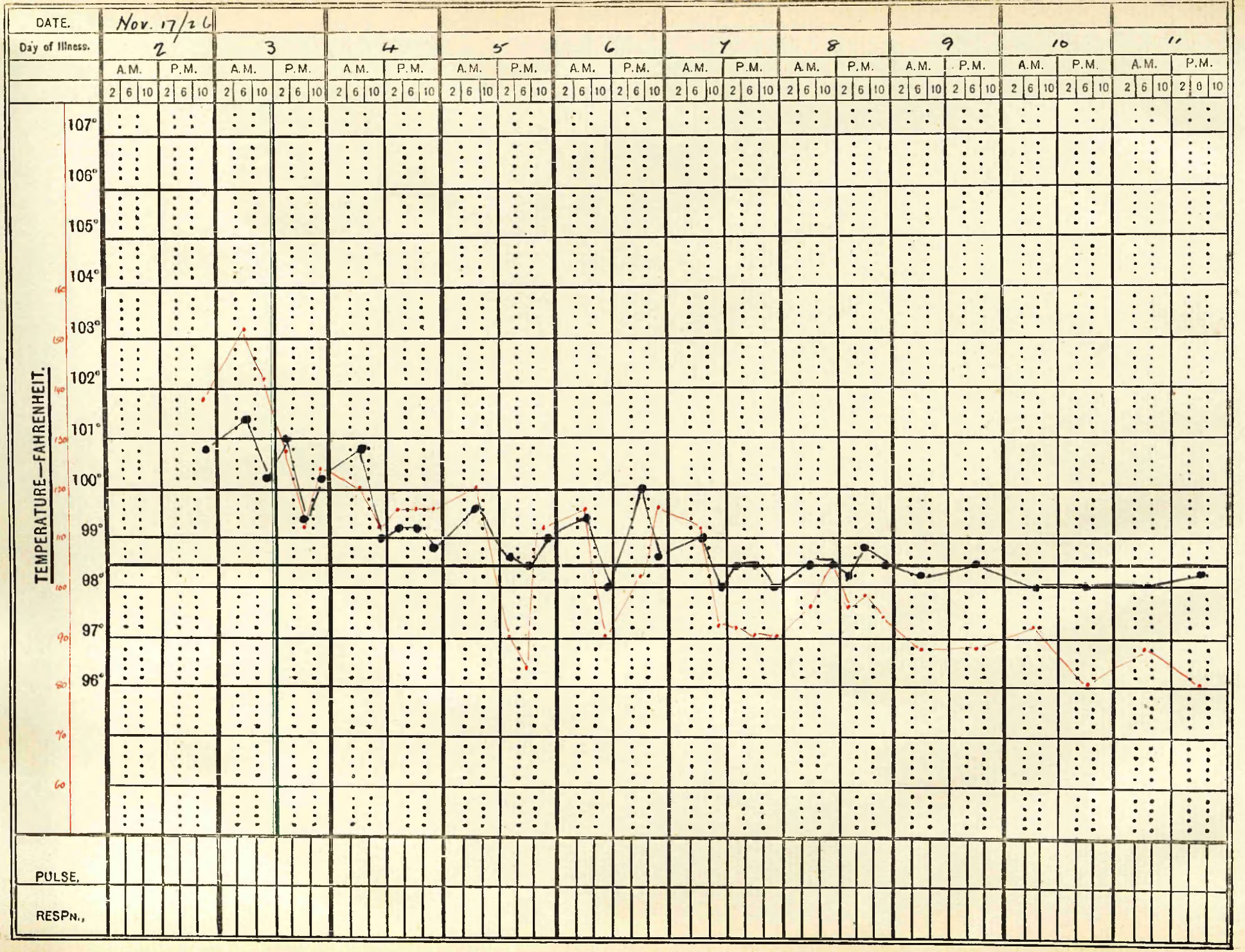
PULSE.

RESPN.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TEMPERATURE—FAHRENHEIT.
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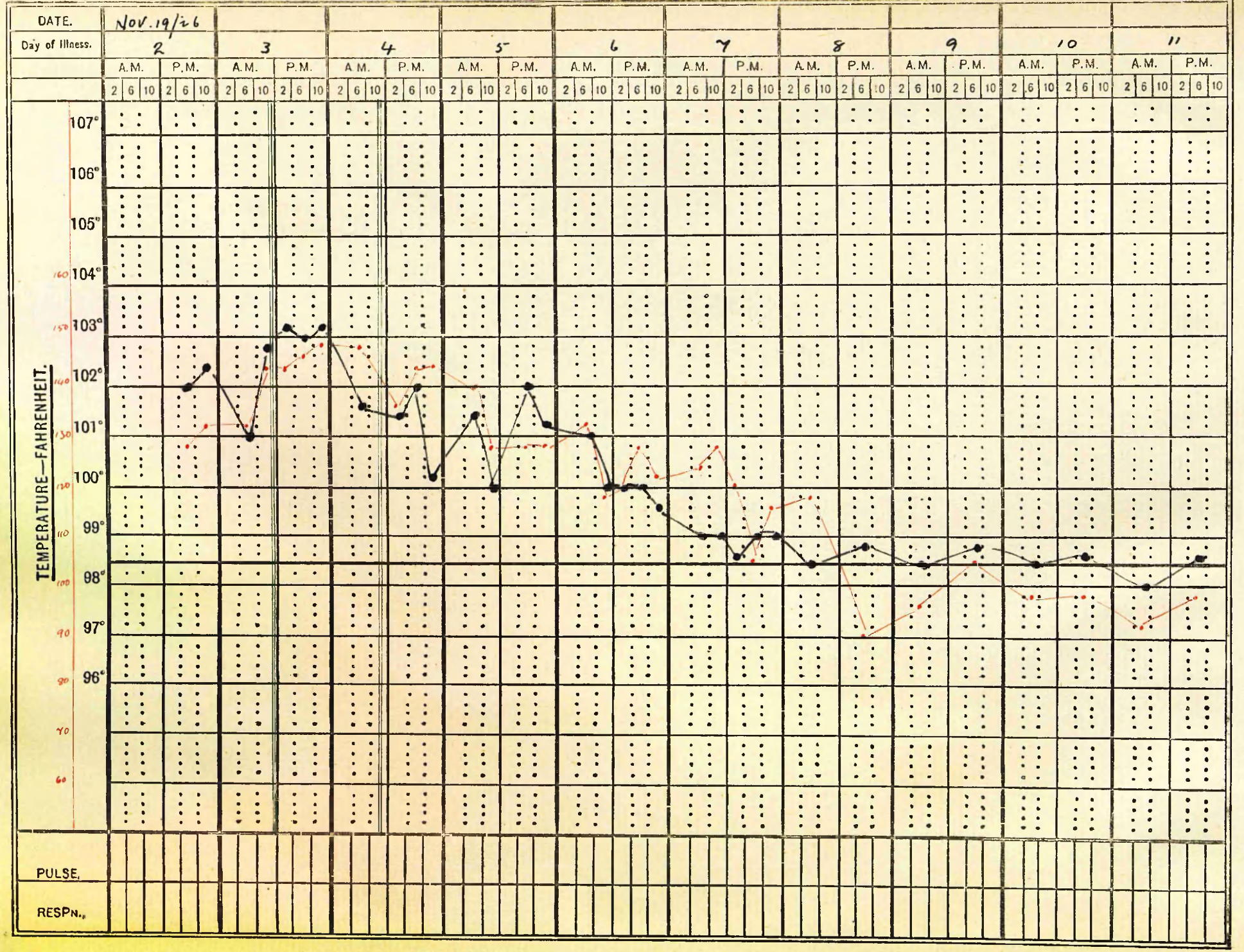
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TEMPERATURE—FAHRENHEIT.
PULSE.
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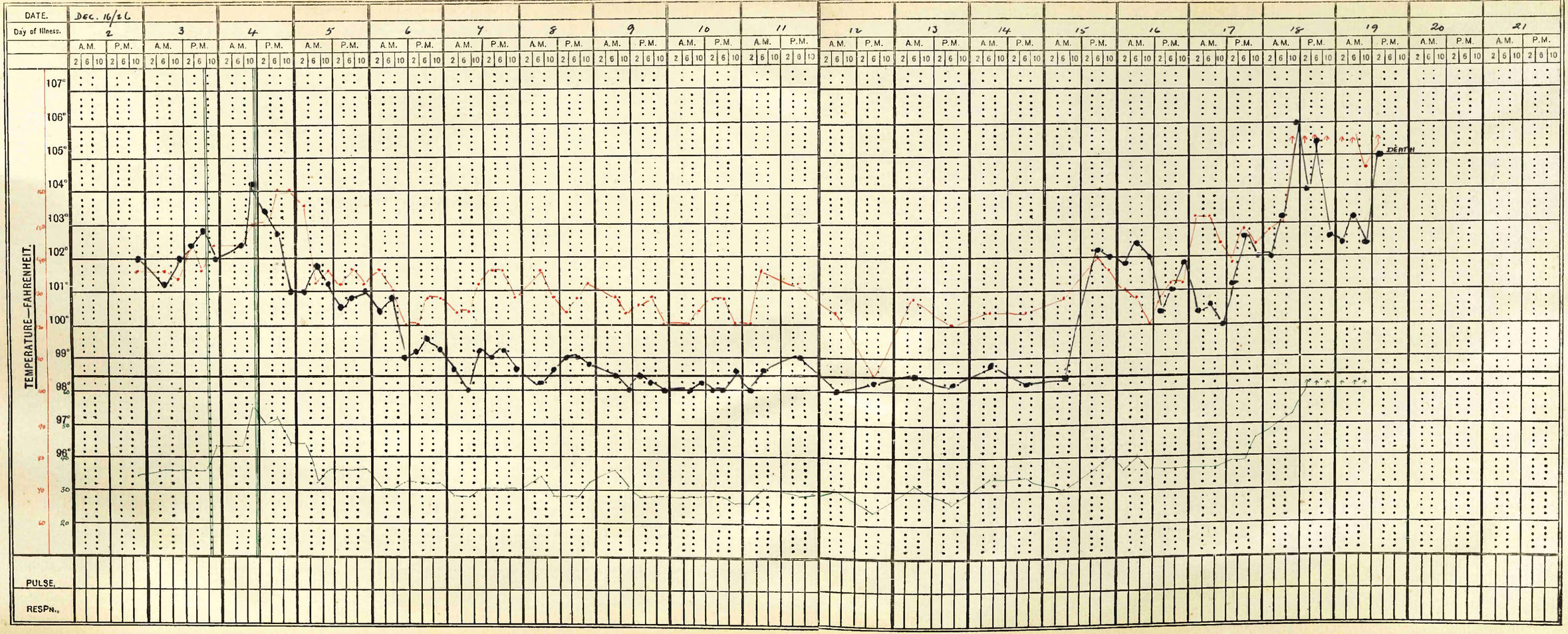
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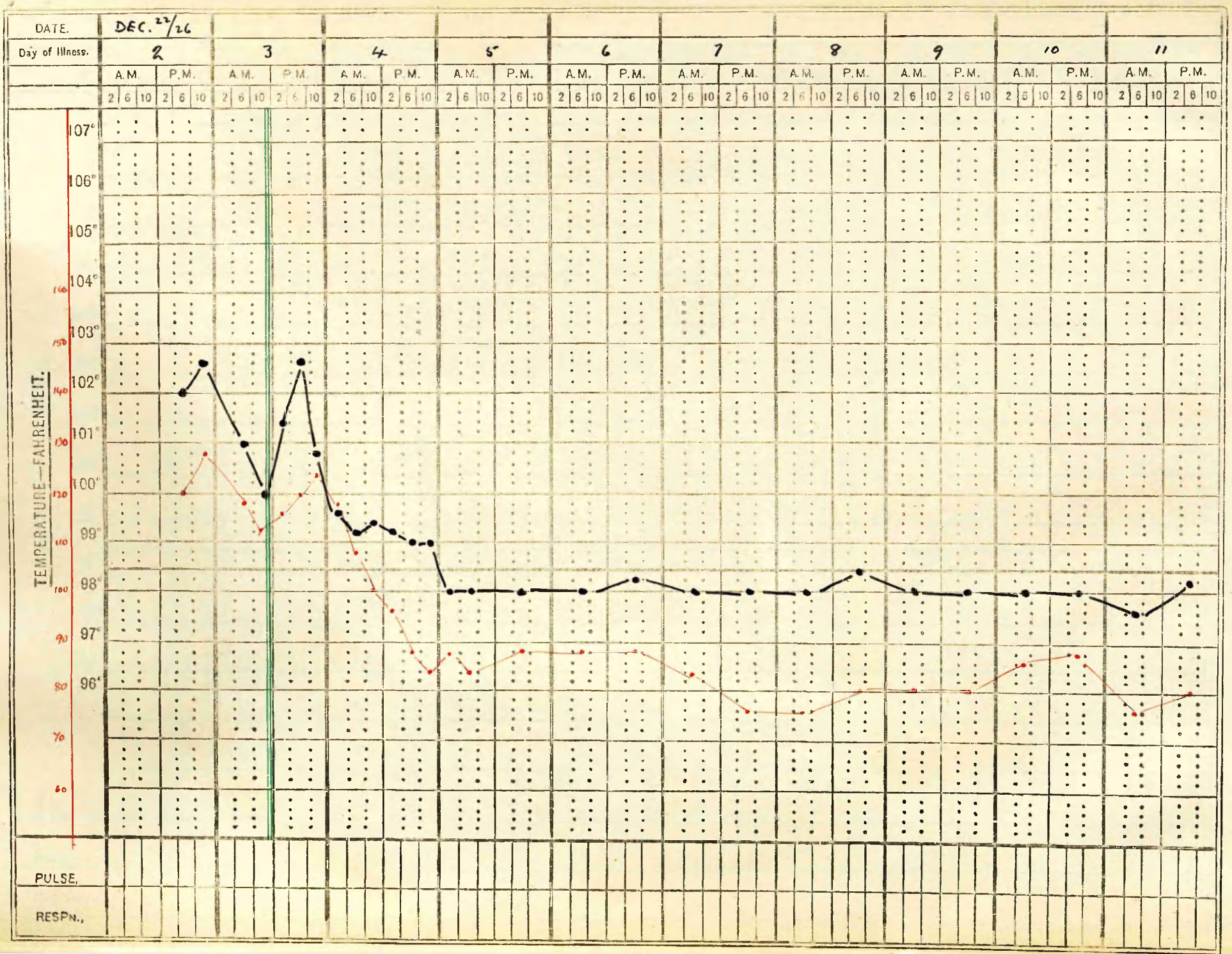
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
A.M. P.M.
2 6 10 2 6 10
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
TEMPERATURE—FAHRENHEIT.
DEATH
PULSE.
RESPN.


DATE.
DEC. 22/26
Day of Illness.
2
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11
A.M.
P.M.
2 6 10
107°
106°
105°
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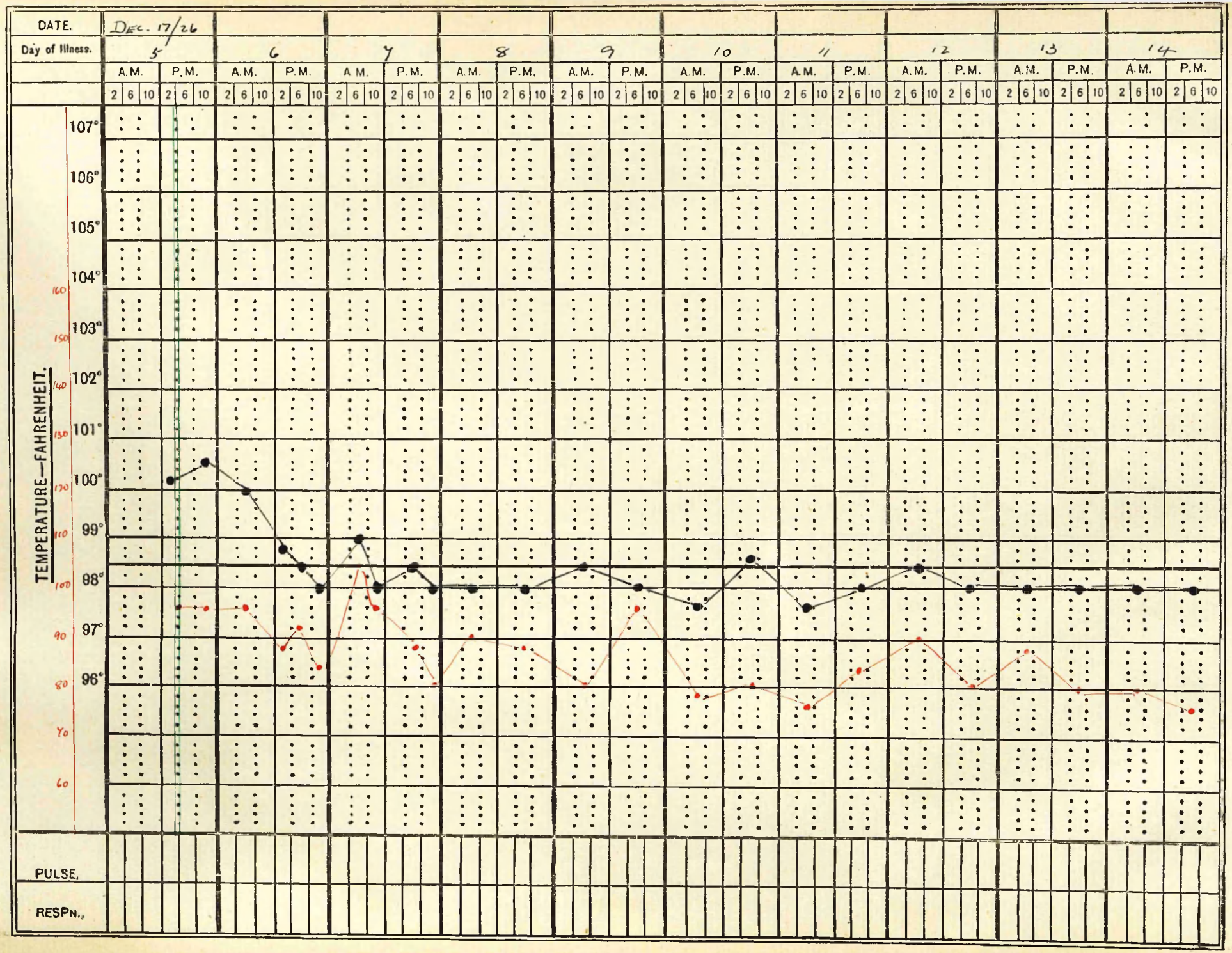
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
Dec. 17/26
Day of Illness.
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13
14
A.M.
P.M.
2 6 10
107°
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97°
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160
150
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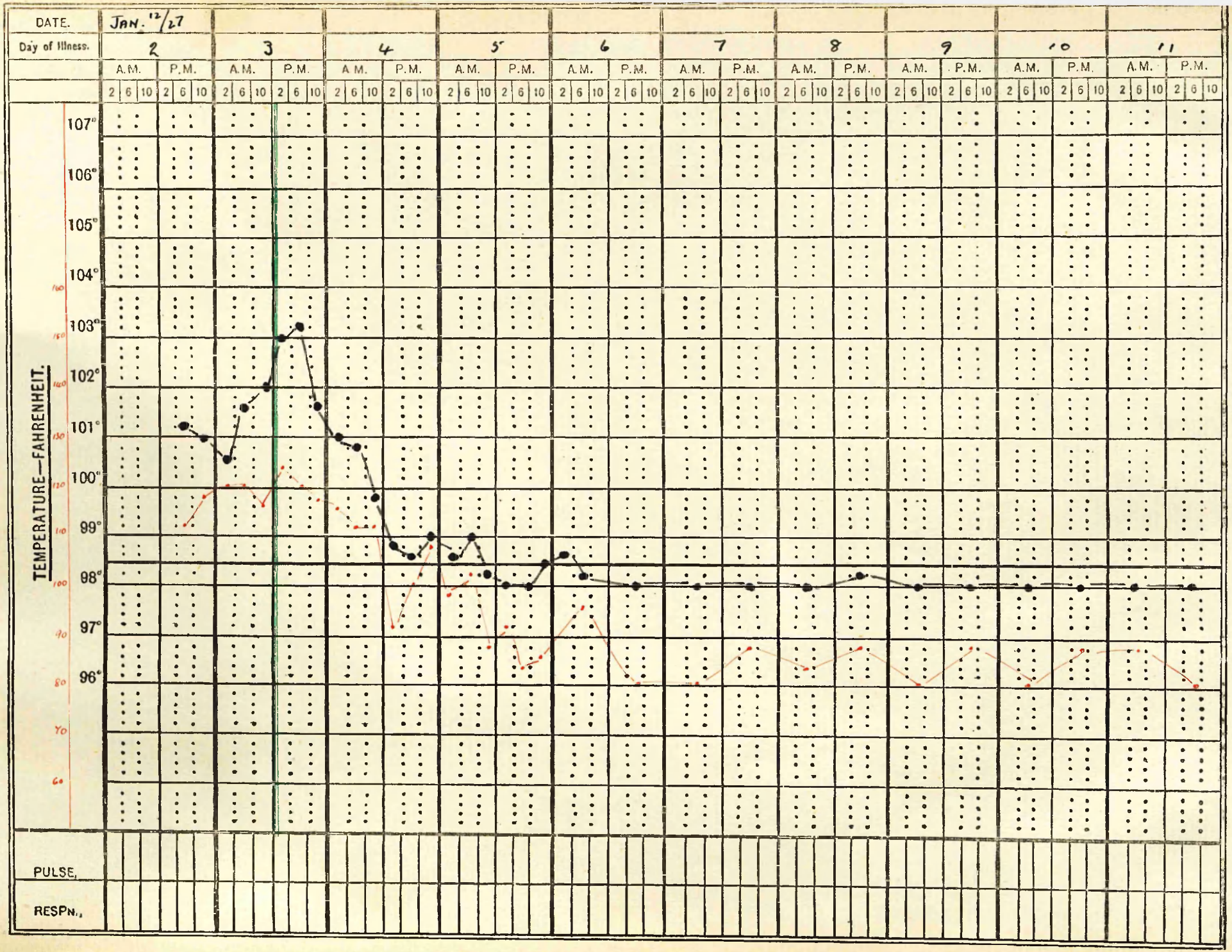
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

9


DATE.
JAN. 12/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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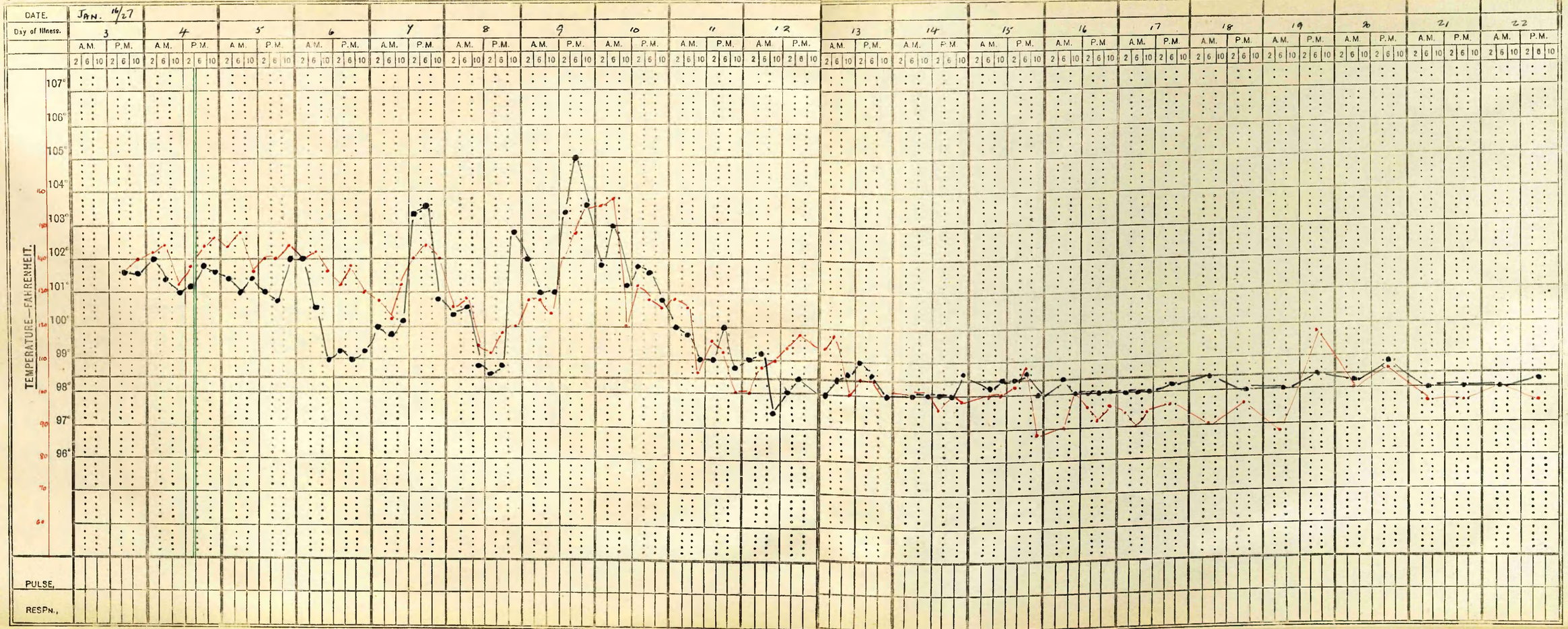
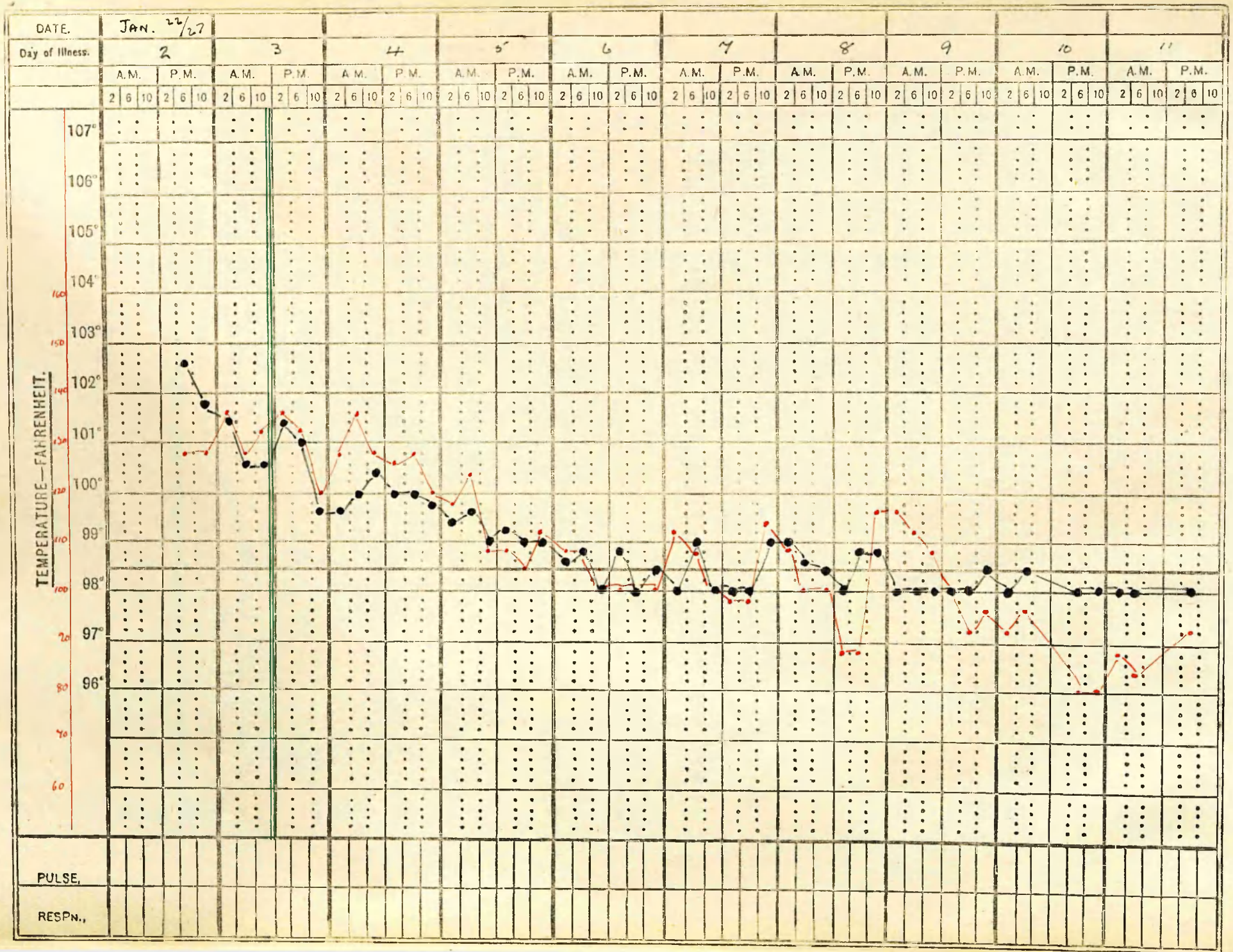
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

11


DATE.
JAN. 16/27
Day of Illness.
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
A.M. P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
PULSE.
RESPN.


DATE.
JAN. 22/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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96°
TEMPERATURE—FAHRENHEIT.
160
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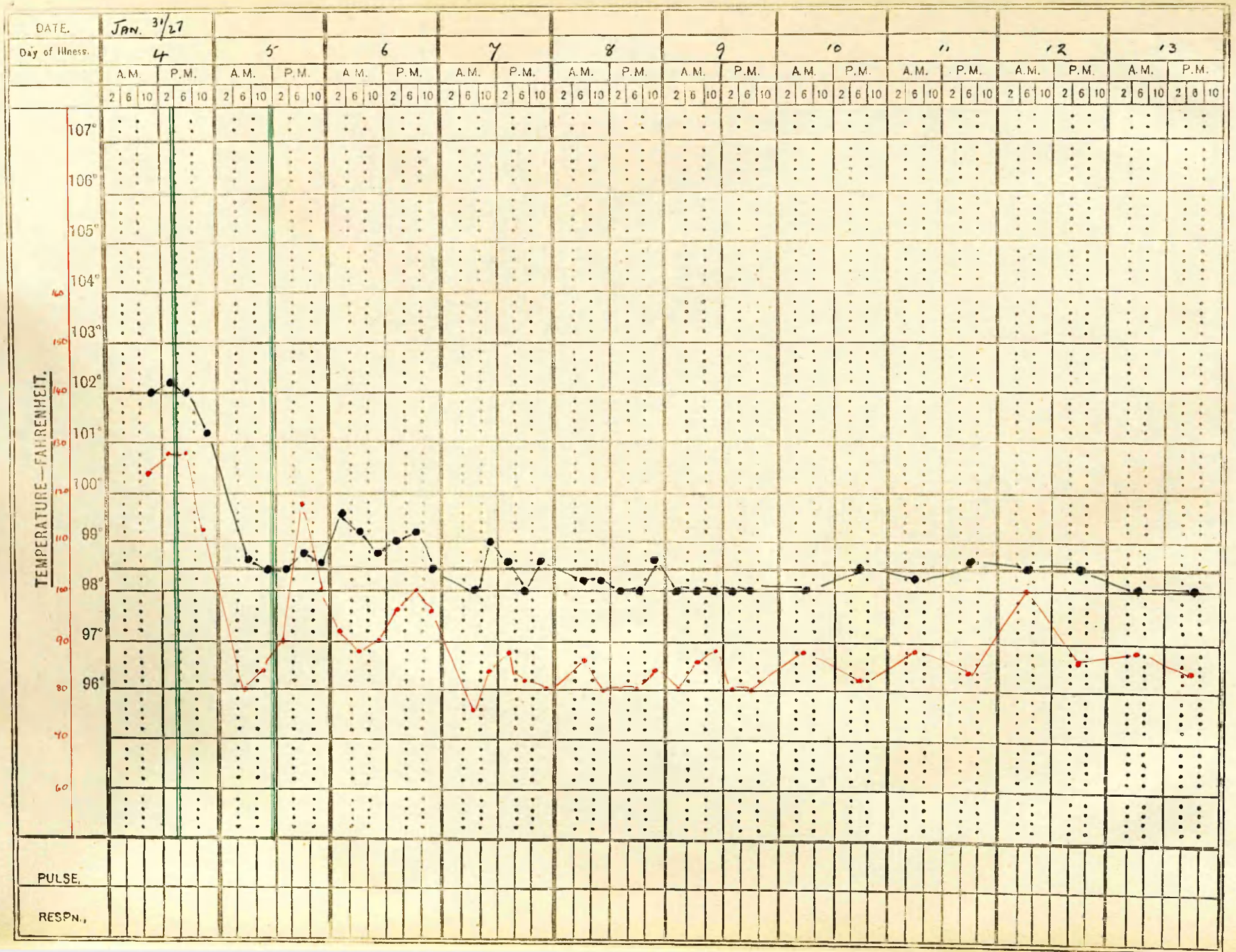
70
60
PULSE.
RESPN.,


DATE.
Jan. 31/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
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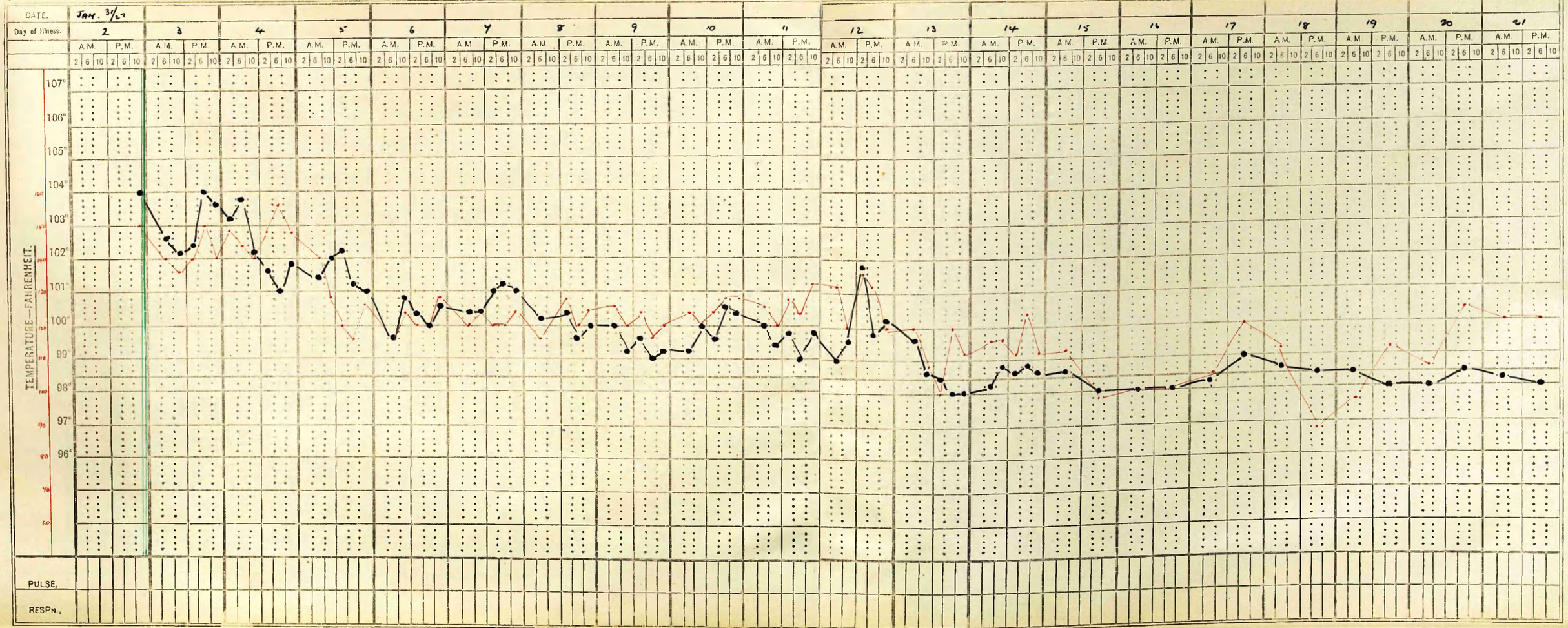
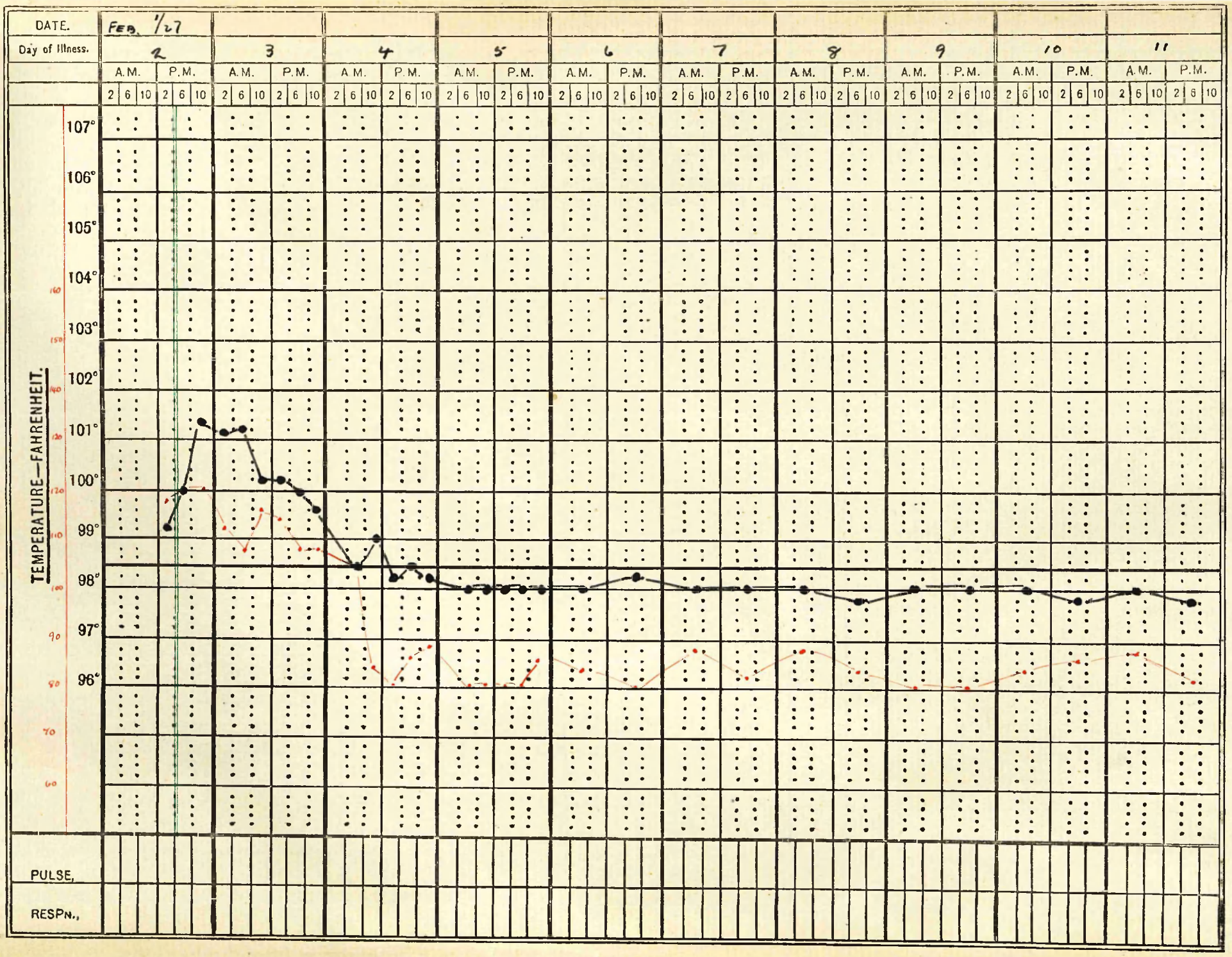
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
Jan. 31/27
Day of Illness.
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
A.M. P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
PULSE.
RESPN.


DATE.
FEB. 1/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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104°
103°
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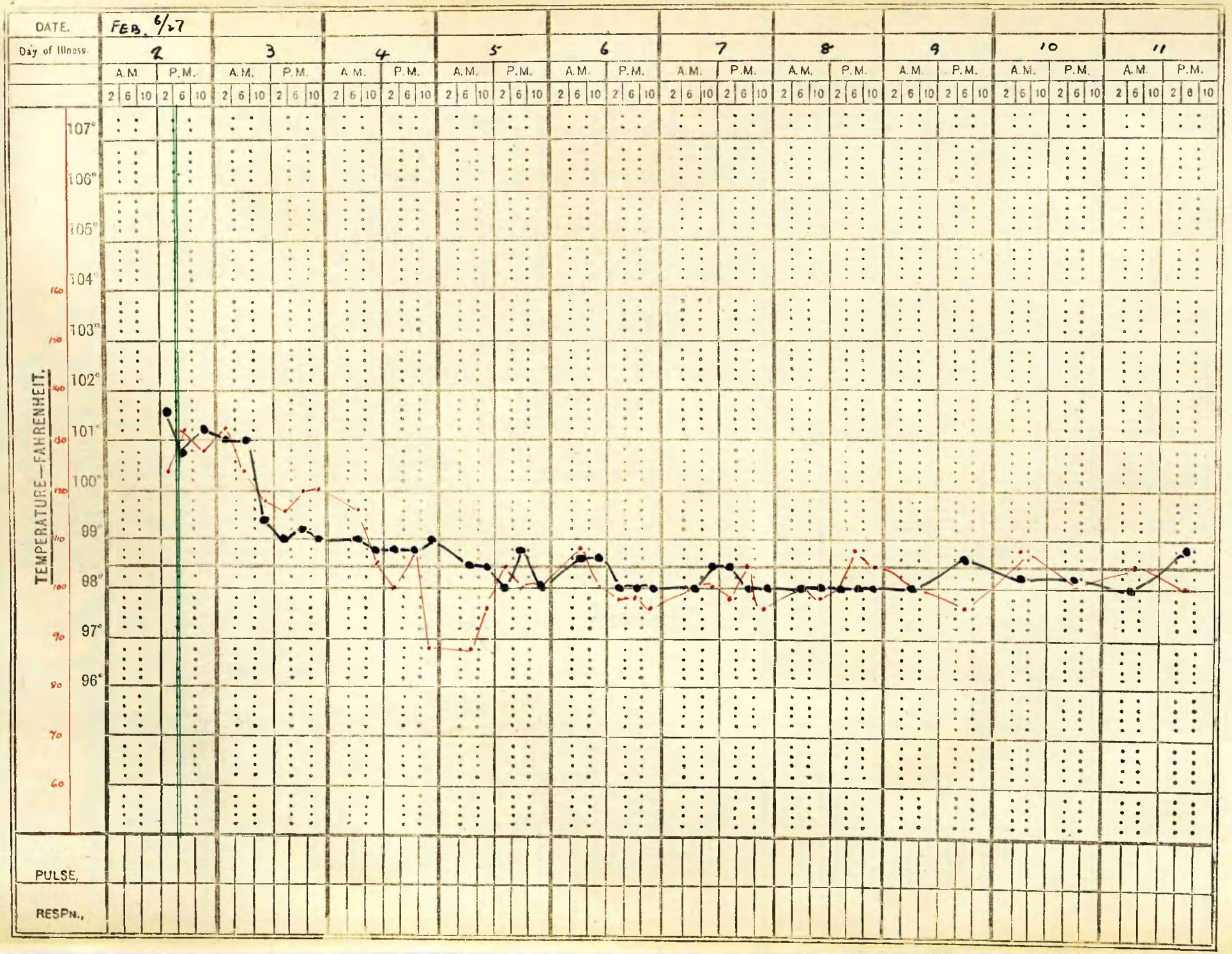
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
FEB. 6/27
Day of Illness.
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11
A.M.
P.M.
2 6 10
107°
106°
105°
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103°
102°
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100°
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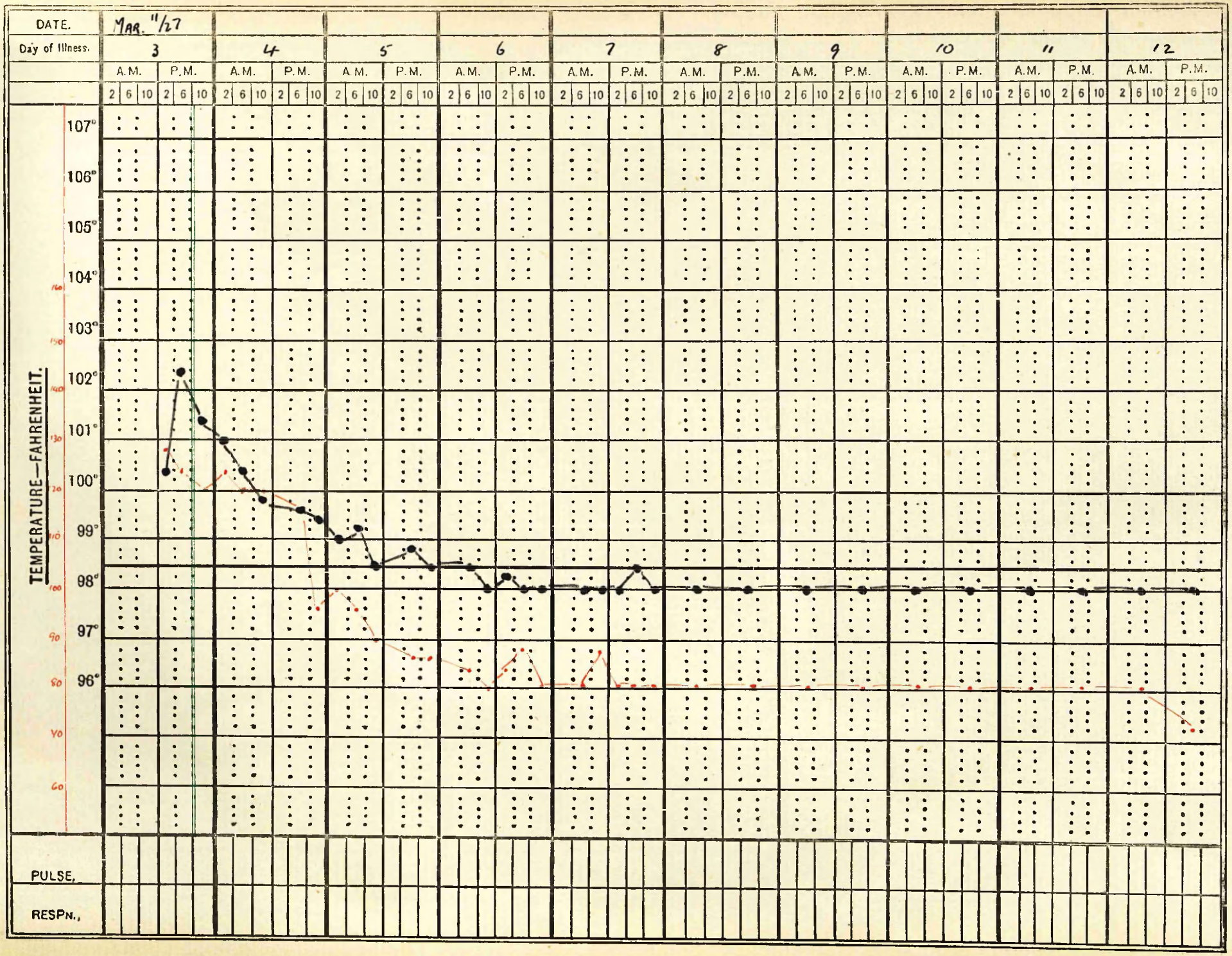
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
Mar. 11/27
Day of Illness.
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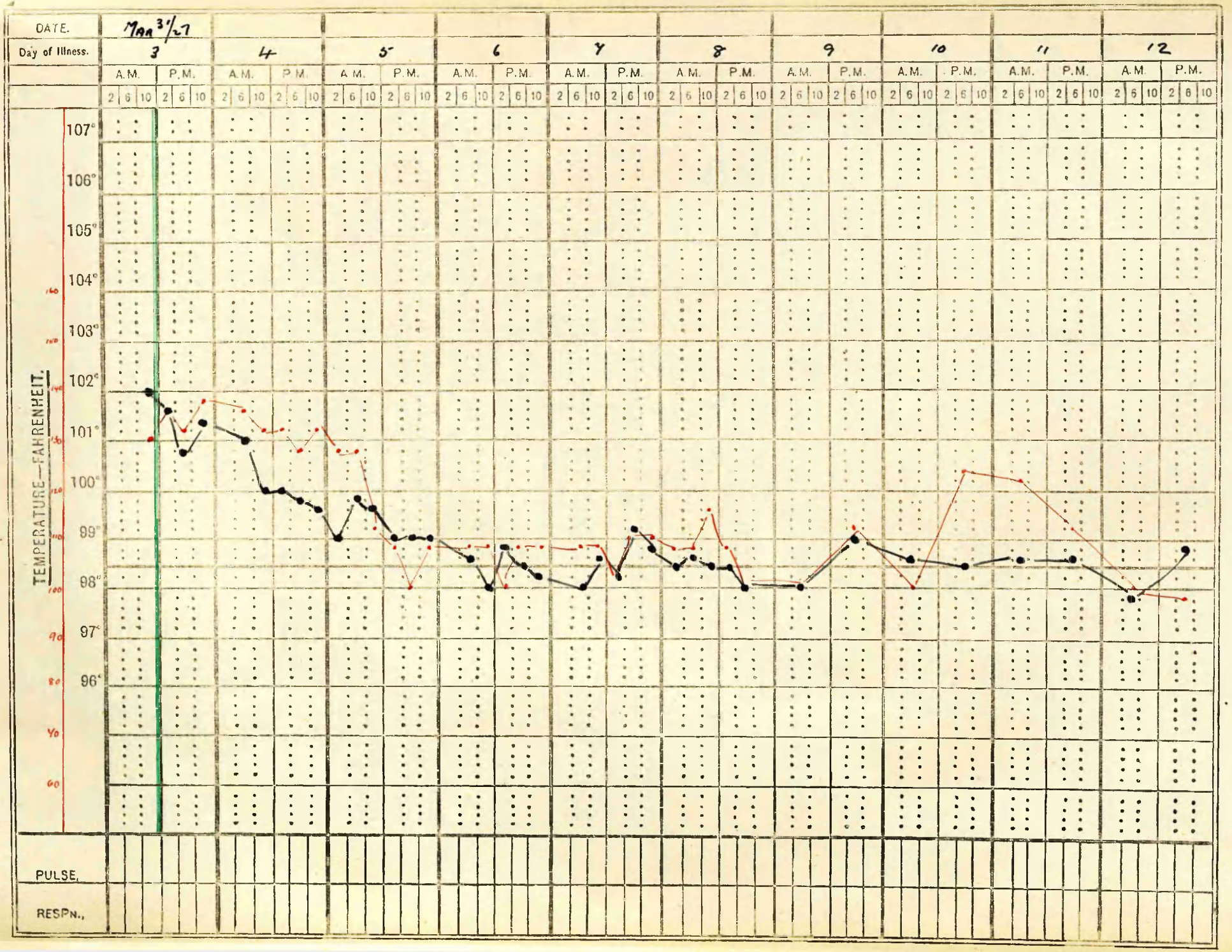
12
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
PULSE.
RESPN.


DATE.
Mar 31/27
Day of Illness.
3
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10
11
12
A.M.
P.M.
2 6 10
107°
106°
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104°
103°
102°
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100°
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98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

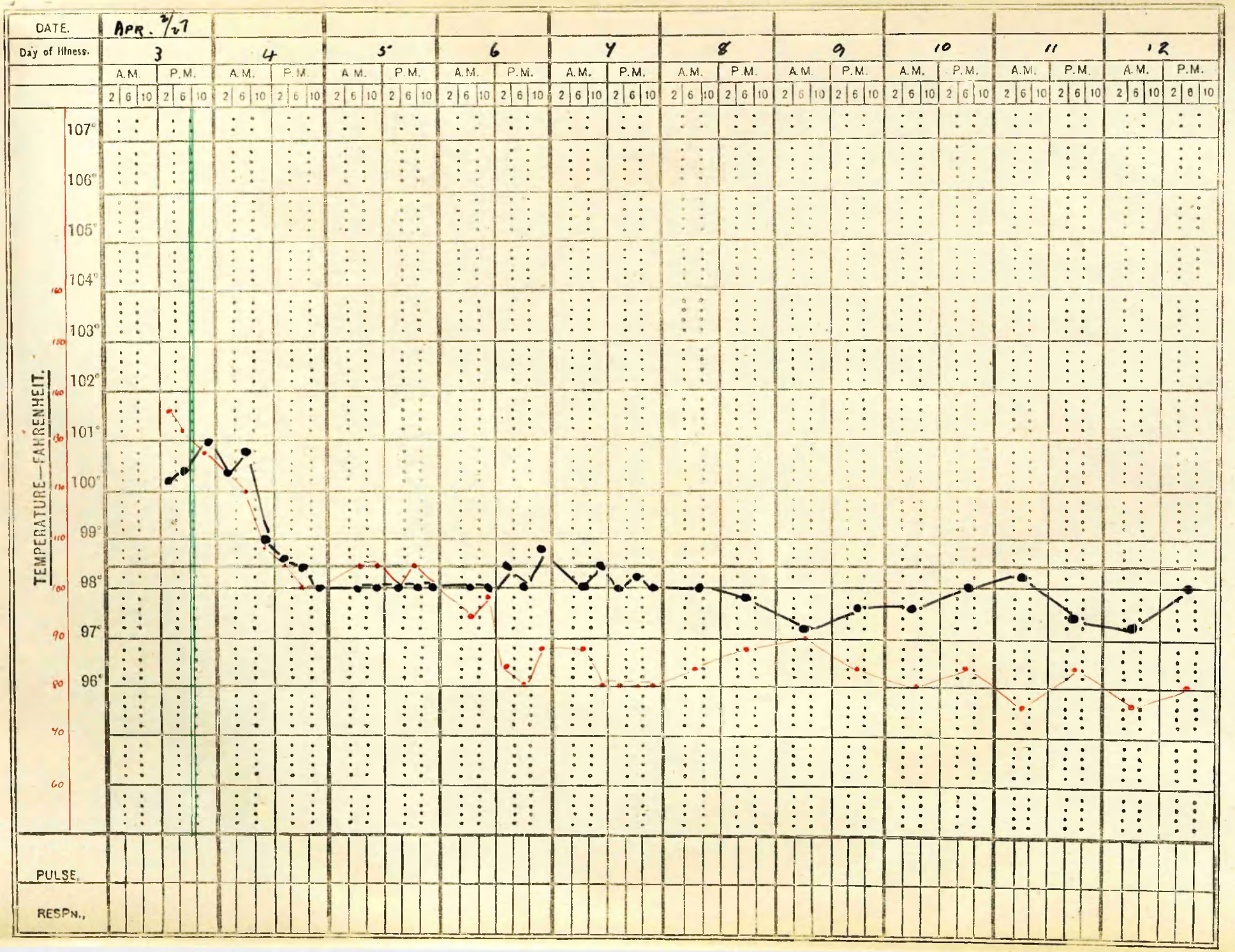
DATE.	Apr. 19/27																					
Day of Illness.	1		2		3		4		5		6		7		8		9		10			
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.		
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	

TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

PULSE.

RESPN.


DATE.
Apr. 2/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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103°
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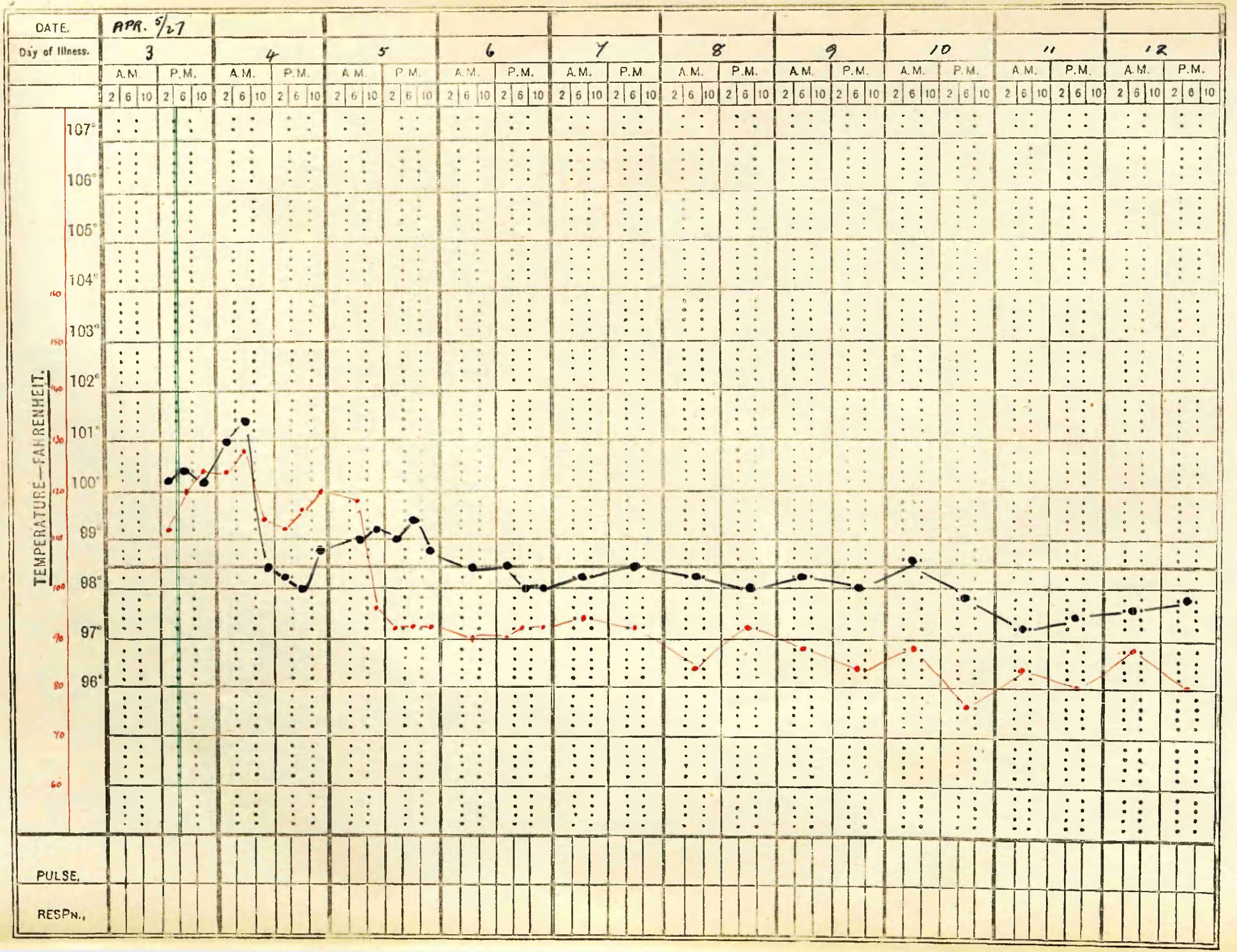
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
APR. 5/27
Day of Illness.
3
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11
12
A.M.
P.M.
2 6 10
107°
106°
105°
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103°
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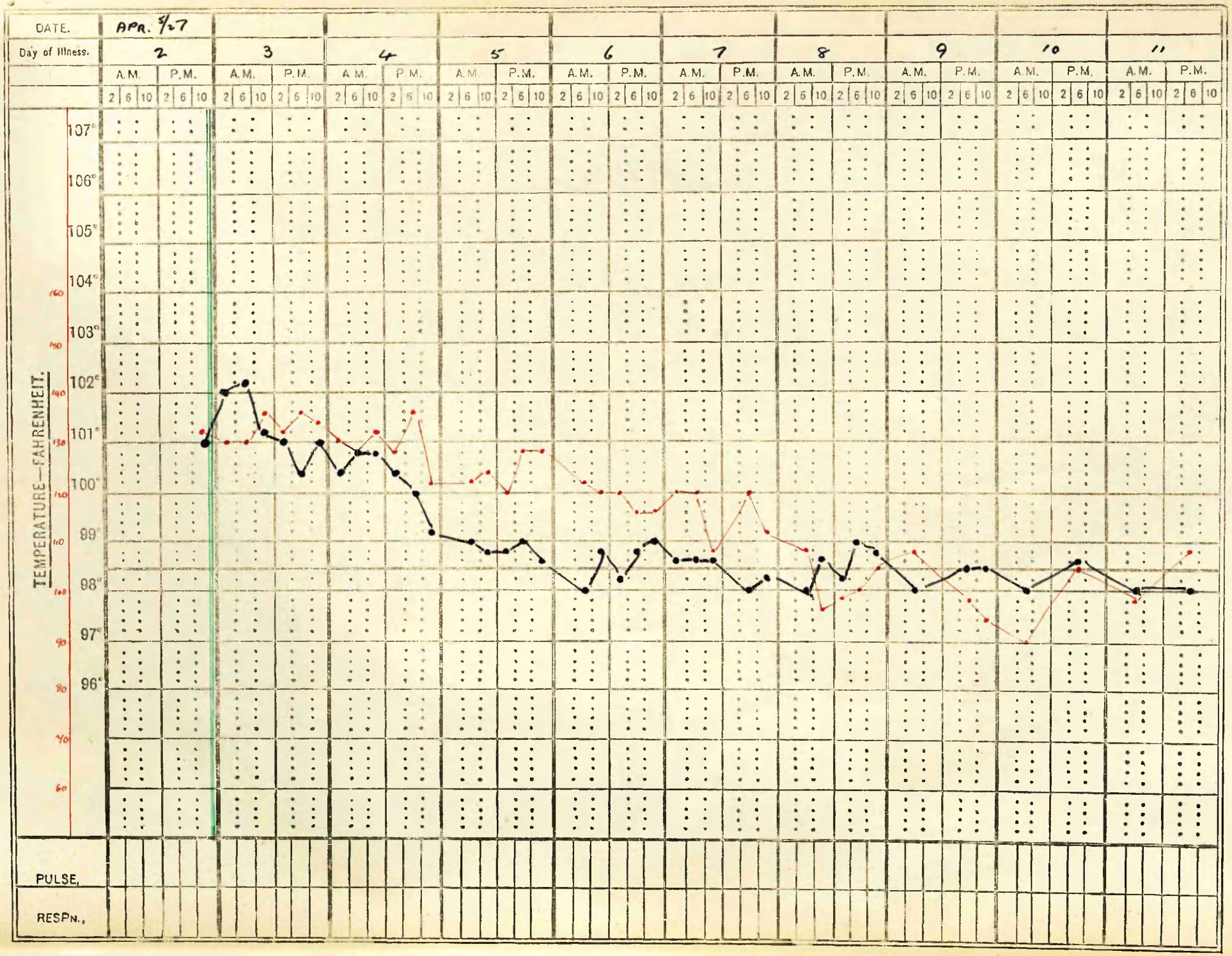
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
APR. 5/27
Day of Illness.
2
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A.M.
P.M.
2 6 10
107°
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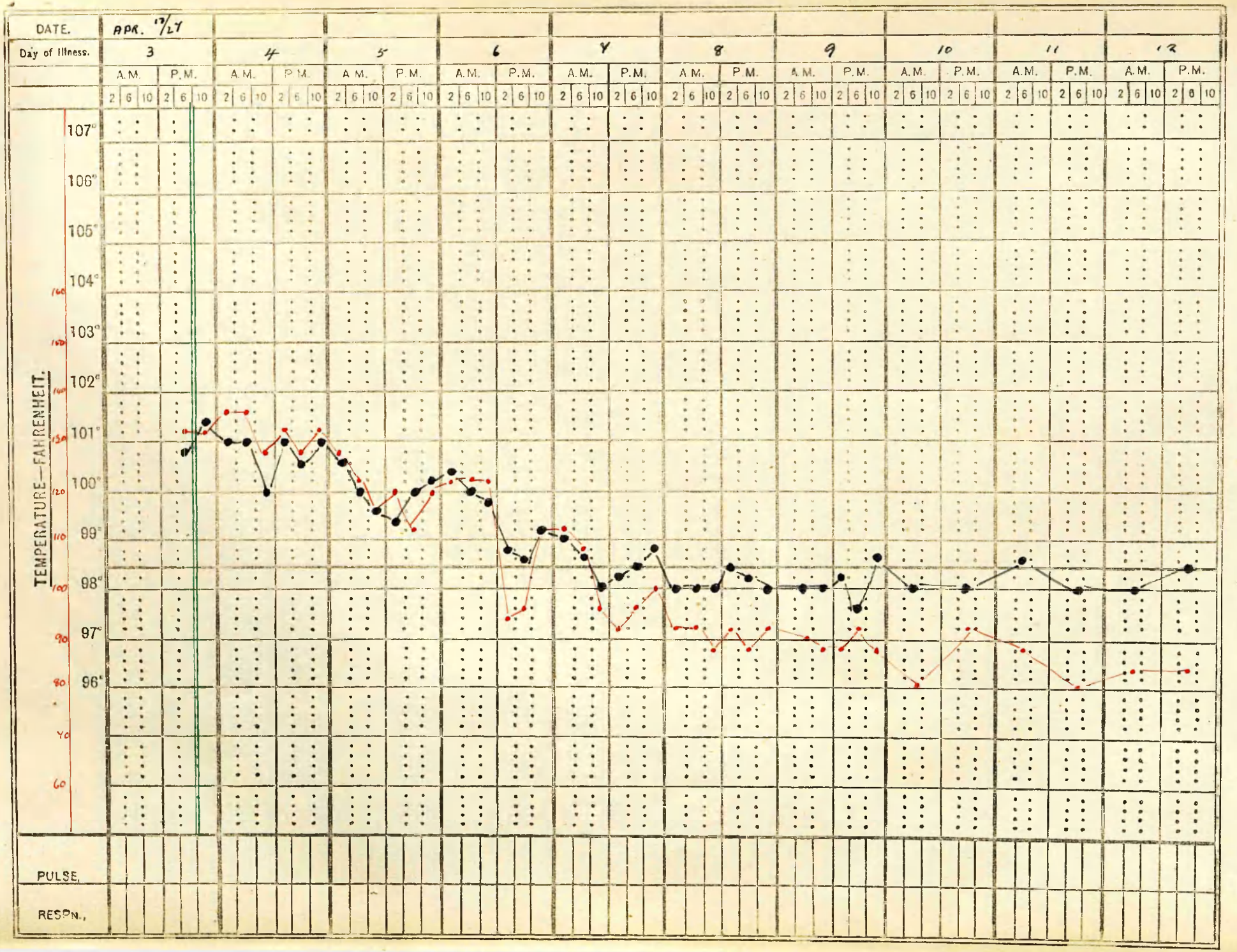
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

23


DATE.
APR. 17/27
Day of Illness.
3
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11
12
A.M.
P.M.
2 6 10
107°
106°
105°
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103°
102°
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100°
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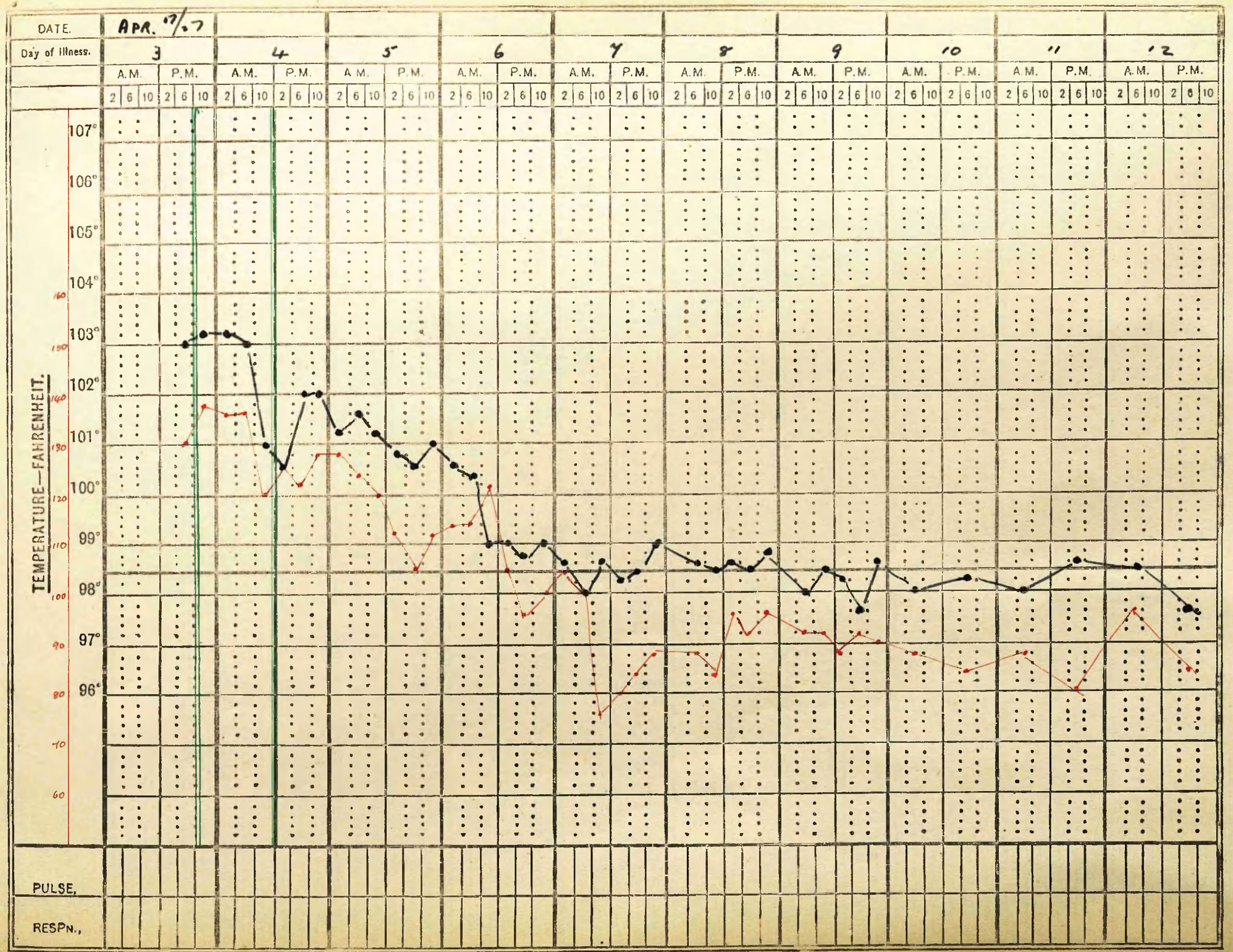
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
APR. 17/27
Day of Illness.
3
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A.M.
P.M.
2 6 10
107°
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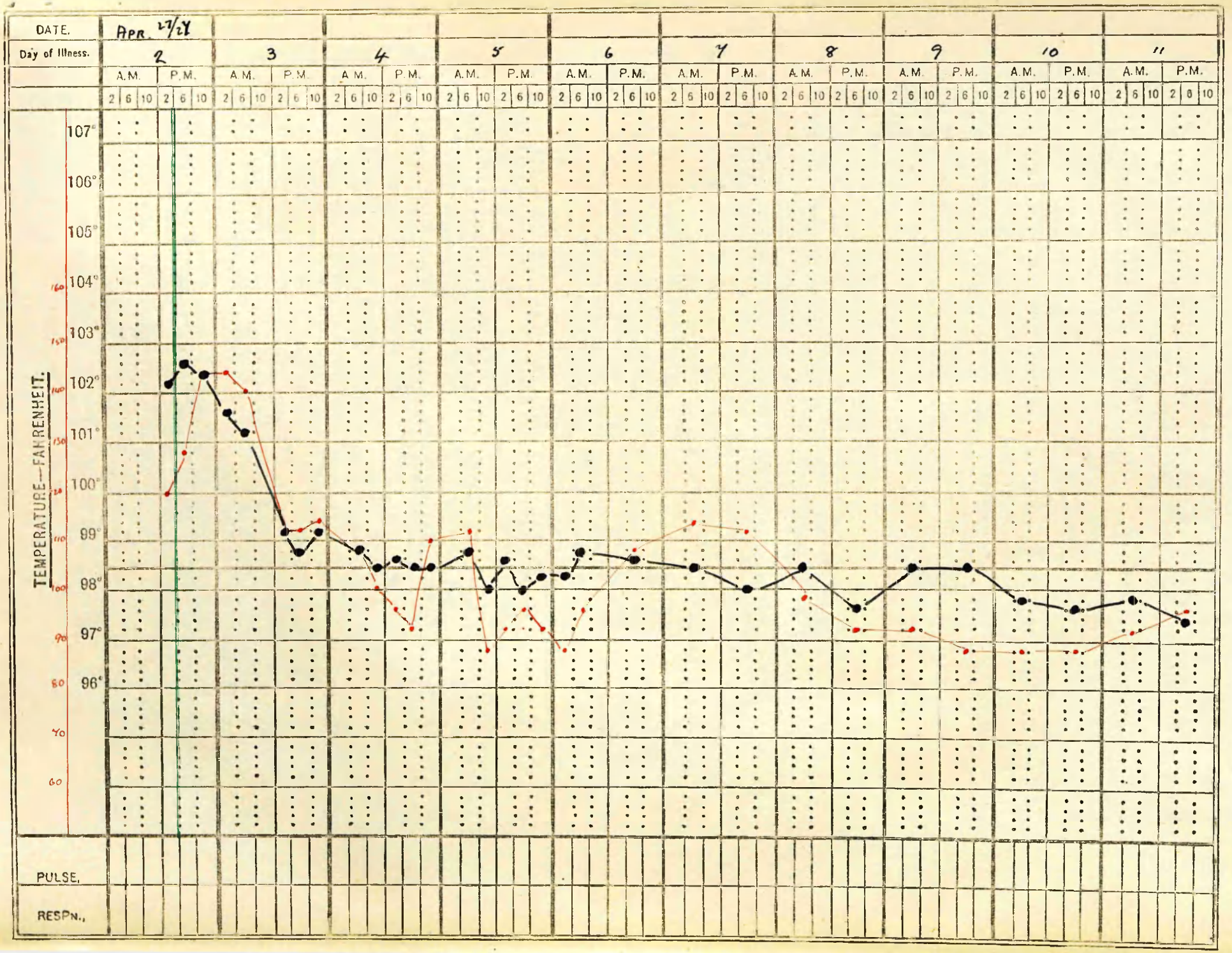
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

25


DATE.
Apr. 27/28
Day of Illness.
2
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A.M.
P.M.
2 6 10
107°
106°
105°
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103°
102°
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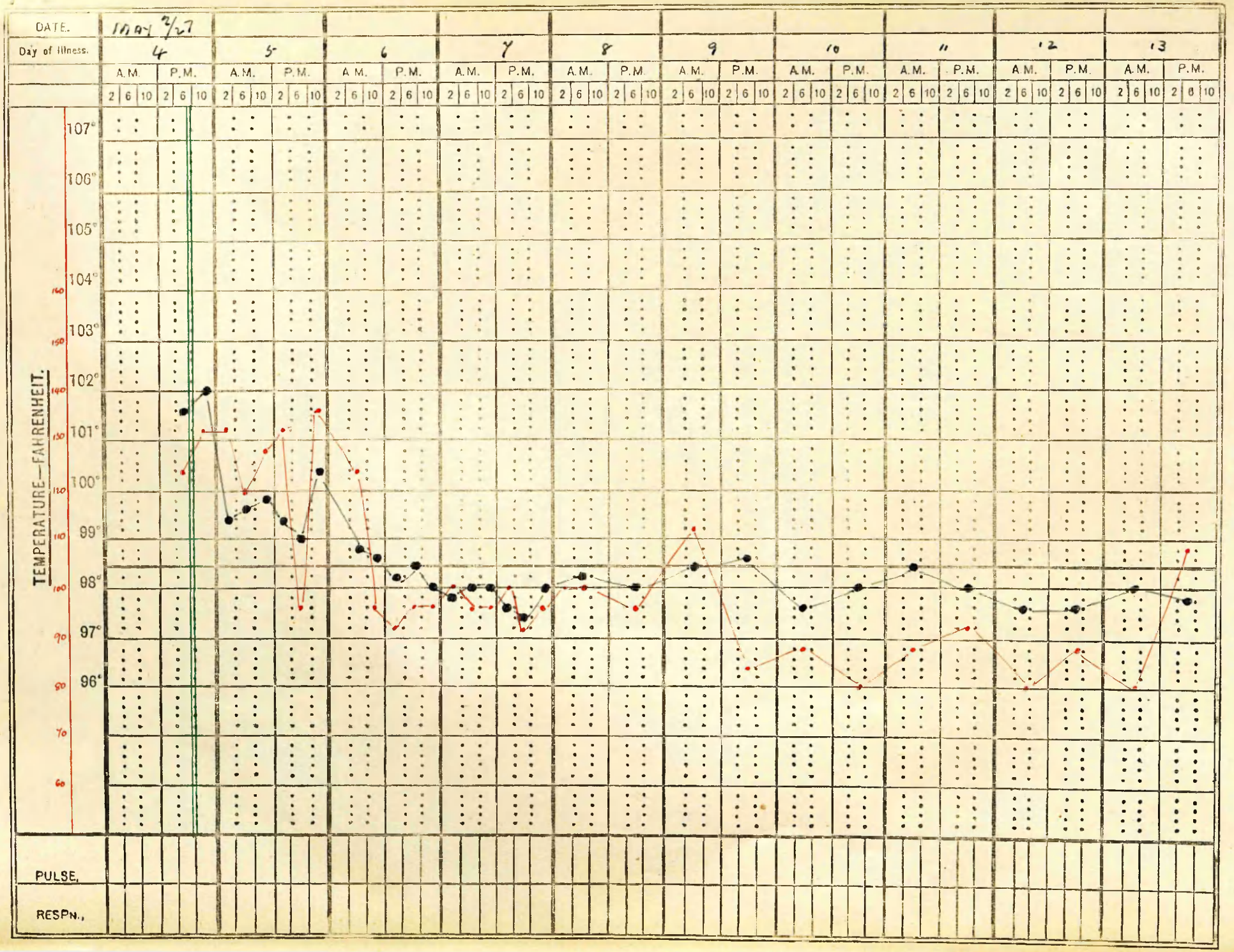
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May 2/27
Day of illness.
4
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12
13
A.M.
P.M.
2 6 10
107°
106°
105°
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102°
101°
100°
99°
98°
97°
96°
160
150
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70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

27

DATE. May 4/27

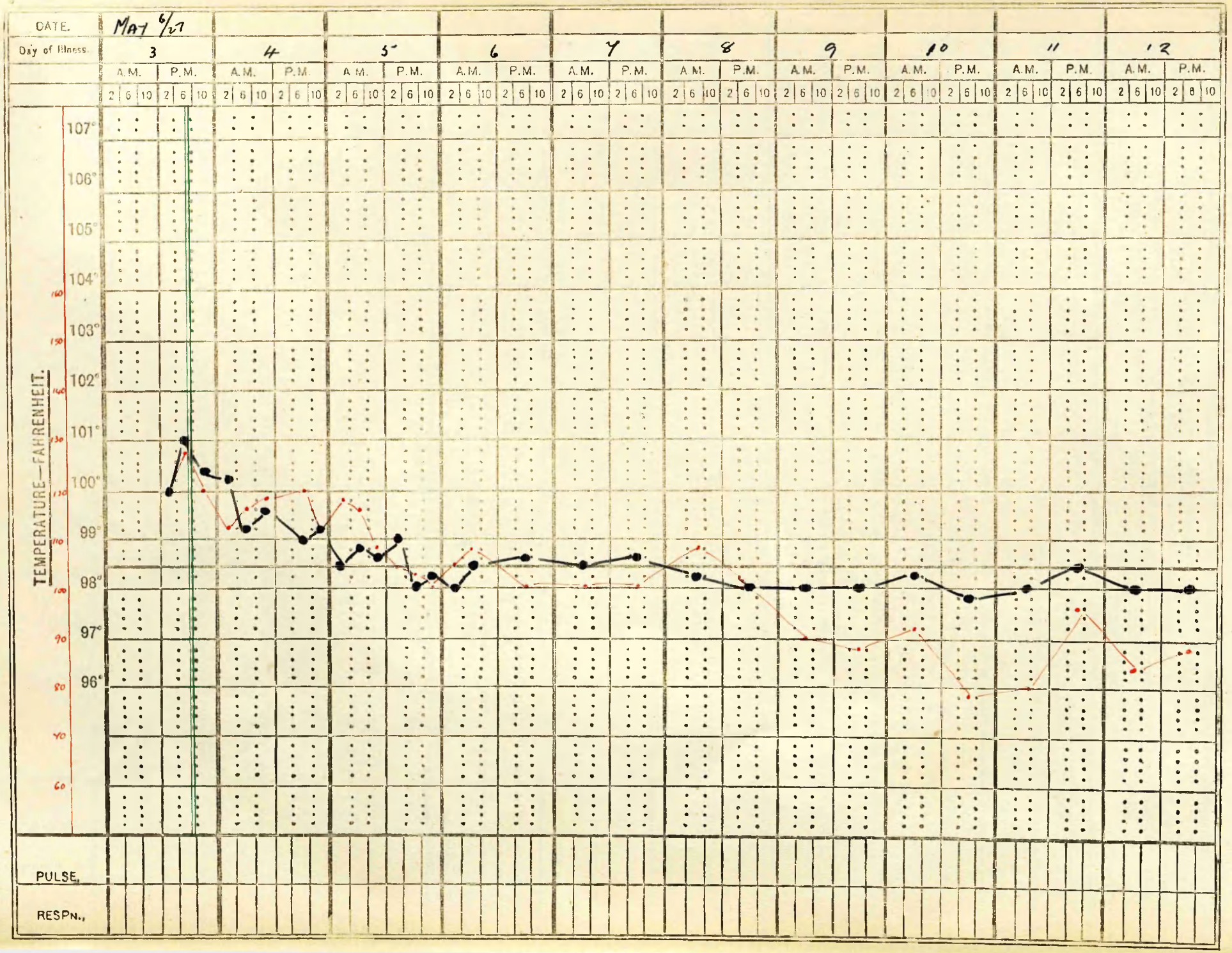
Day of Illness	3		4		5		6		7		8		9		10		11		12	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

PULSE.

RESPN.


DATE.
May 6/17
Day of Illness.
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12
A.M.
P.M.
2 6 10
107°
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100°
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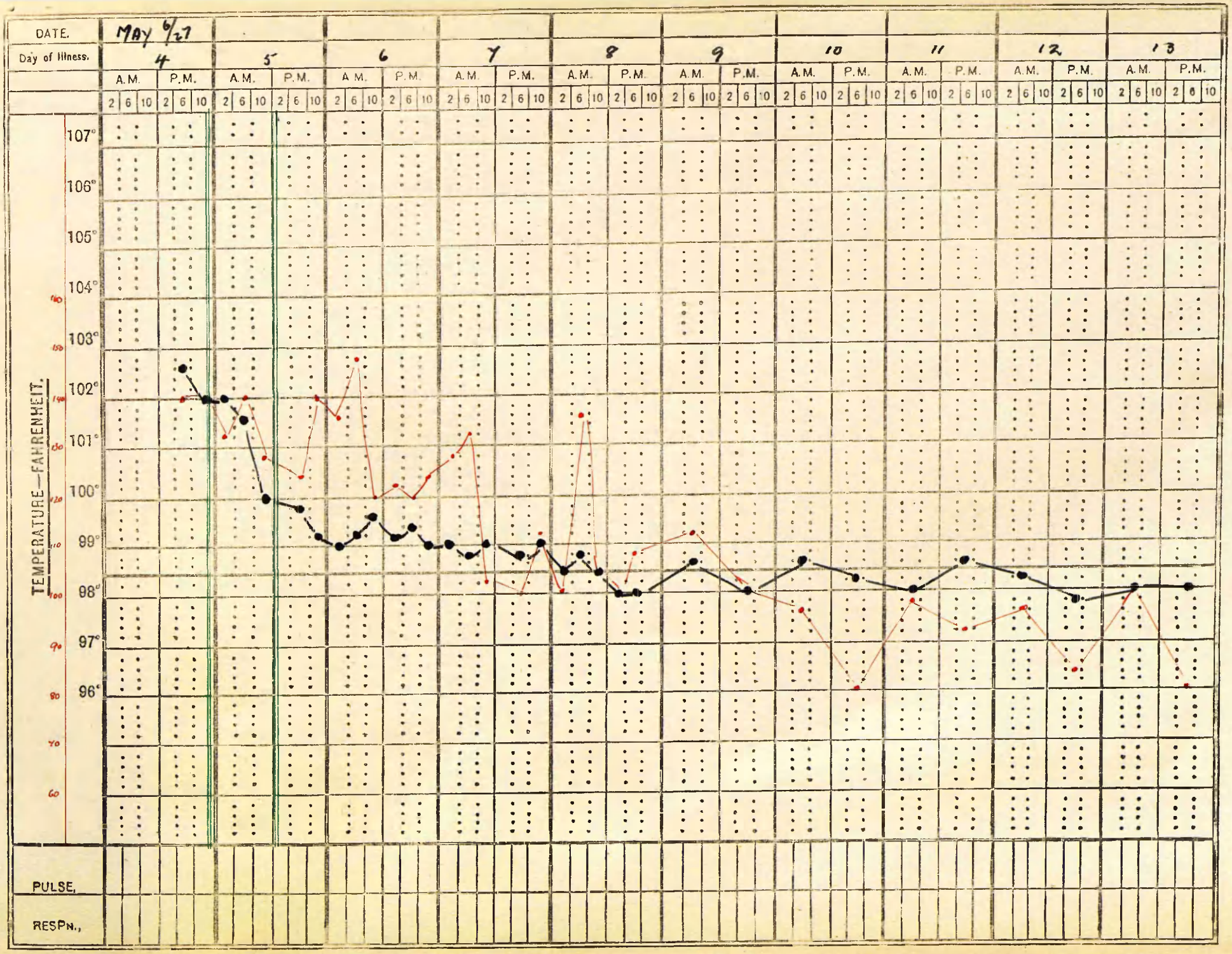
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
MAY 6/27
Day of Illness.
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13
A.M.
P.M.
2 6 10
107°
106°
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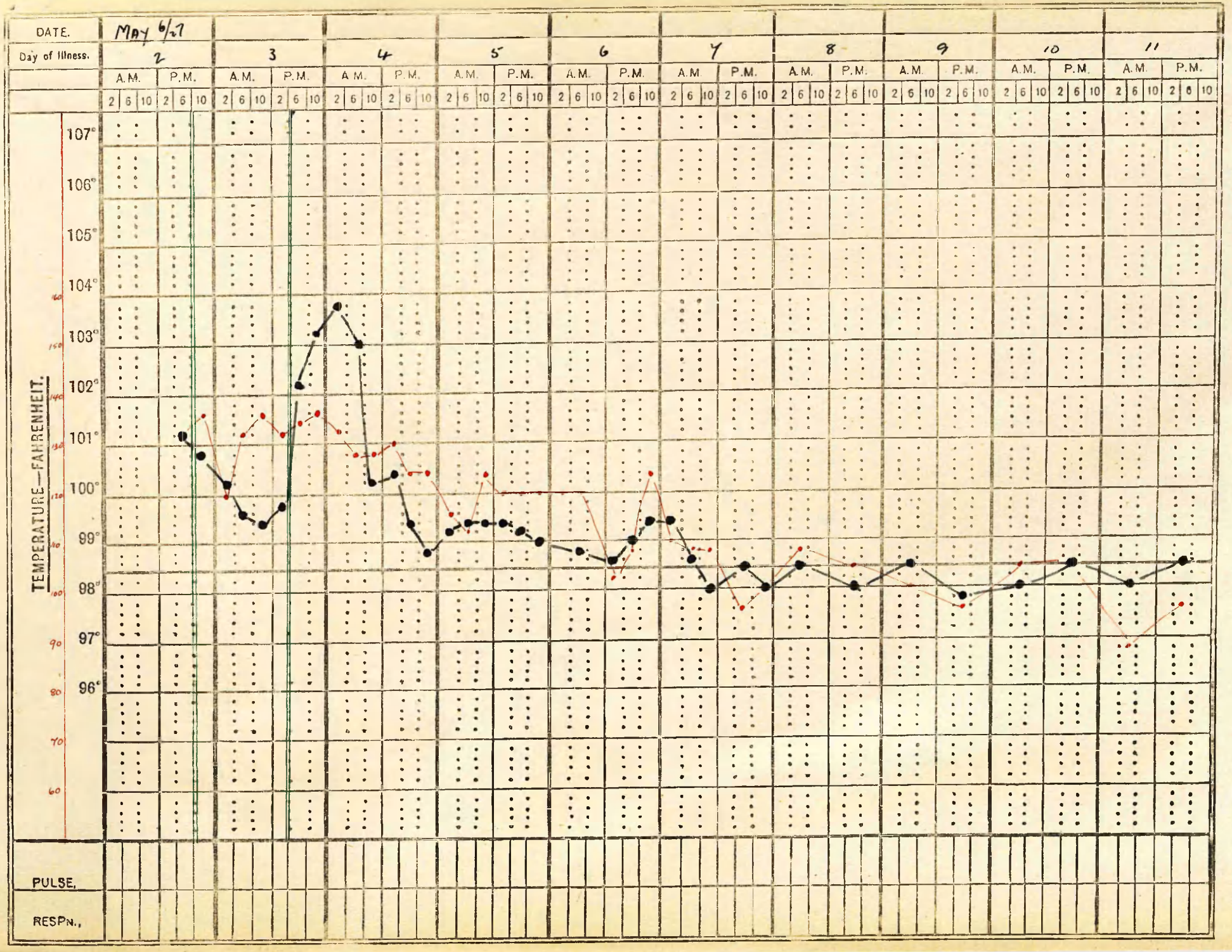
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
May 6/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
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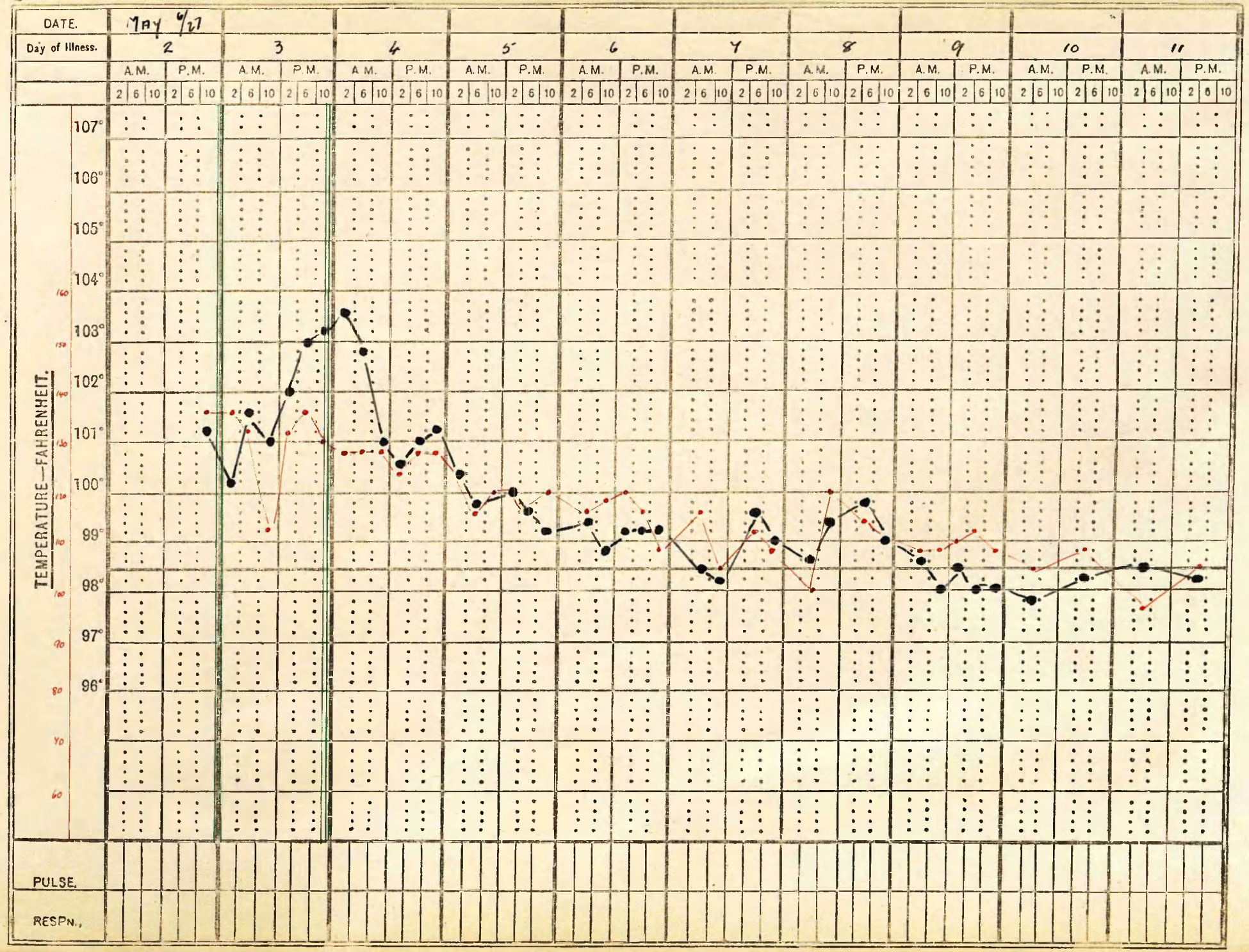
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May 6/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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103°
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101°
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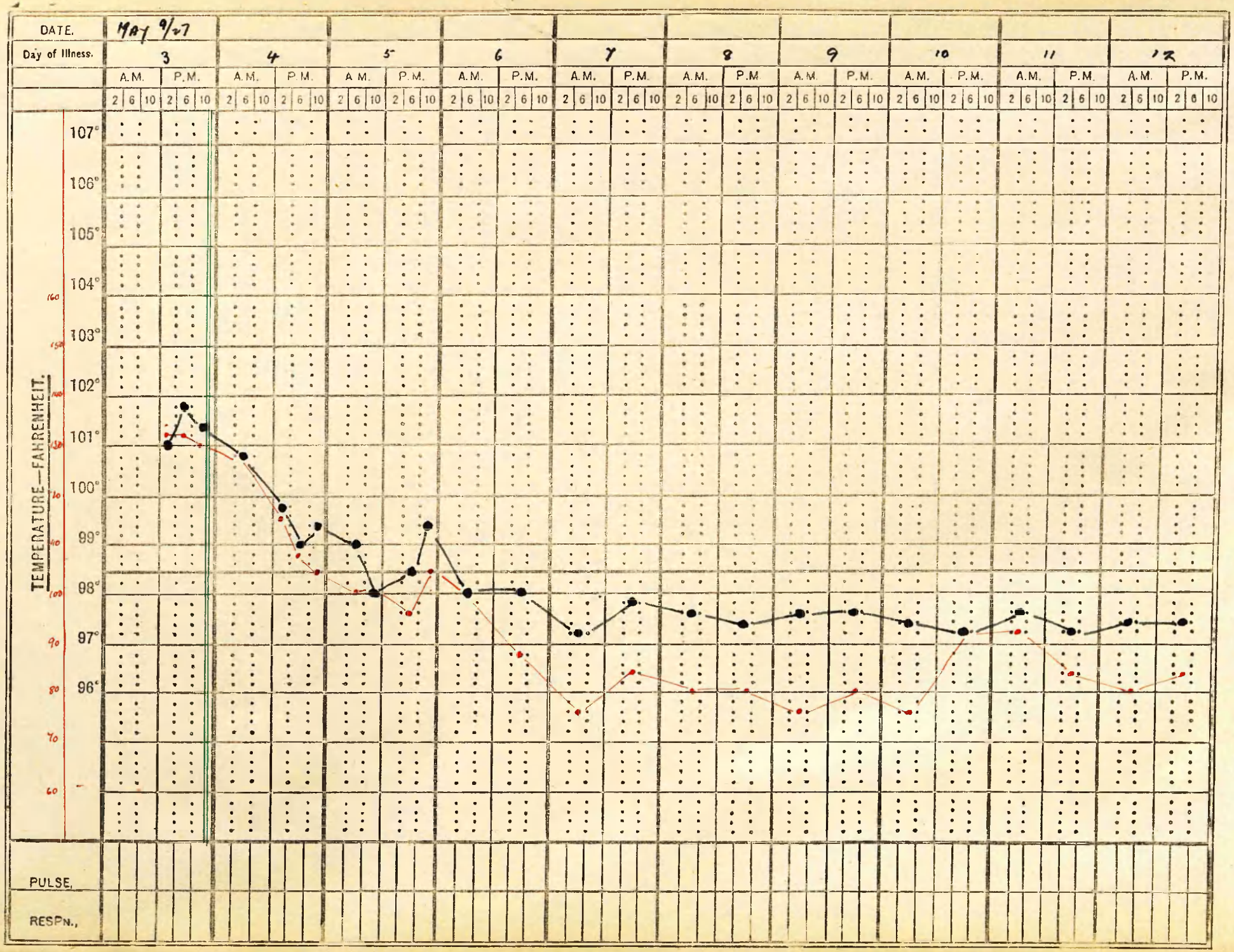
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
May 9/27
Day of Illness.
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12
A.M.
P.M.
2 6 10
107°
106°
105°
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103°
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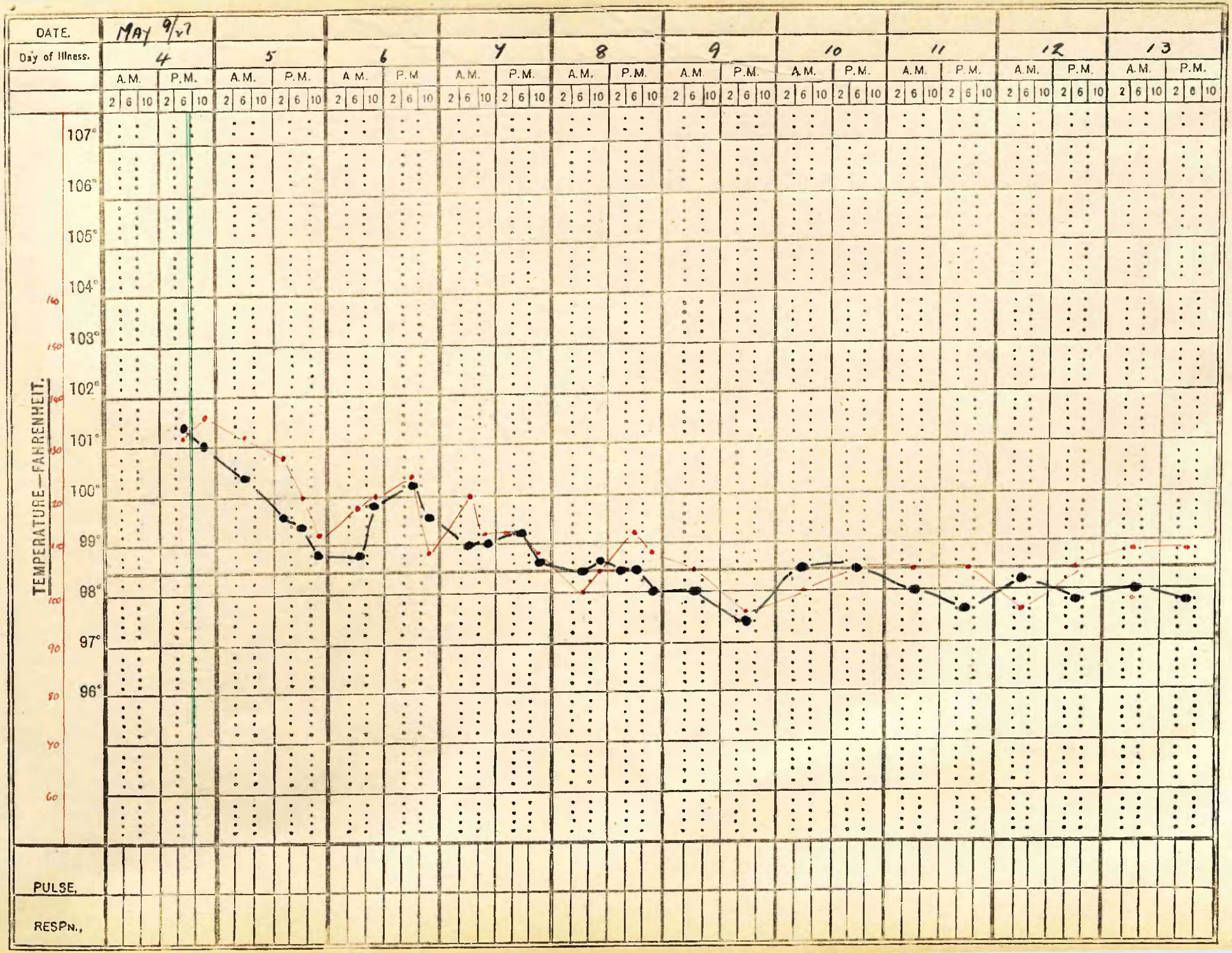
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May 9/17
Day of Illness.
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A.M.
P.M.
2 6 10
107°
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103°
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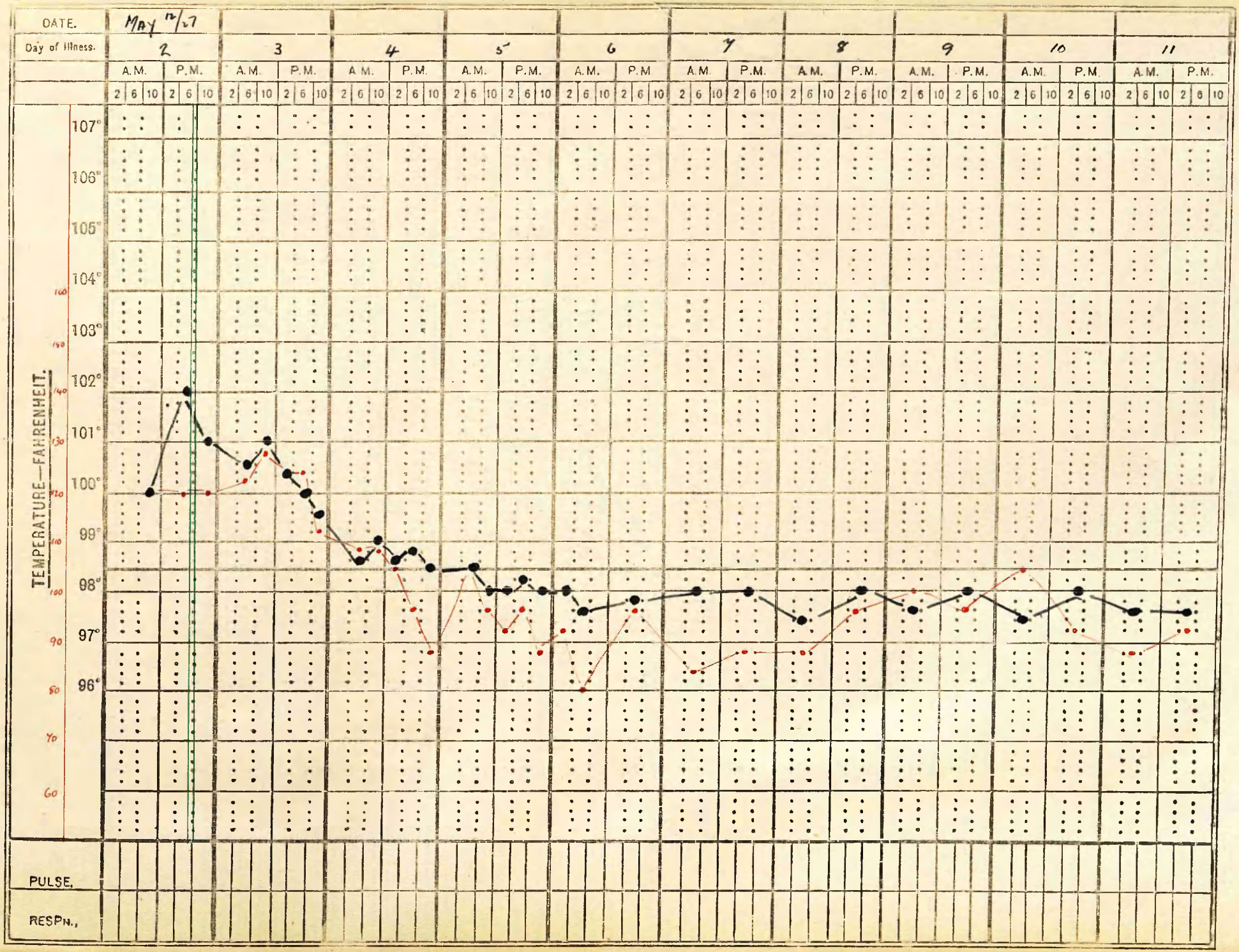
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
MAY 12/27
Day of Illness.
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11
A.M.
P.M.
2 6 10
107°
106°
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103°
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100°
99°
98°
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96°
TEMPERATURE—FAHRENHEIT.
160
150
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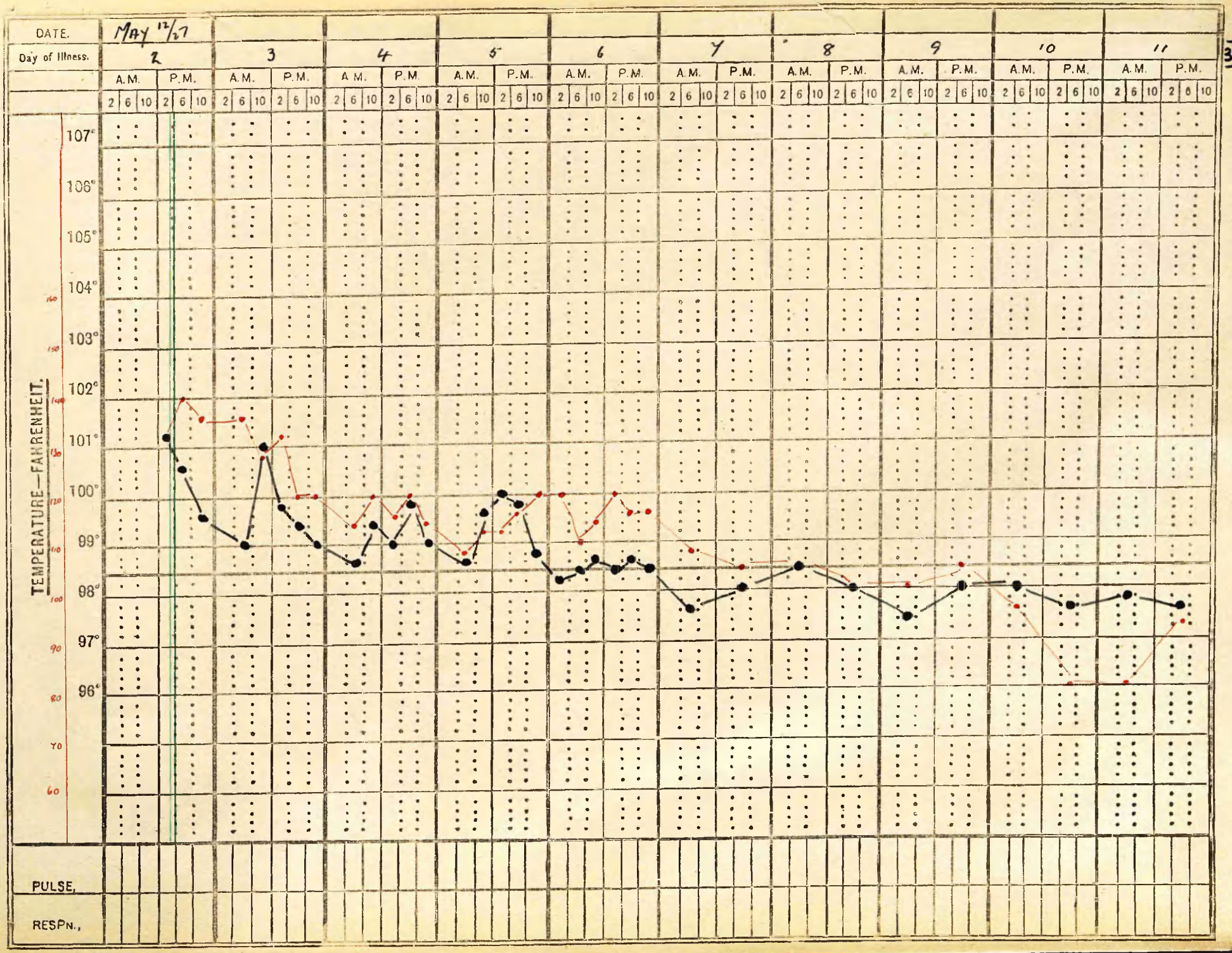
60
PULSE.
RESPN.,


DATE.
May 12/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
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103°
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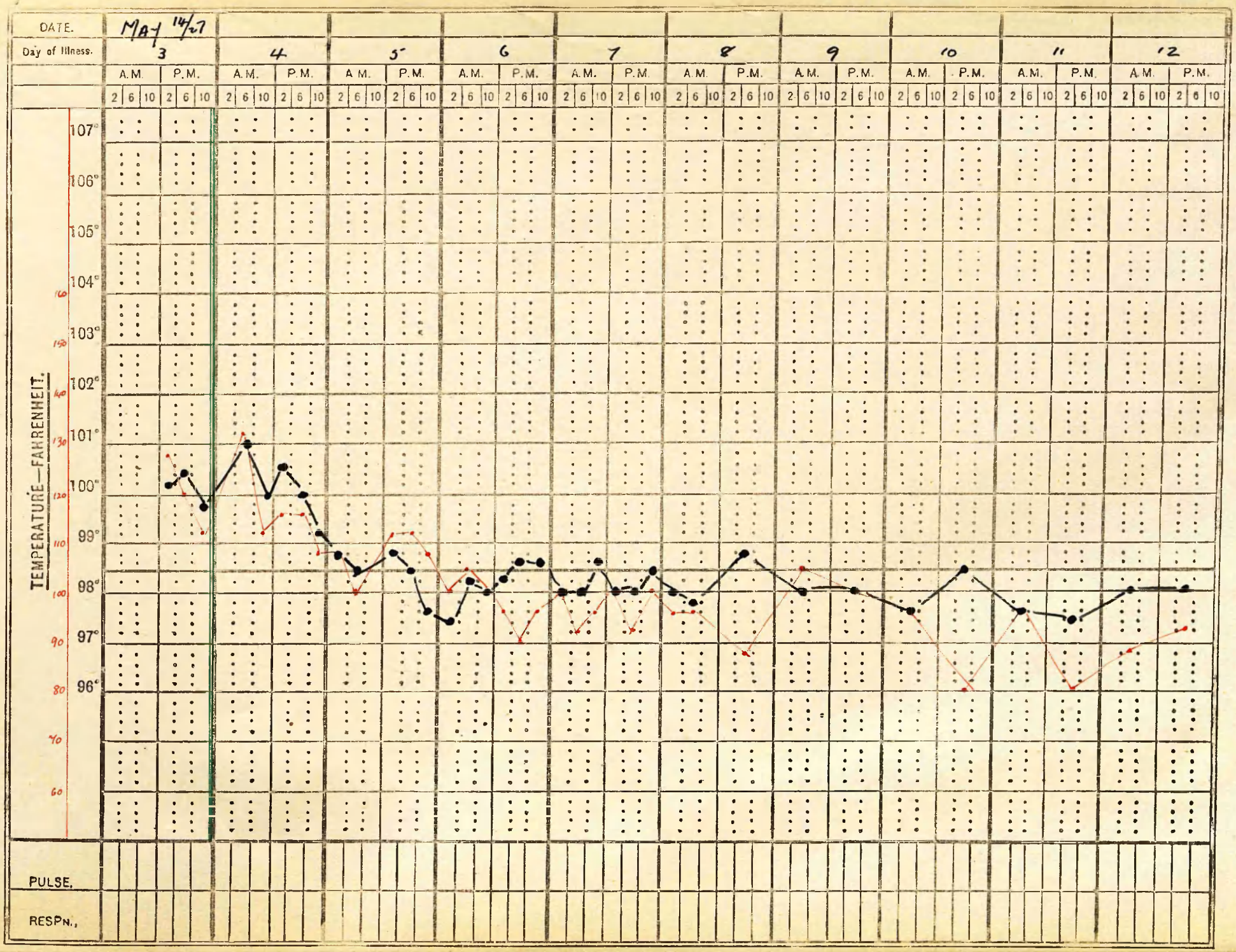
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
MAY 14/27
Day of Illness.
3
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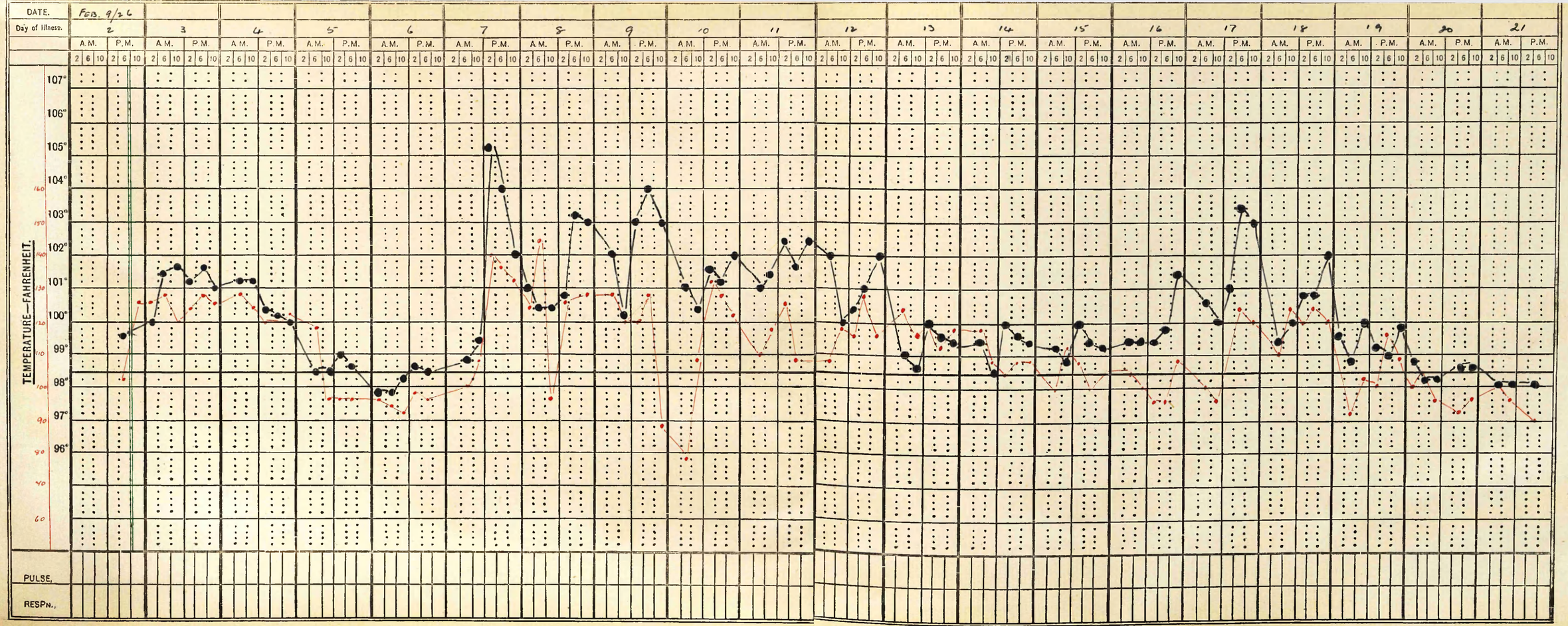
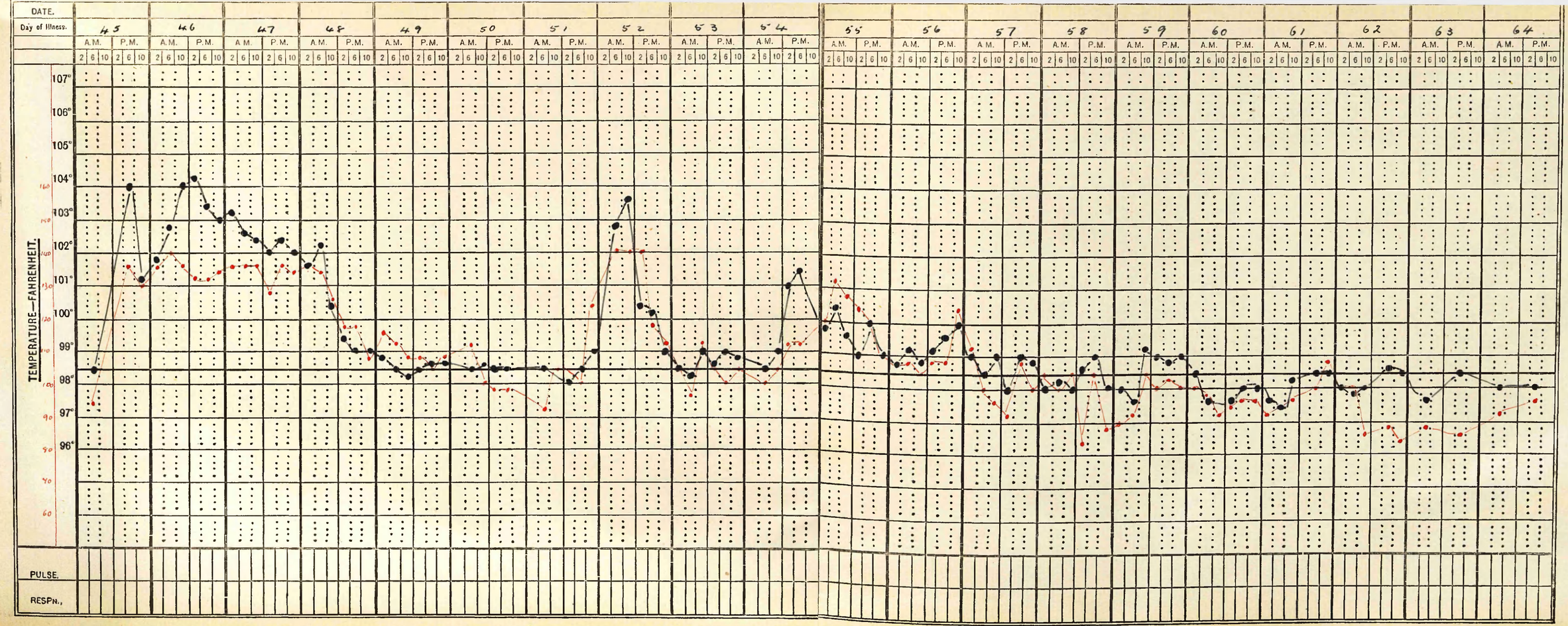
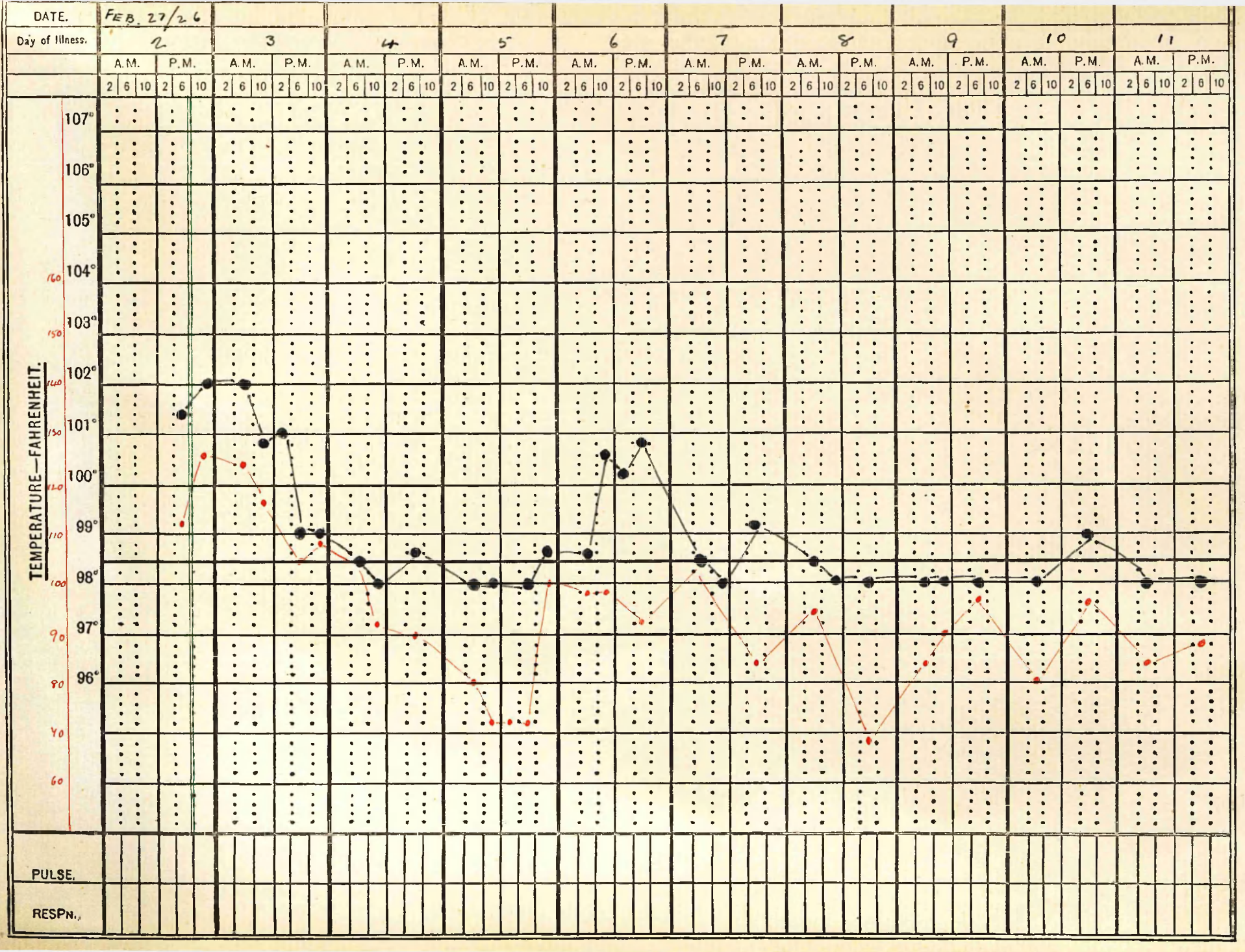
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

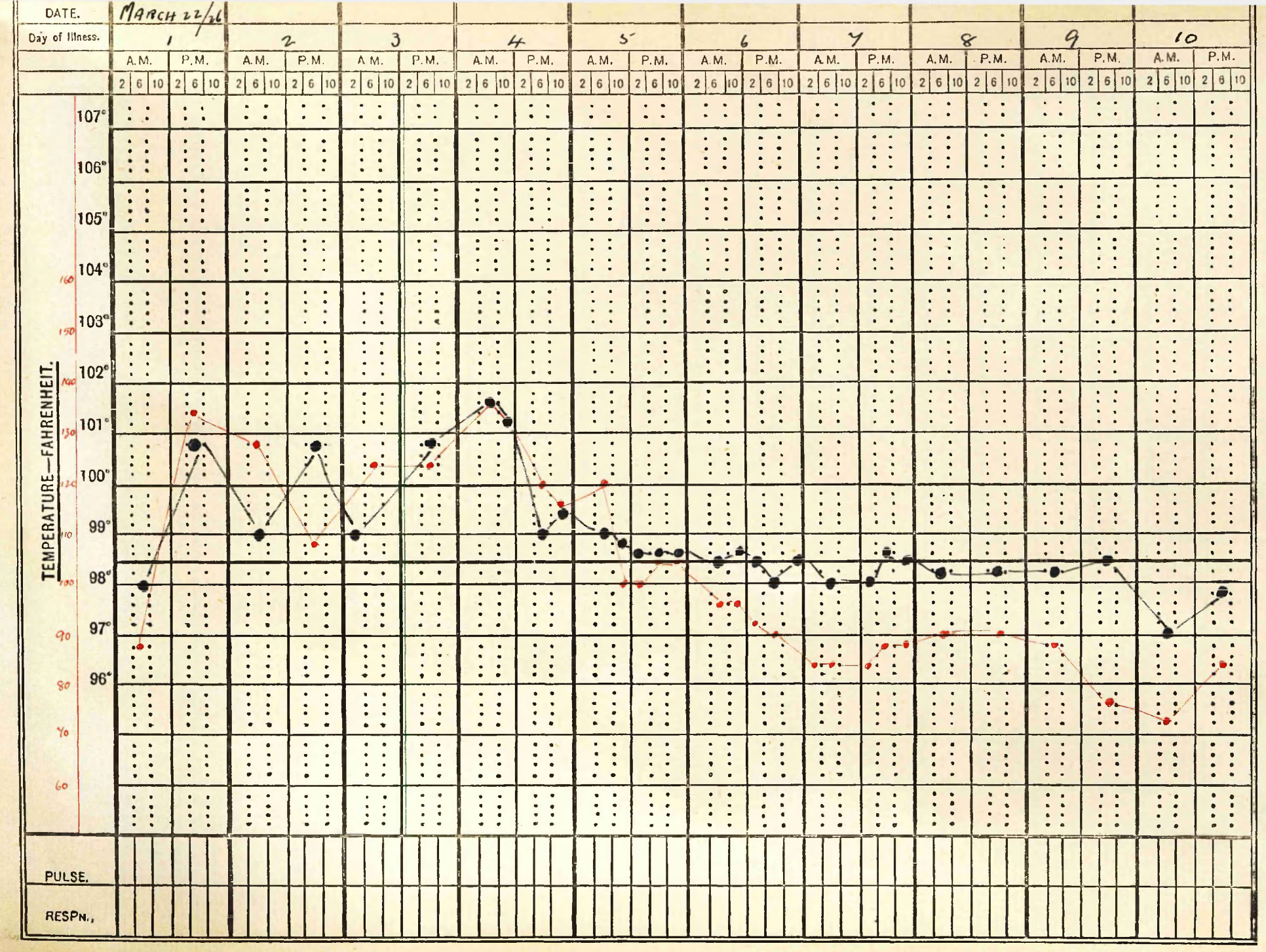
3 4


DATE.
FEB. 9/26
Day of Illness.
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
A.M. P.M.
2 6 10 2 6 10
TEMPERATURE—FAHRENHEIT.
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
160 150 140 130 120 110 100 90 80 70 60
PULSE.
RESPN.

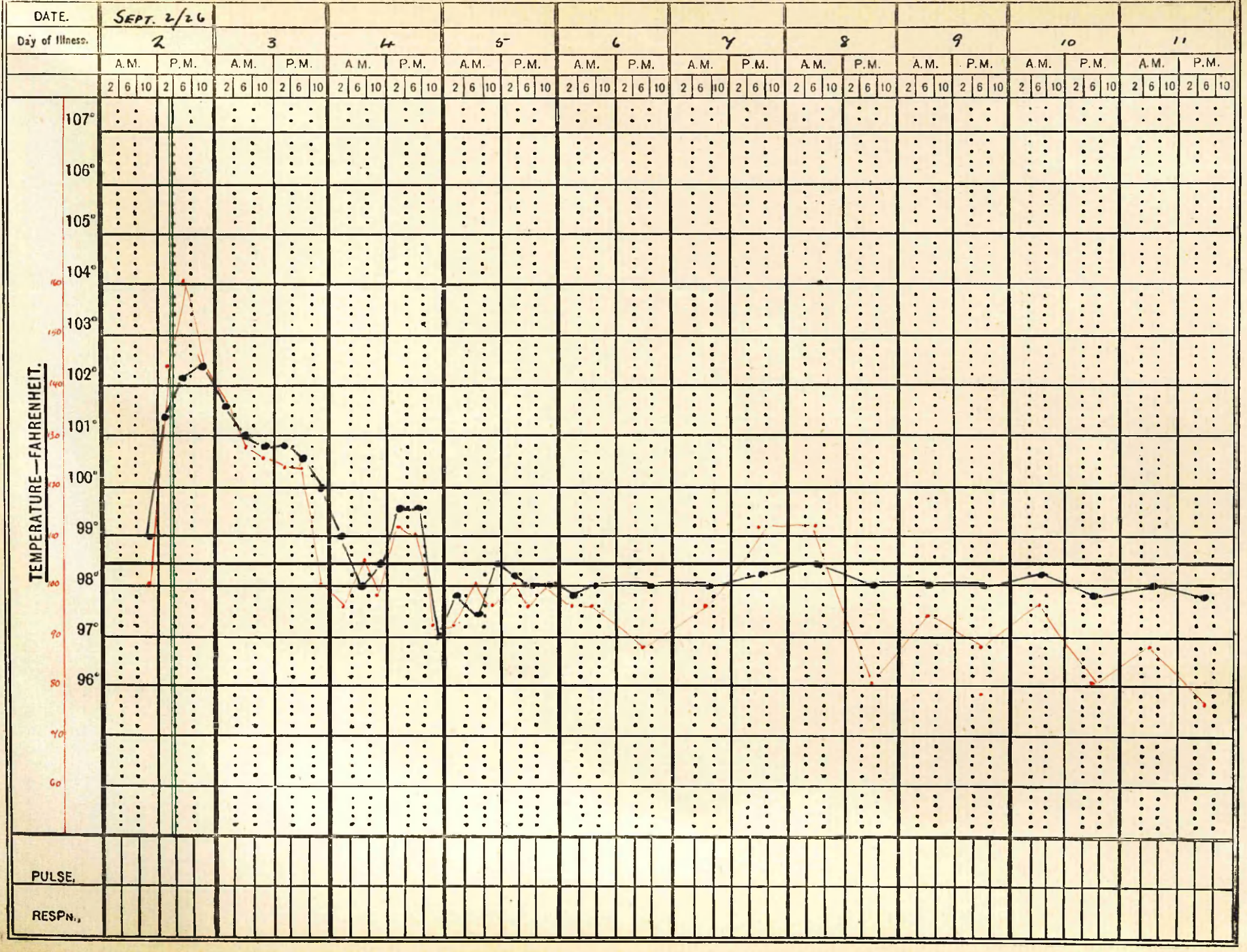

DATE.
Day of Illness.
45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64
A.M. P.M.
2 6 10
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
FEB. 27/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.

39


DATE.
MARCH 22/26
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.,

40


DATE.
SEPT. 2/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

DATE.	SEPT. 1/26																					
Day of Illness.	2		3		4		5		6		7		8		9		10		11			
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.		
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10		

TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

160 150 140 130 120 110 100 90 80 70 60

PULSE.

RESPN.,

DATE.	SEPT. 9/26																			
Day of Illness.	1		2		3		4		5		6		7		8		9		10	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

PULSE.

RESPN.,

DATE. Oct. 30/26

Day of Illness. 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14

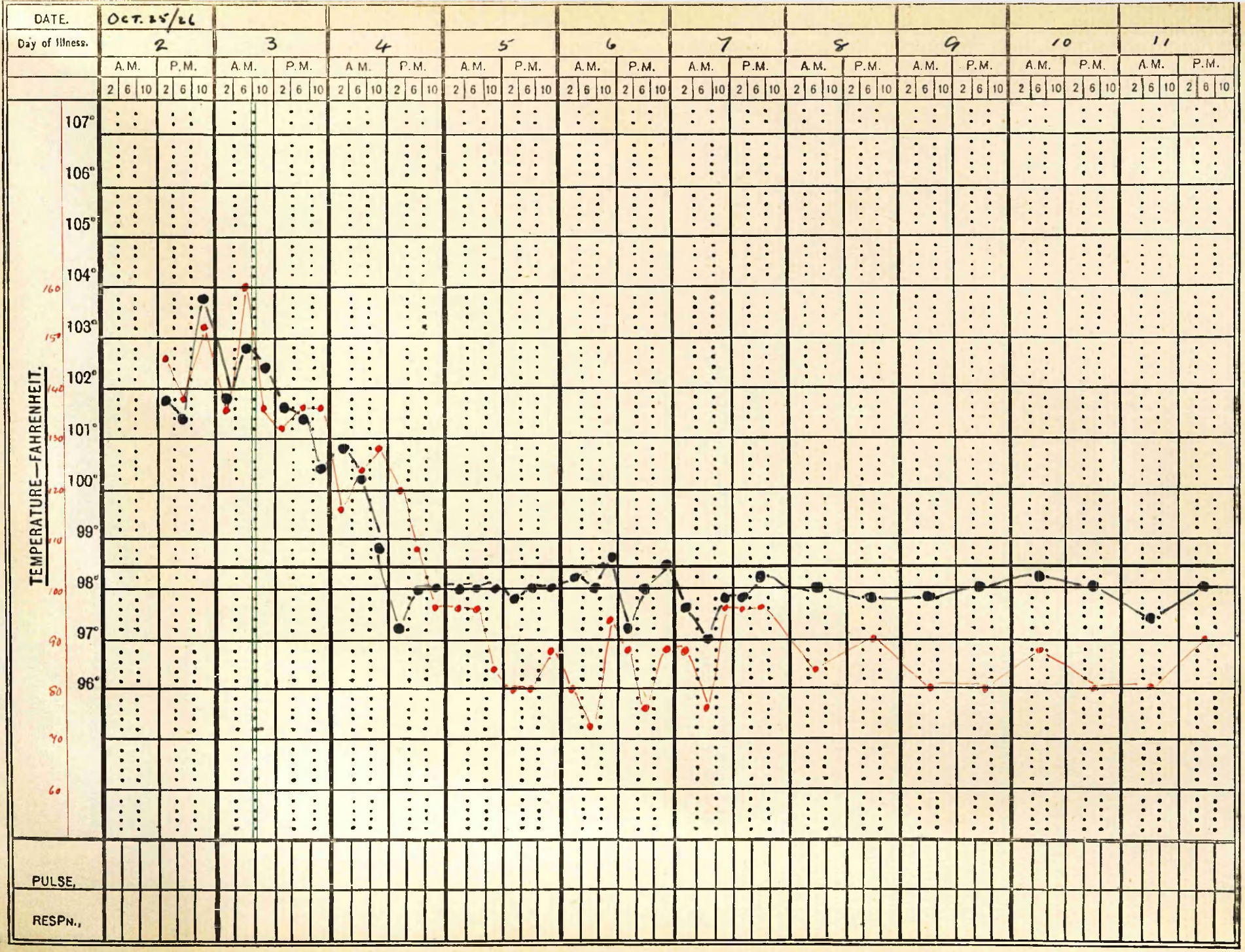
A.M. | P.M. — 2 | 6 | 10

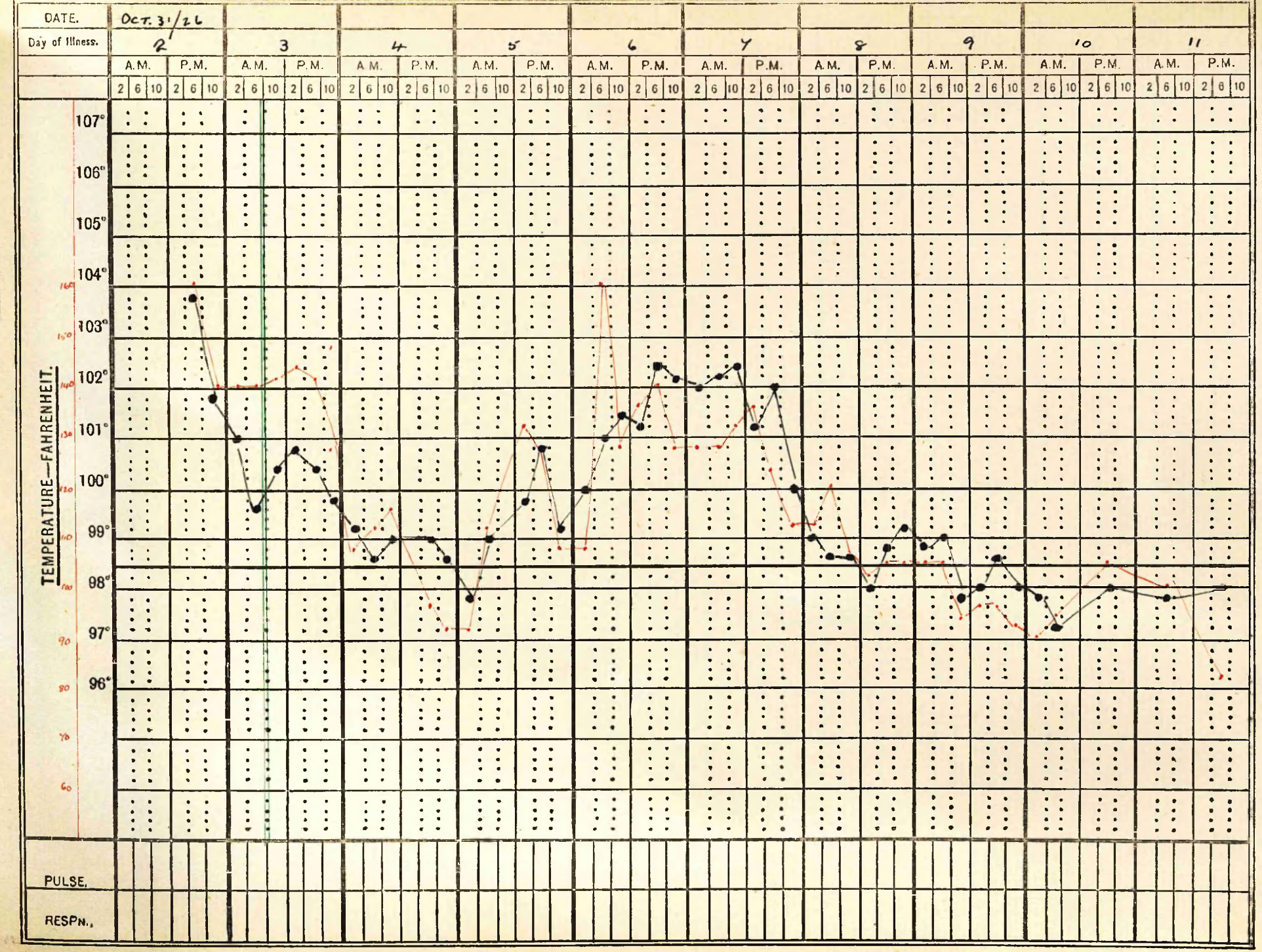
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

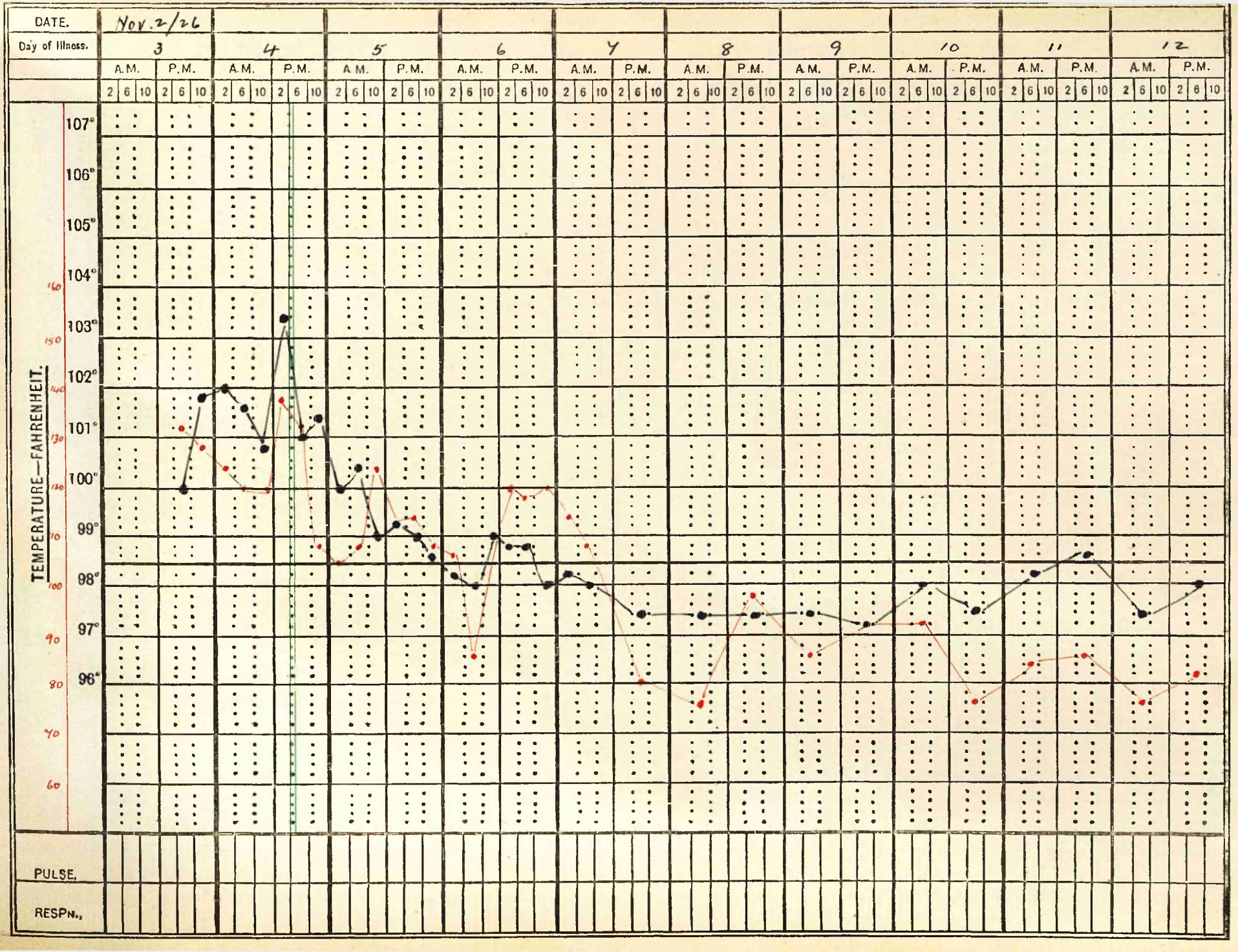
PULSE.

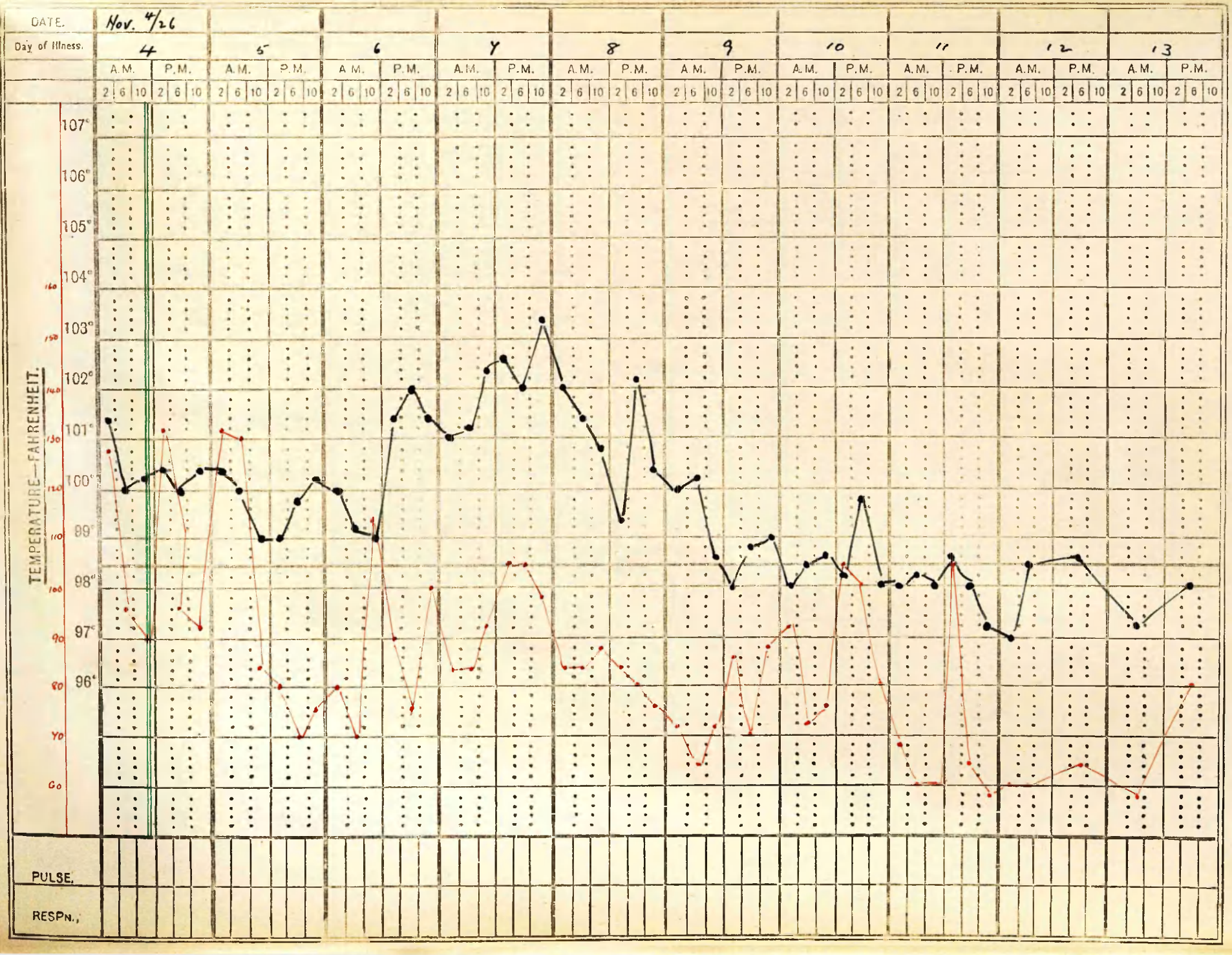
RESPN.


DATE.
Oct. 25/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE,
RESPN.,

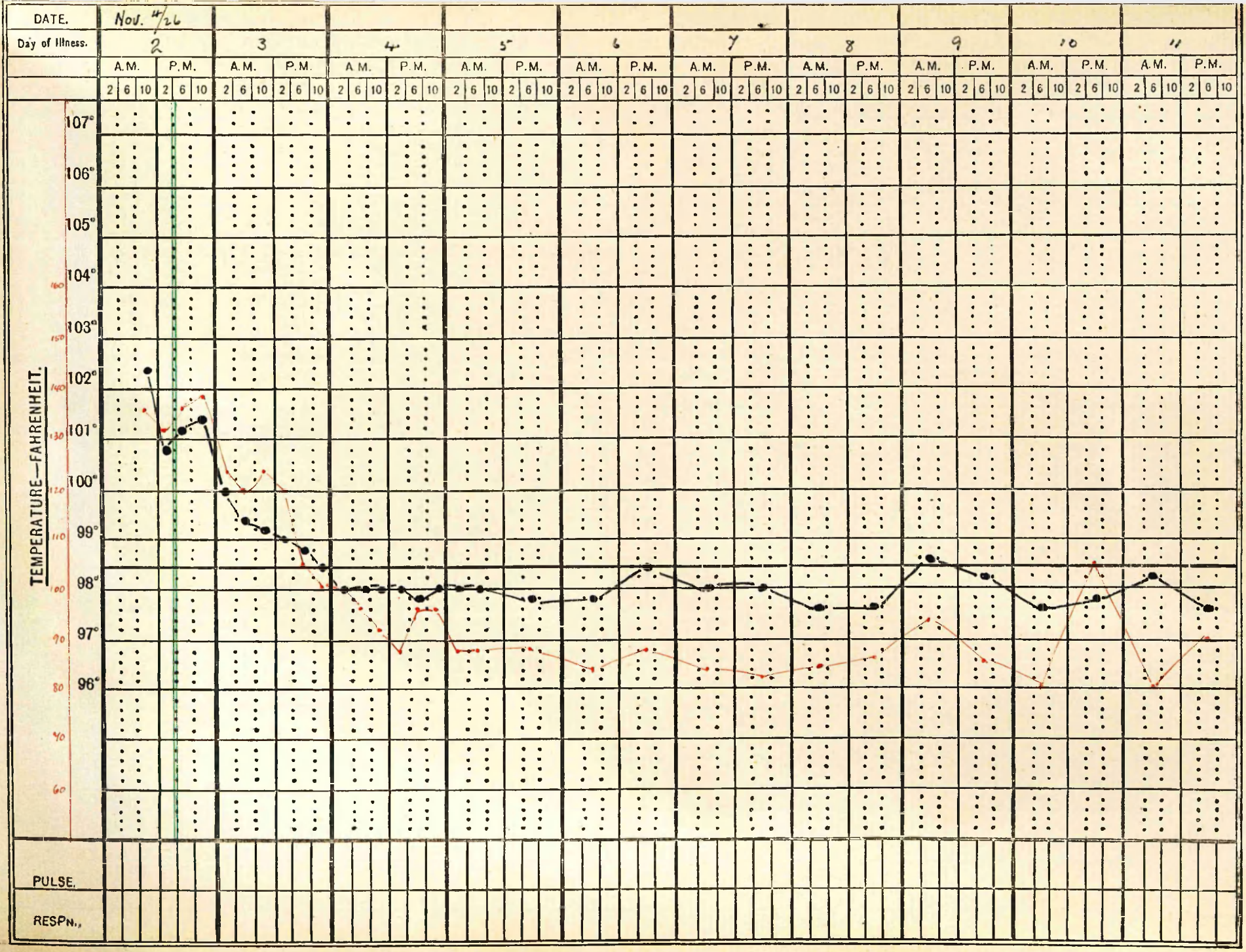

DATE.
Oct. 31/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.

46

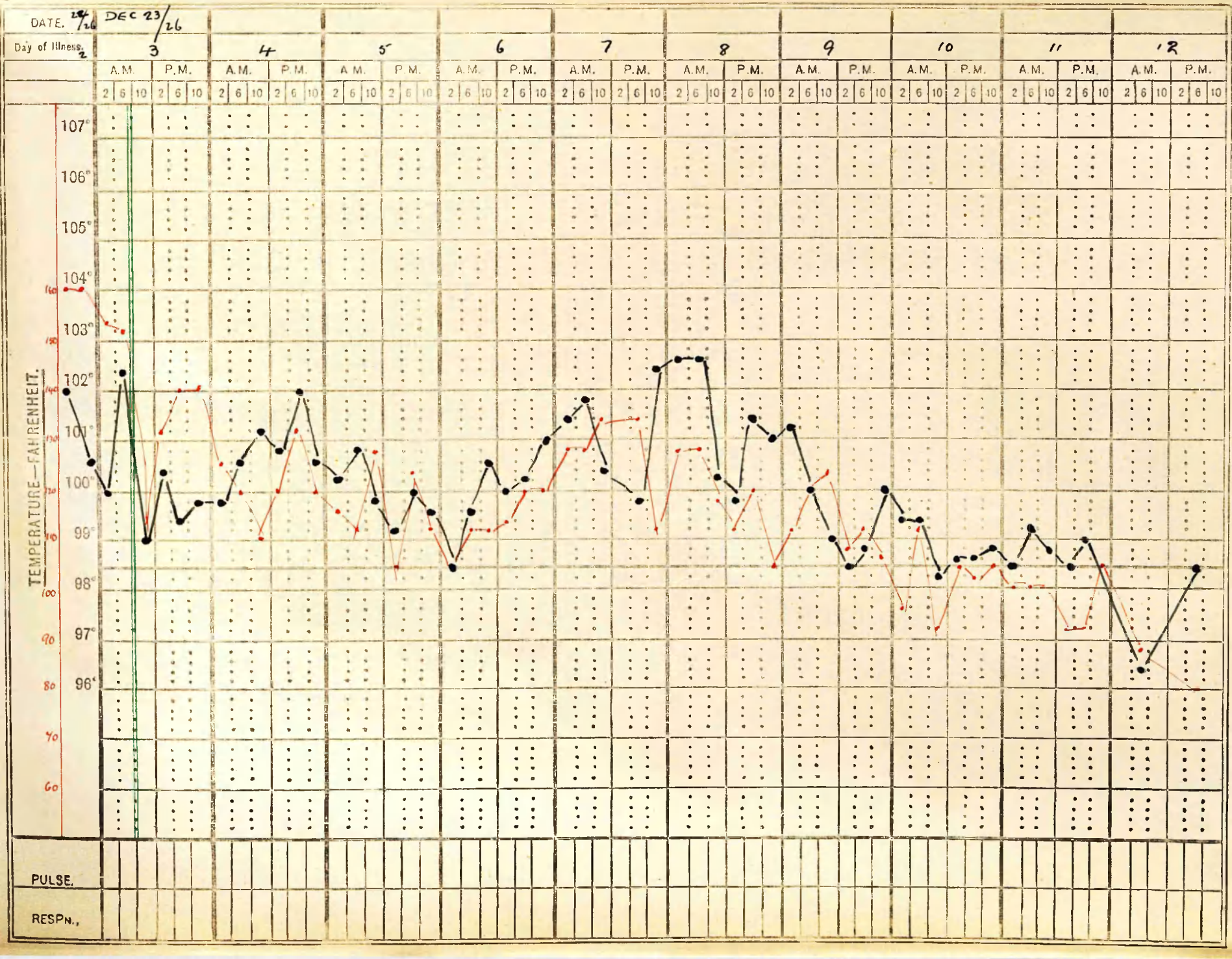

DATE.
Nov. 2/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.,


DATE.
Nov. 4/26
Day of Illness.
4
5
6
7
8
9
10
11
12
13
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.

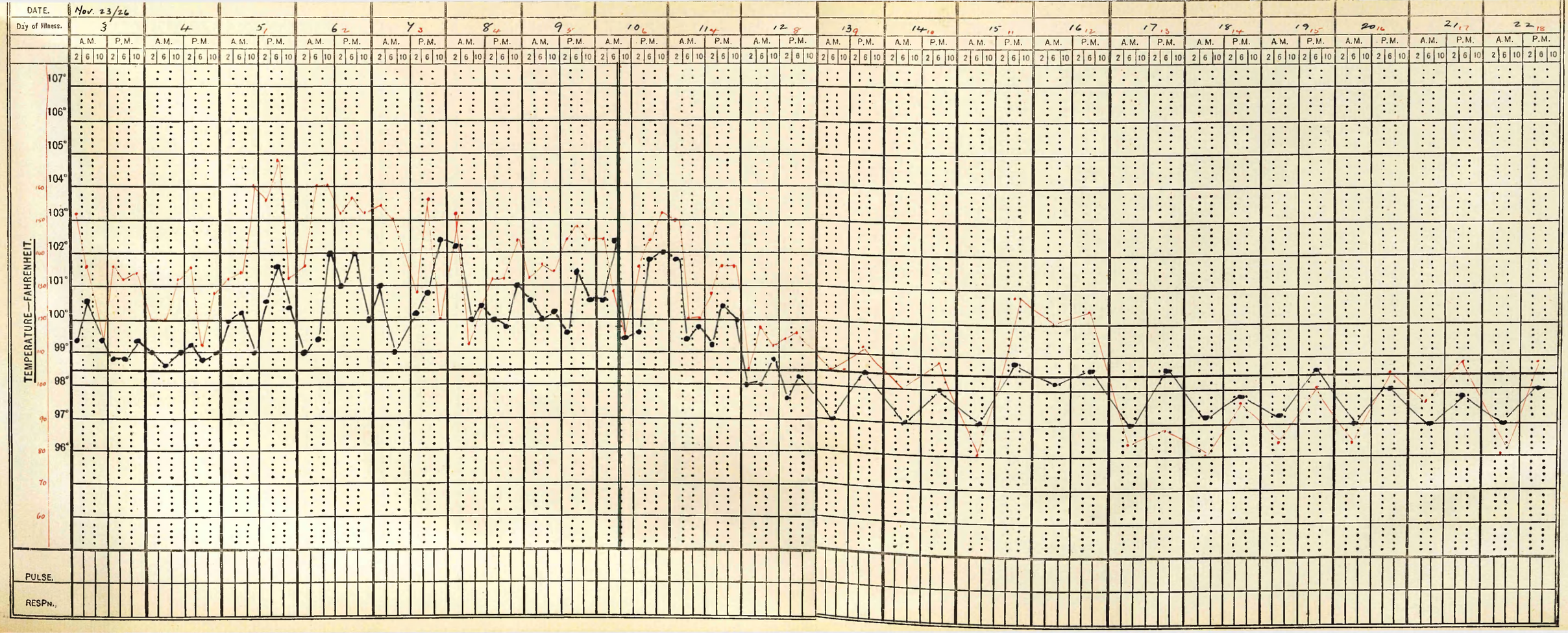
48


DATE.
Nov. 4/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

49


DATE. 12/26 DEC 23/26
Day of Illness. 2
3 4 5 6 7 8 9 10 11 12
A.M. P.M.
2 6 10
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
TEMPERATURE—FAHRENHEIT.
160 150 140 130 120 110 100 90 80 70 60
PULSE.
RESPN.,

50


DATE.
Nov. 23/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
PULSE.
RESPN.

DATE.	Dec. 17/26																							
Day of Illness.	2				3				4				5				6				7			
	A.M.			P.M.			A.M.			P.M.			A.M.			P.M.			A.M.			P.M.		
	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10

Day of Illness.	8				9				10				11											
	A.M.			P.M.			A.M.			P.M.			A.M.			P.M.								
	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10						

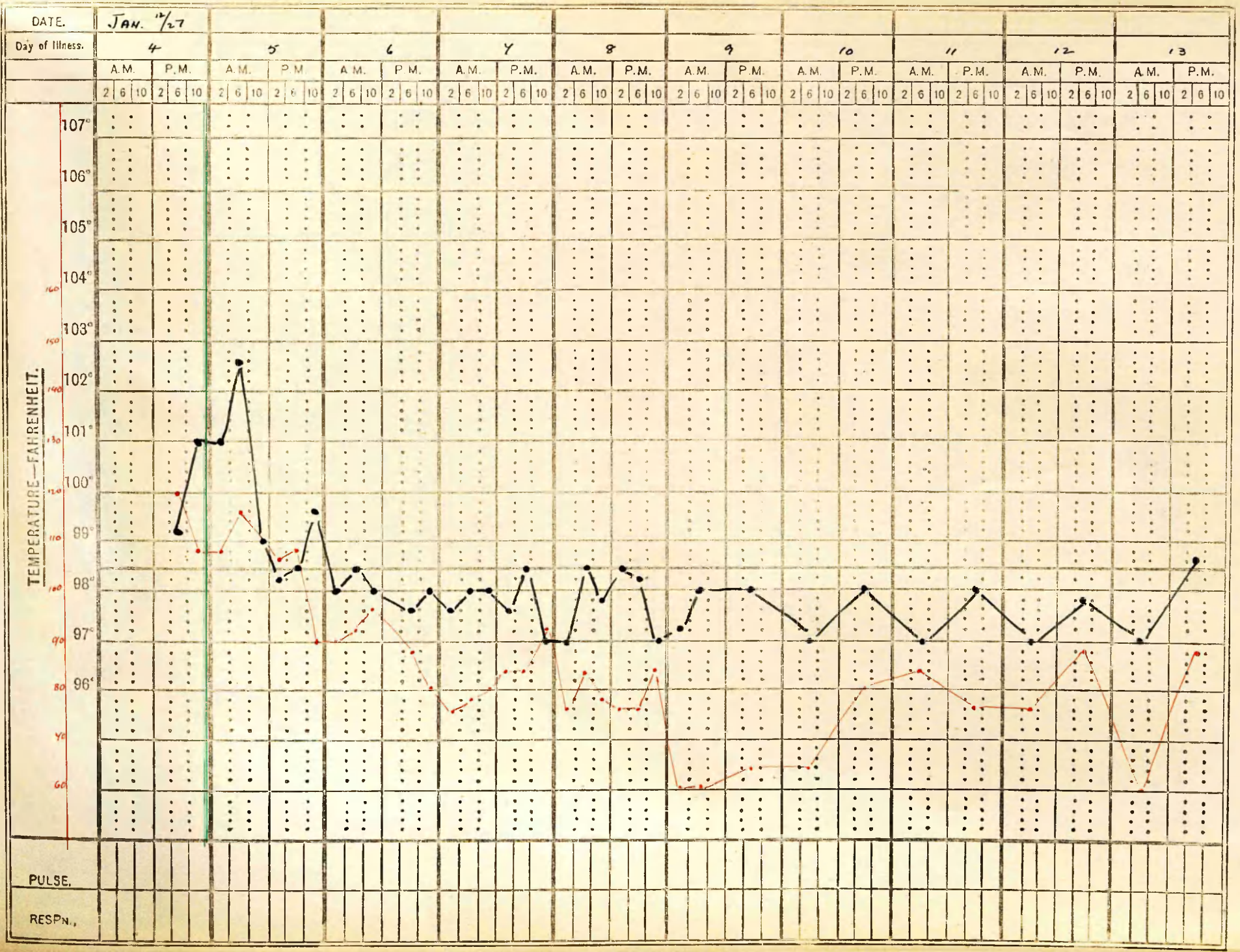
TEMPERATURE—FAHRENHEIT.

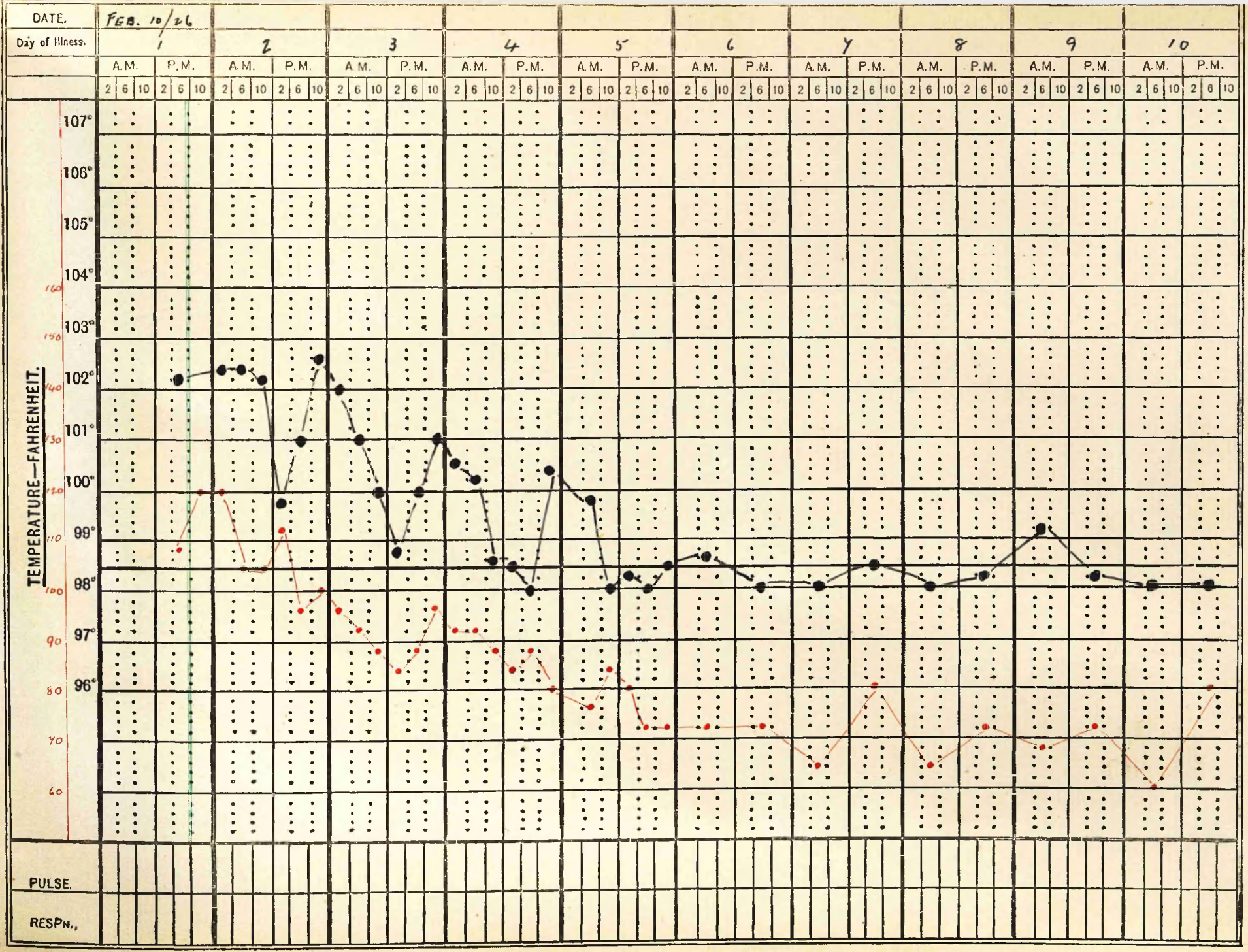
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

160 150 140 130 120 110 100 90 80 70 60

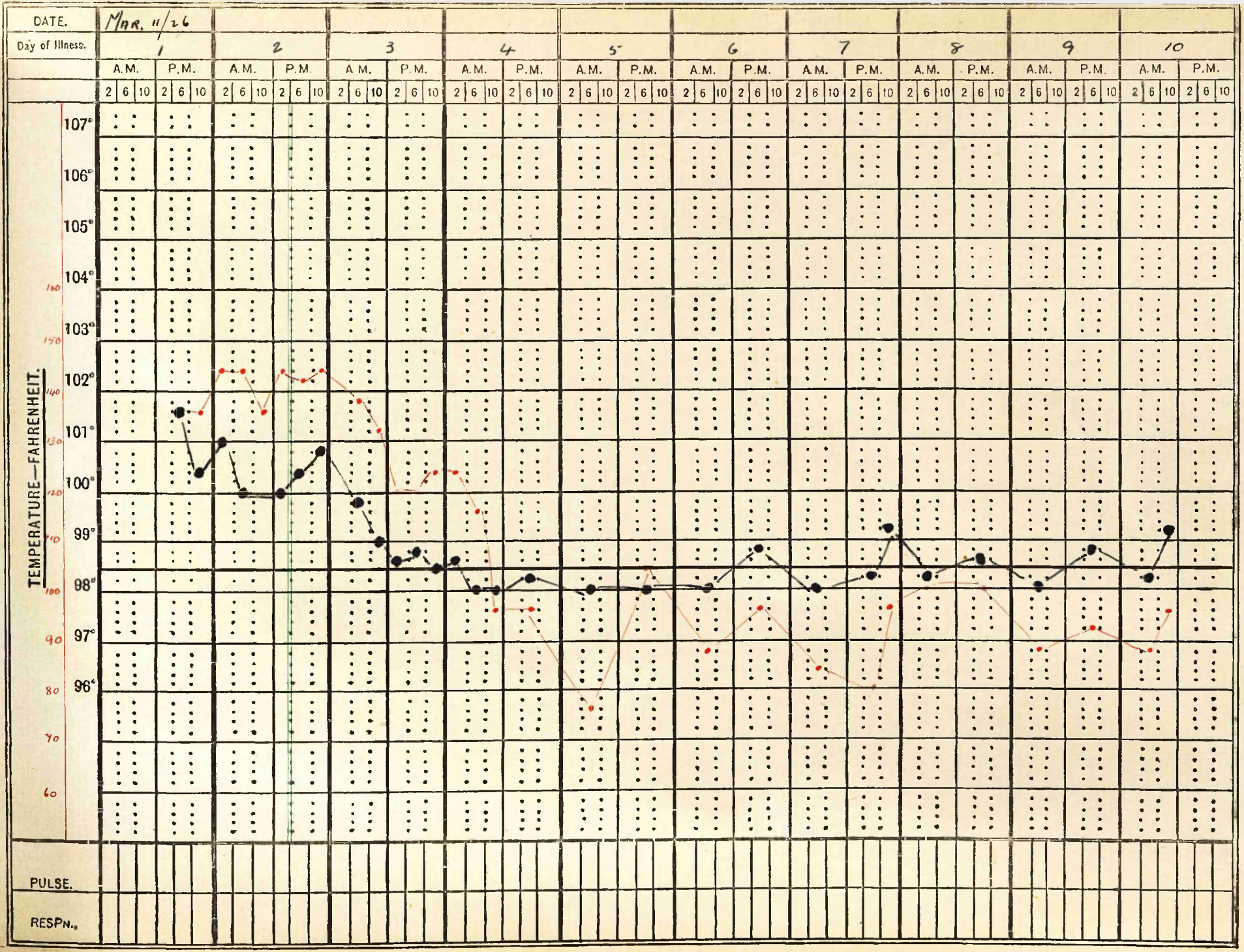
PULSE.

RESPN.,

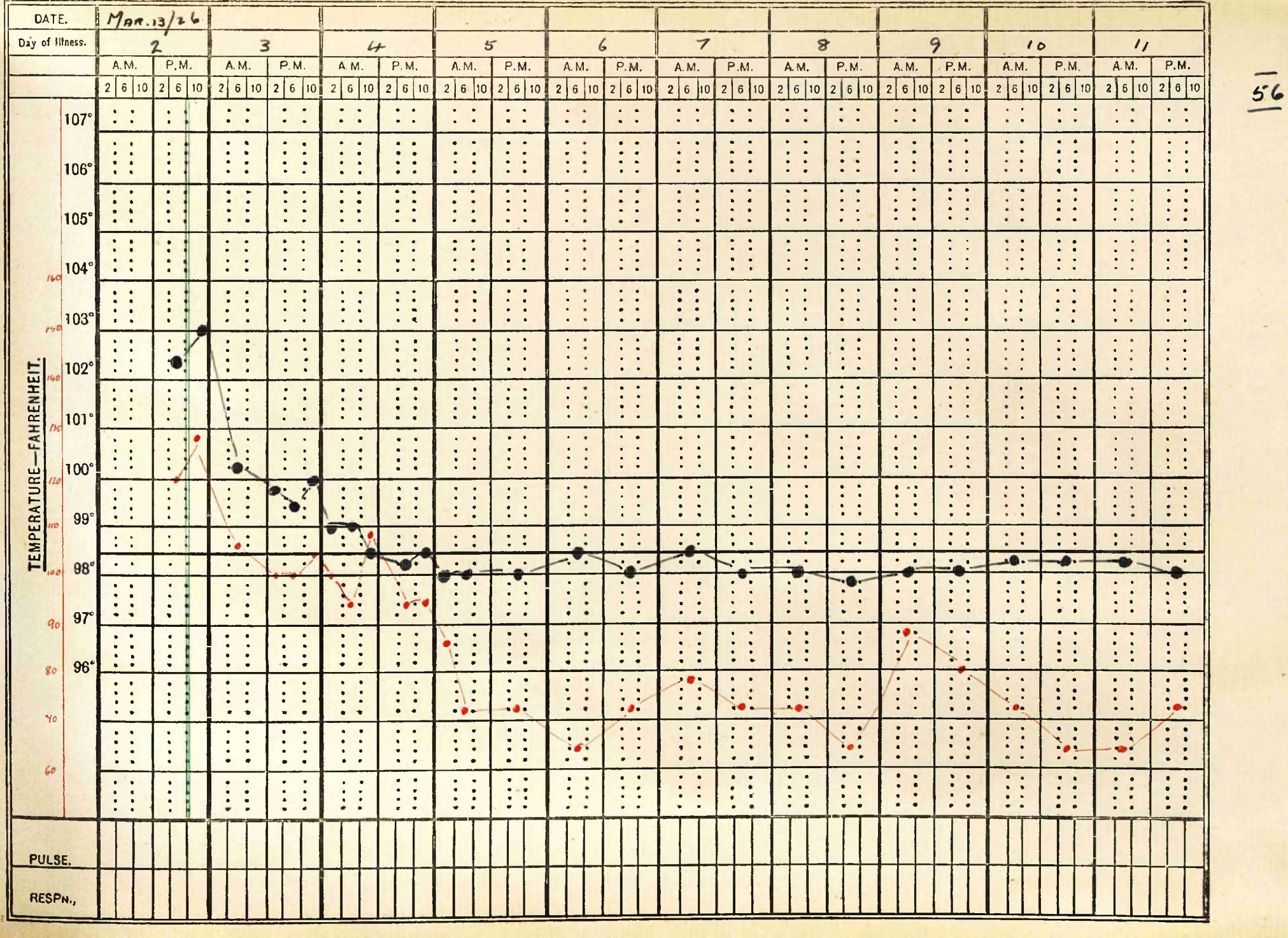

DATE.
JAN. 12/27
Day of Illness.
4
5
6
7
8
9
10
11
12
13
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
FEB. 10/26
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

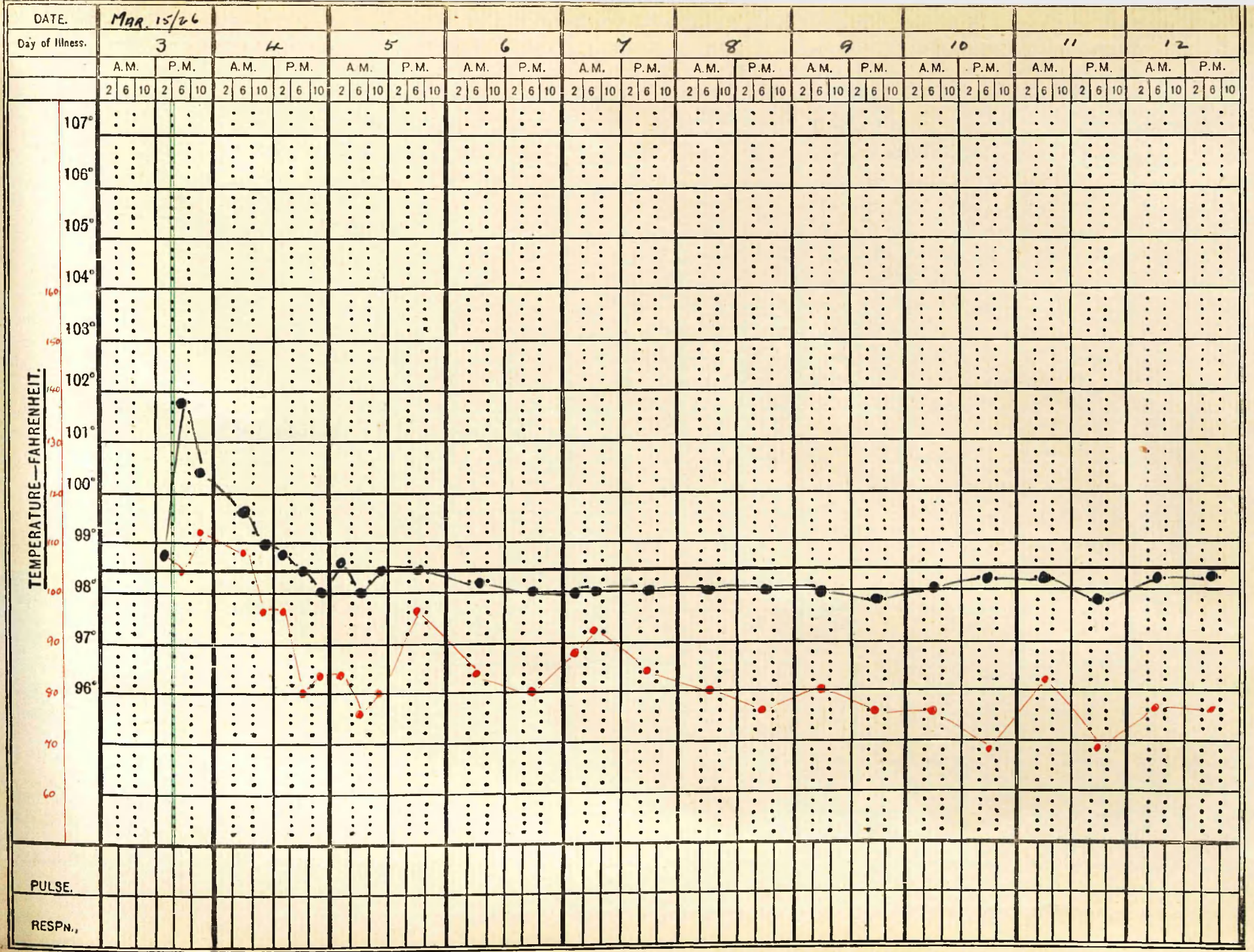
54


DATE.
Mar. 11/26
Day of Illness.
1 2 3 4 5 6 7 8 9 10
A.M. P.M.
2 6 10
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
TEMPERATURE—FAHRENHEIT.
160 150 140 130 120 110 100 90 80 70 60
PULSE.
RESPN.

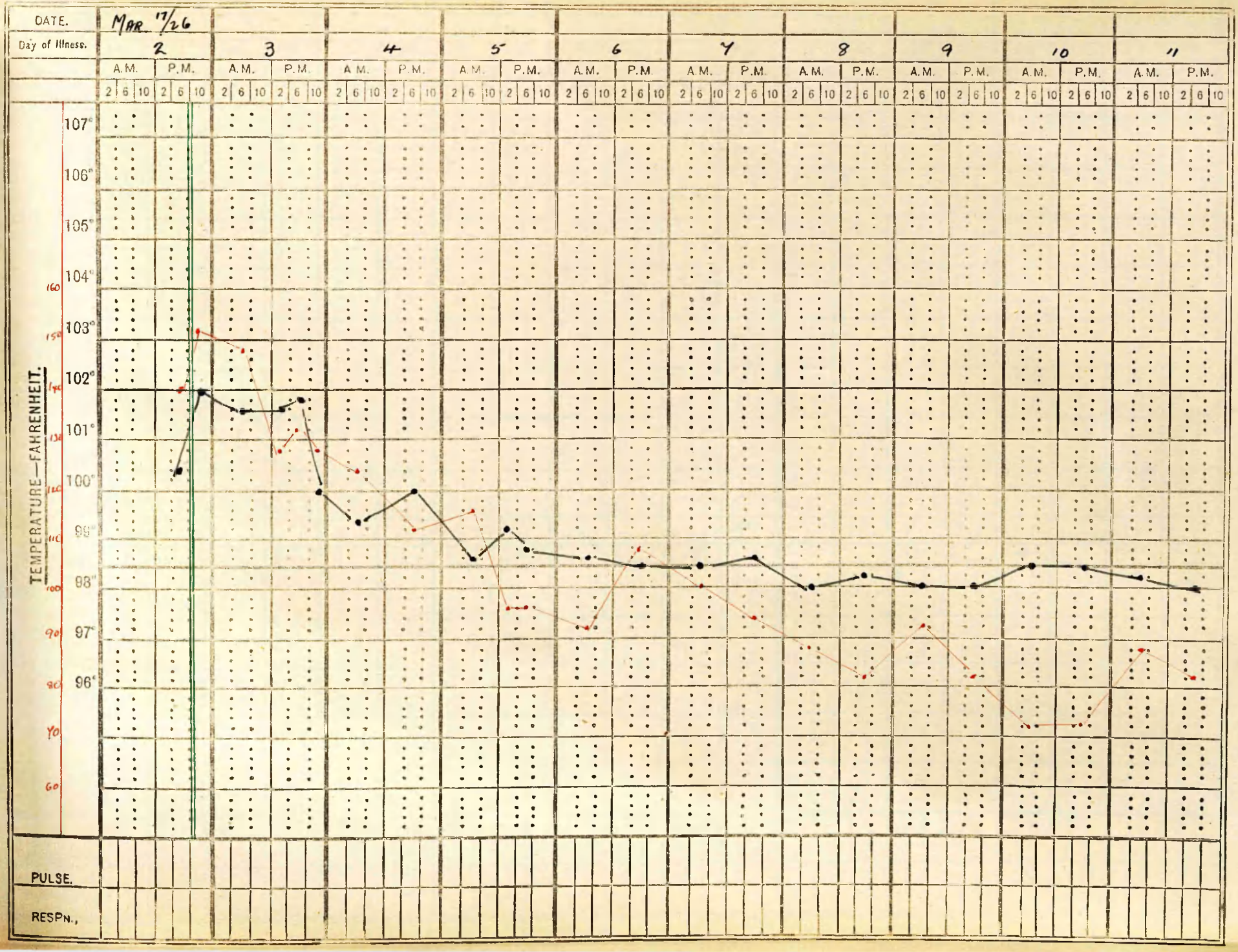
5 5


DATE.
Mar. 13/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

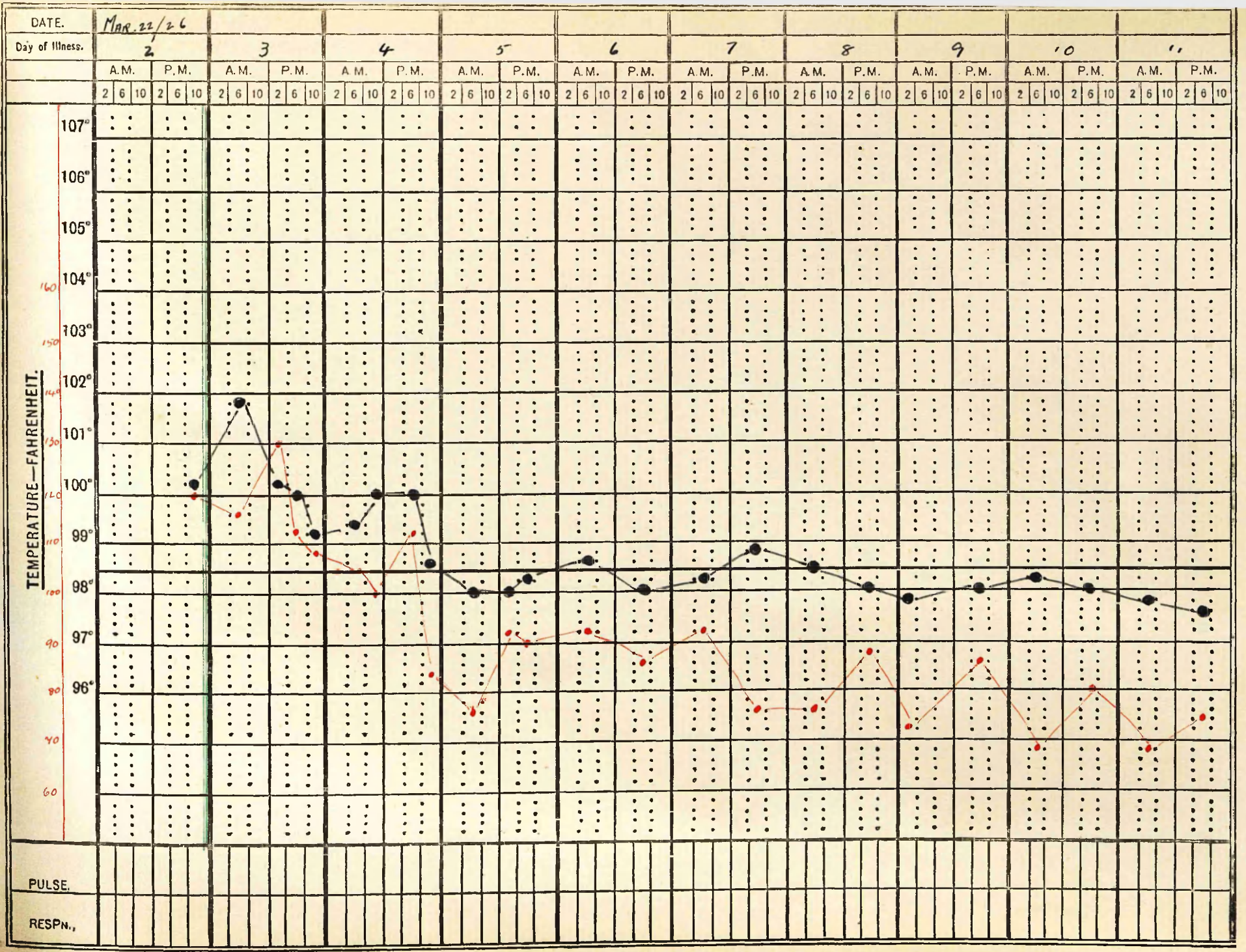
56


DATE.
Mar. 15/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

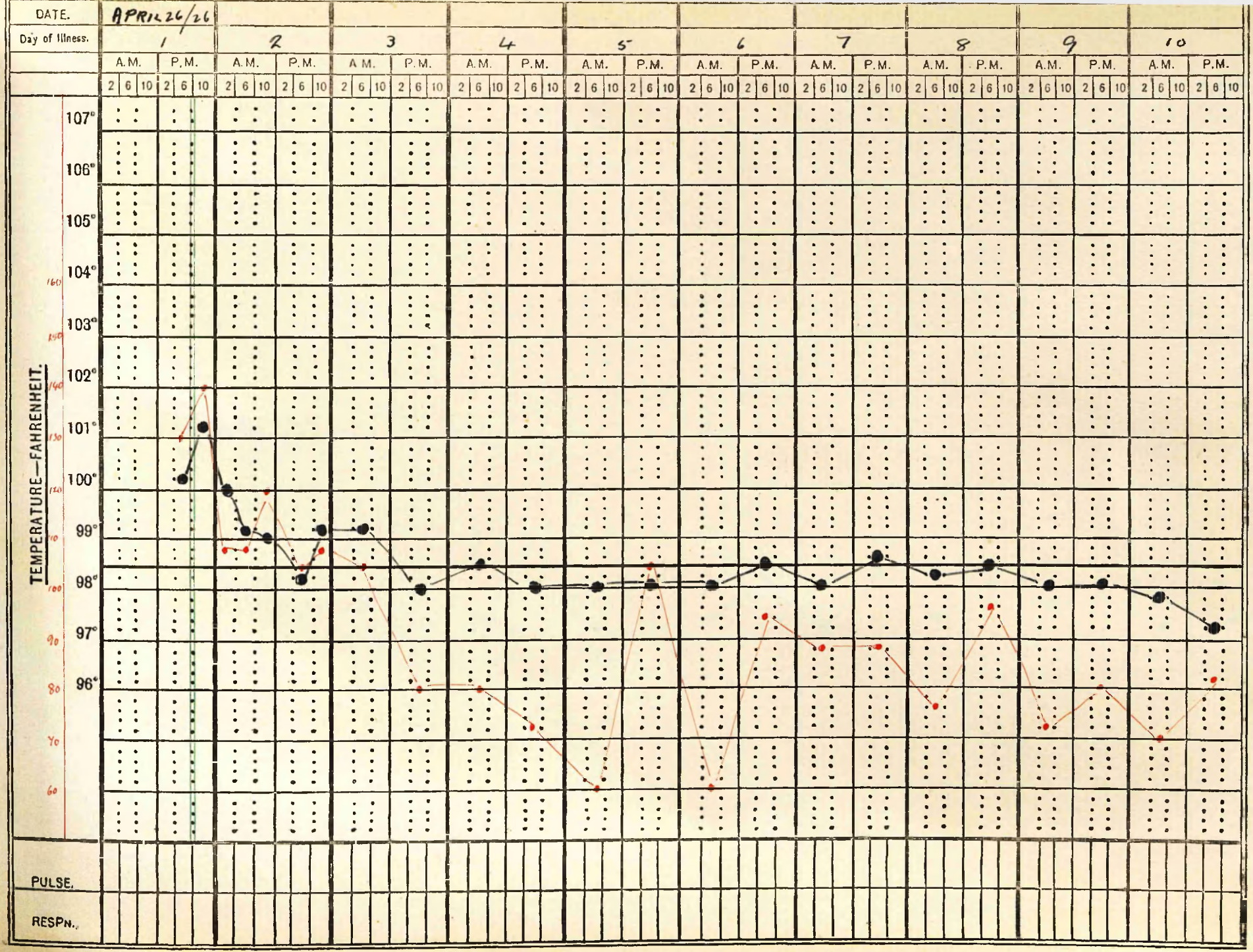
54

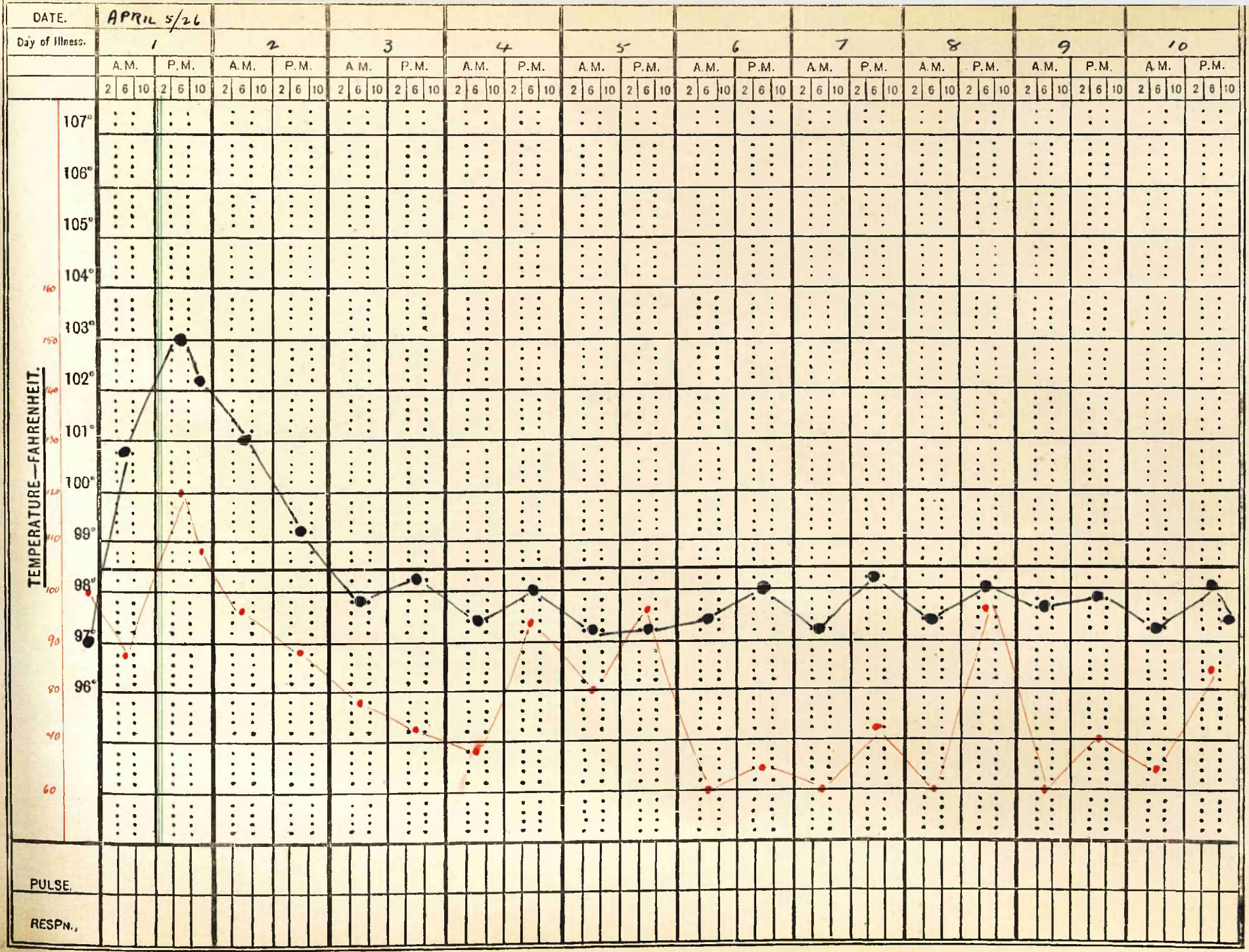

DATE.
Mar 17/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

58


DATE.
Mar. 22/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.,

59


DATE.
APRIL 26/26
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.


DATE.
APRIL 5/26
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
40
60
PULSE.
RESPN.,

DATE. APRIL 10/26

Day of Illness. 1 2 3 4 5 6 7 8 9

A.M. P.M. (2 6 10 for each)

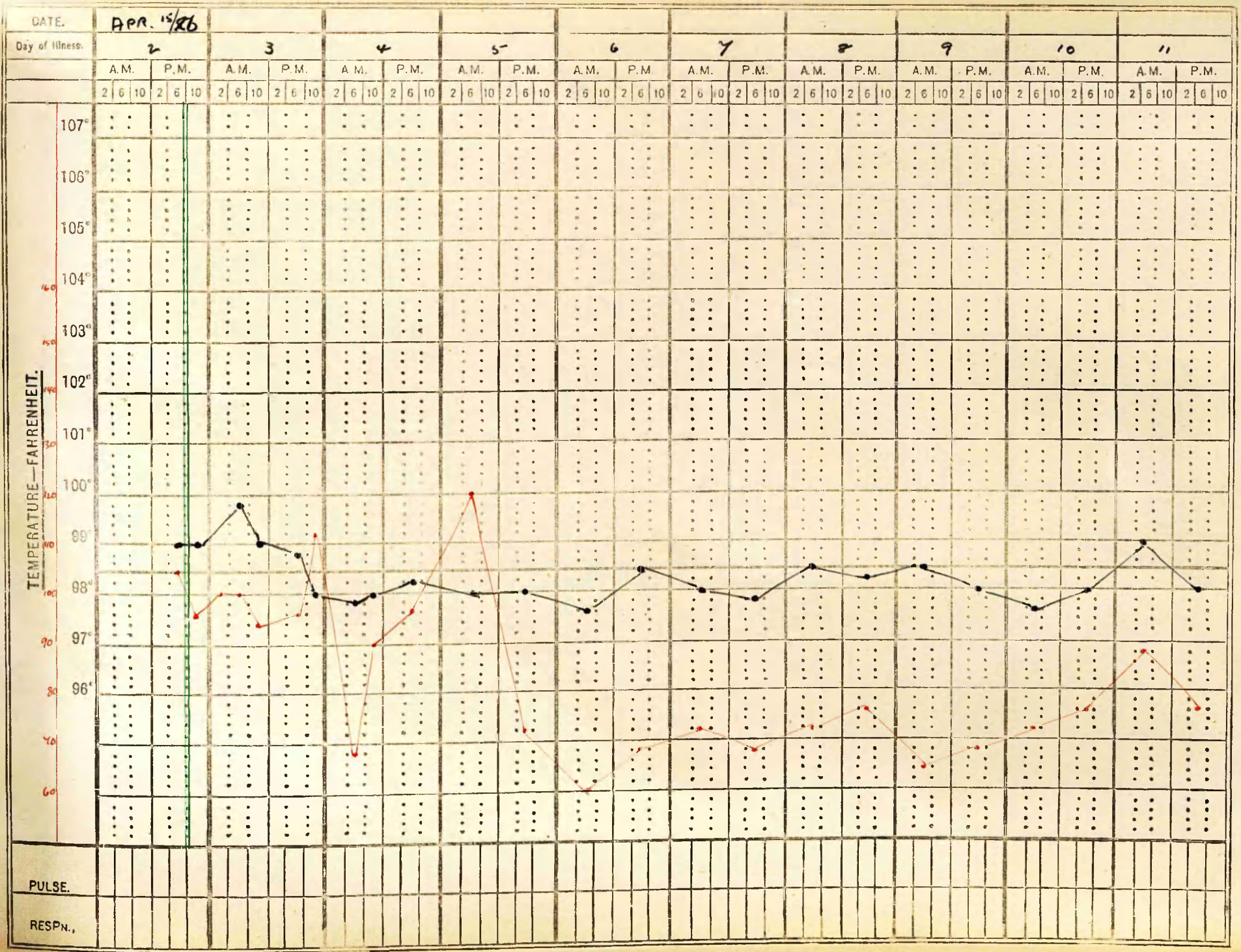
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

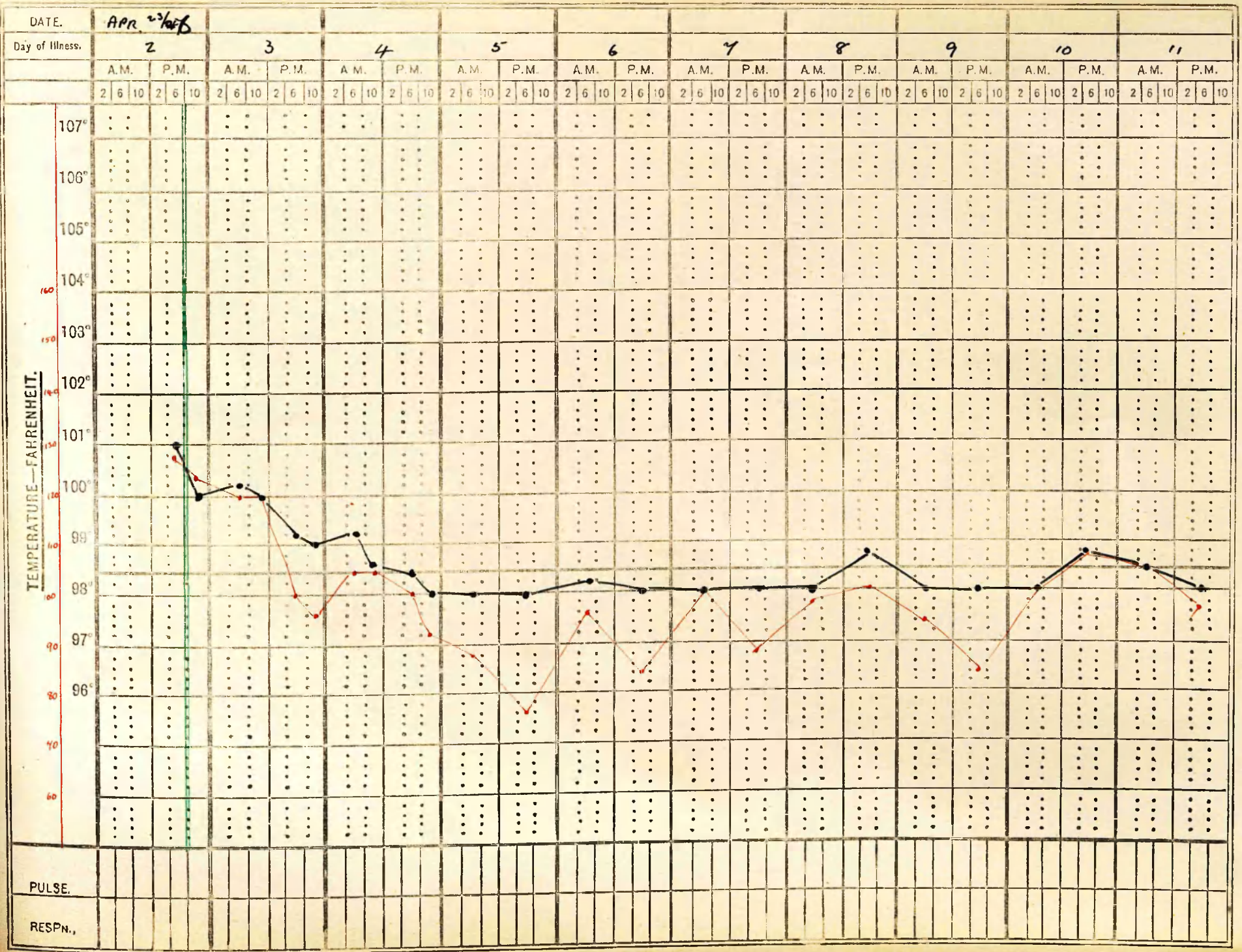
160 150 140 130 120 110 100 90 80 70 60

PULSE.

RESPN.,


DATE.
APR. 15/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

63


DATE.
Apr. 23/16
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

64

DATE. May 25/26

Day of Illness.	2		3		4		5		6		7		8		9		10		11	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

107°	160	
106°		
105°		
104°	150	
103°		
102°	140	
101°	130	
100°	120	
99°	110	
98°	100	
97°	90	
96°	80	
	70	
	60	

PULSE.

RESPN.,

DATE.	May 25/26																					
Day of Illness.	2		3		4		5		6		7		8		9		10		11			
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.		
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10		

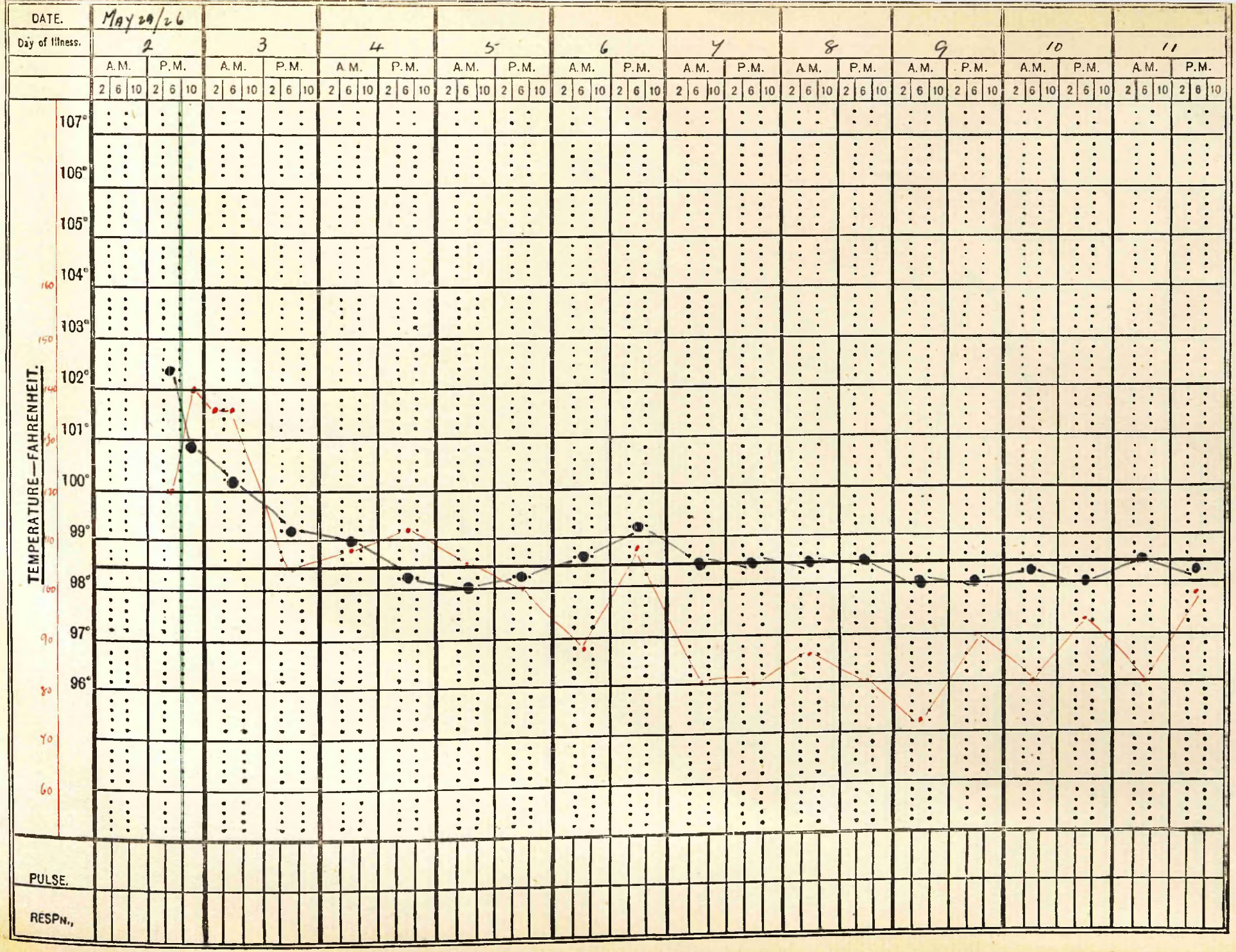
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

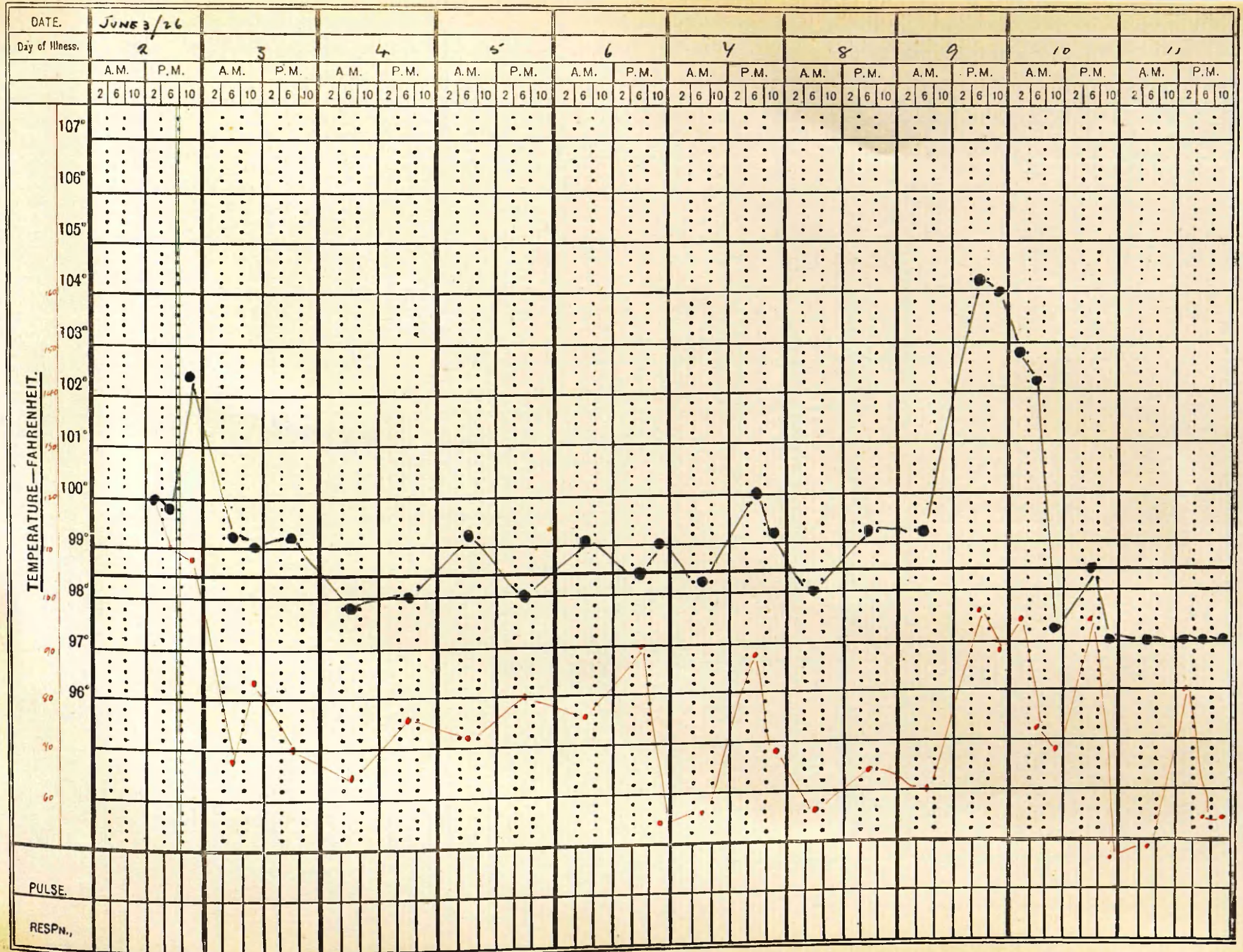
160 150 140 130 120 110 100 90 80 70 60

PULSE.

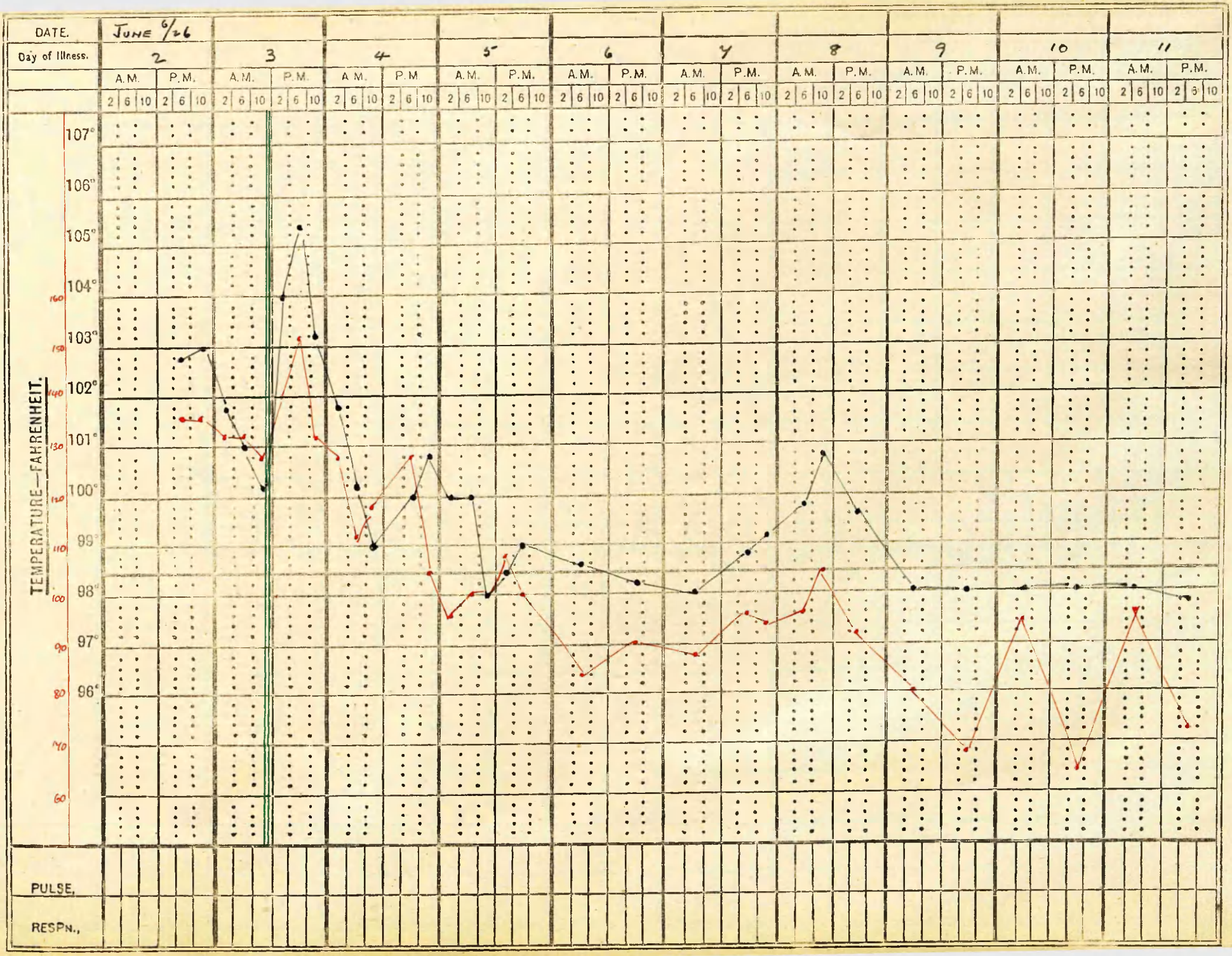
RESPN.,

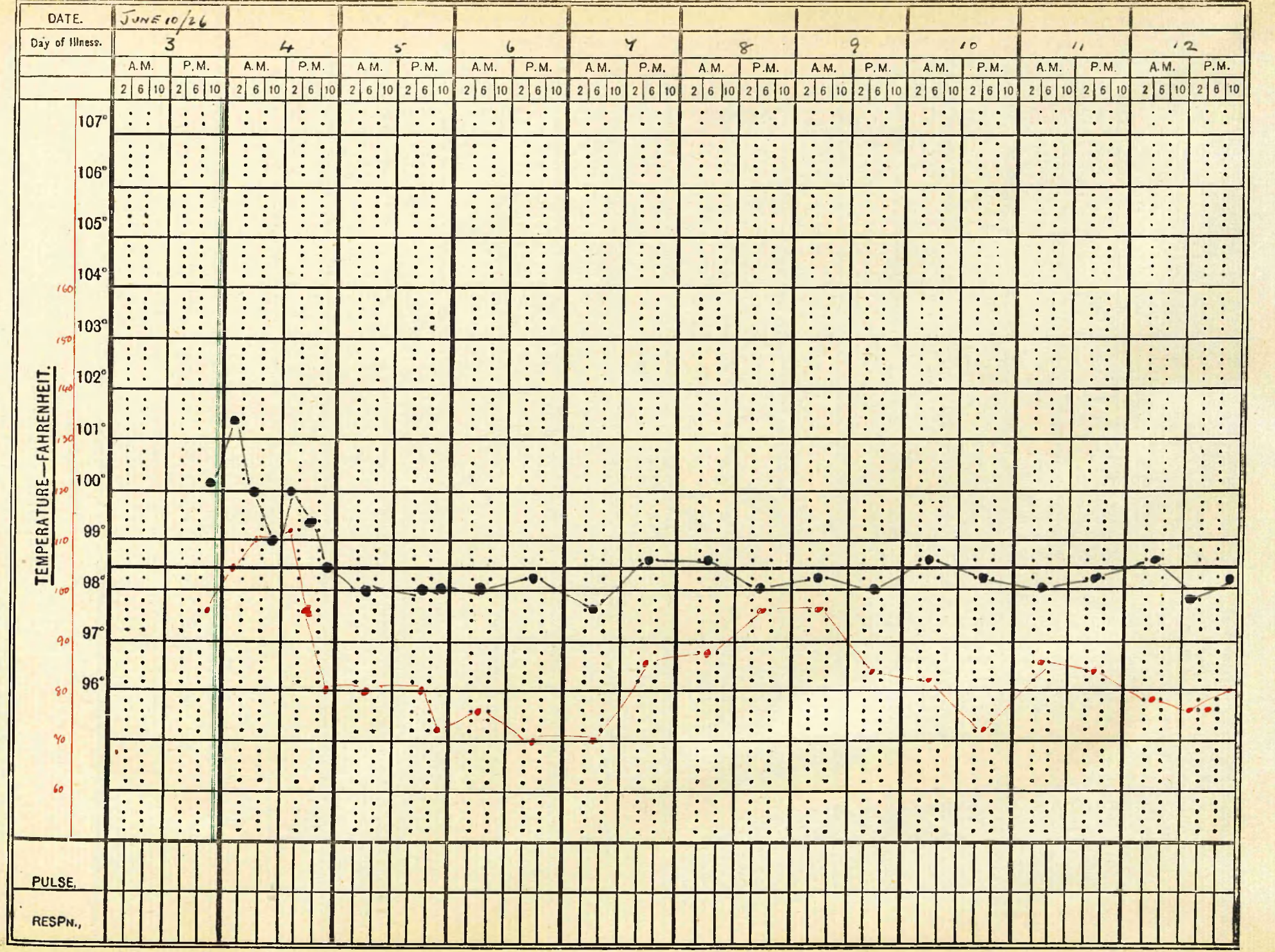

DATE.
May 29/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

64


DATE.
June 3/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

68


DATE.
June 6/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
JUNE 10/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

40

DATE.	June 14/26																					
Day of Illness.	2		3		4		5		6		7		8		9		10		11			
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.		
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10		

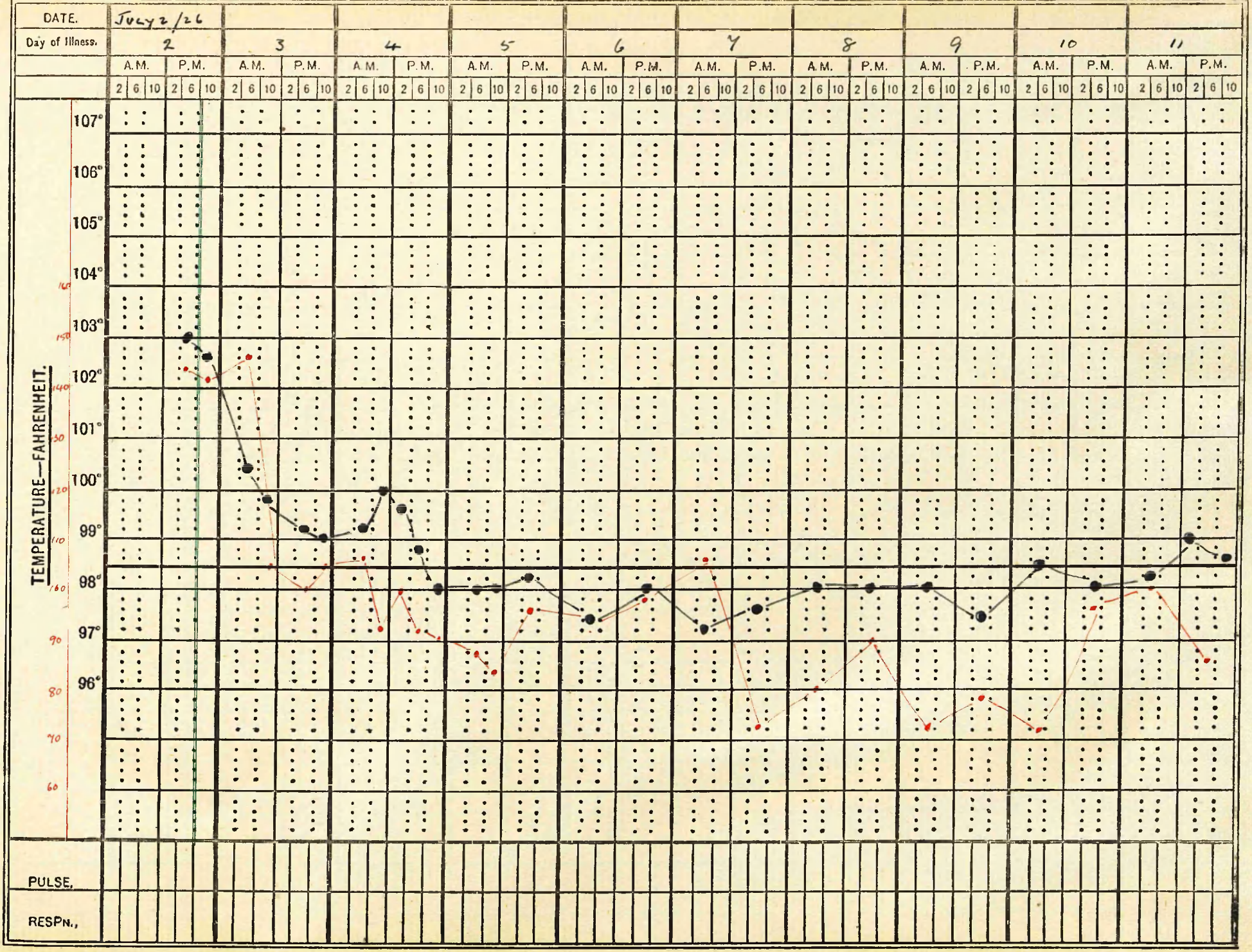
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

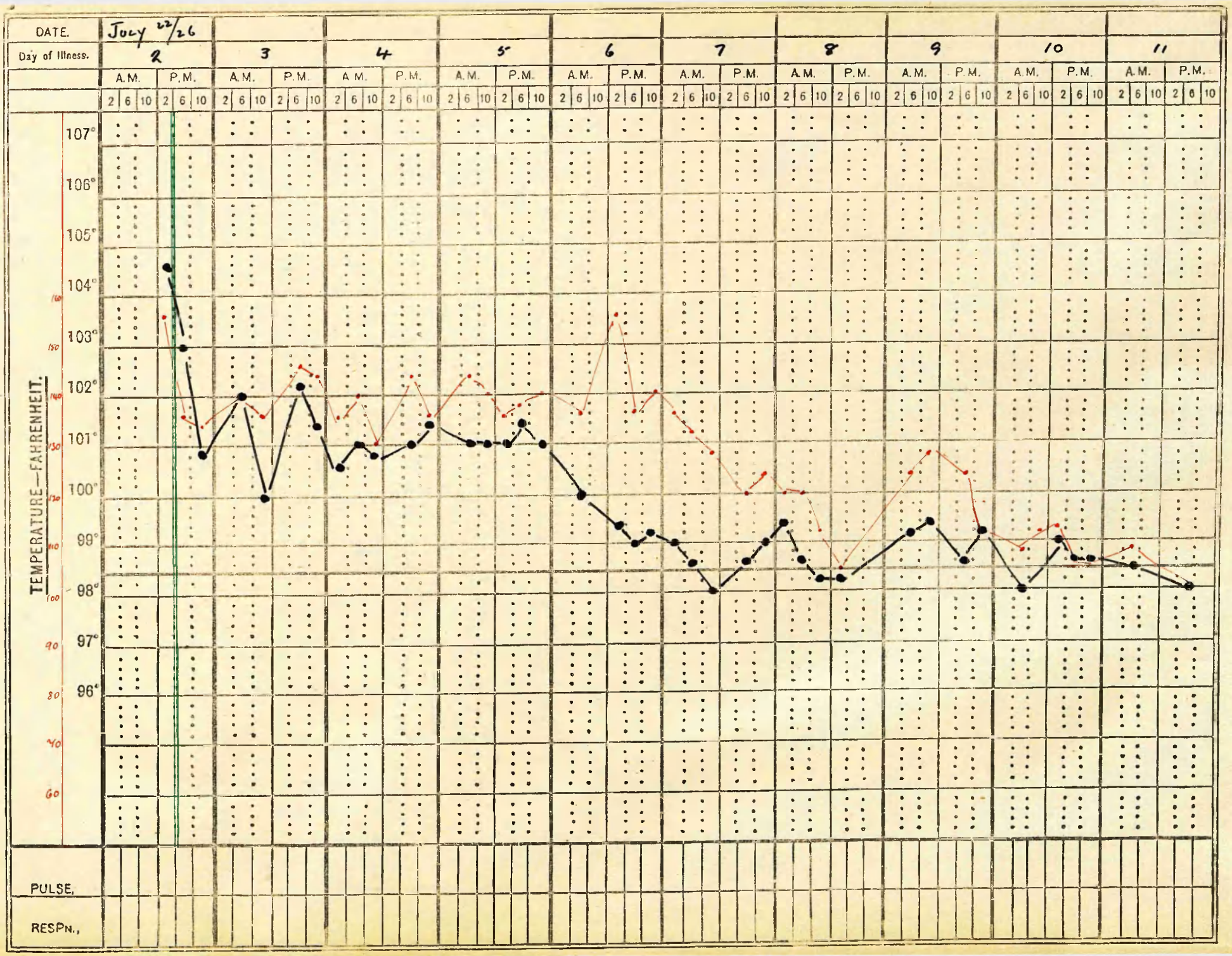
160 150 140 130 120 110 100 90 80 70 60

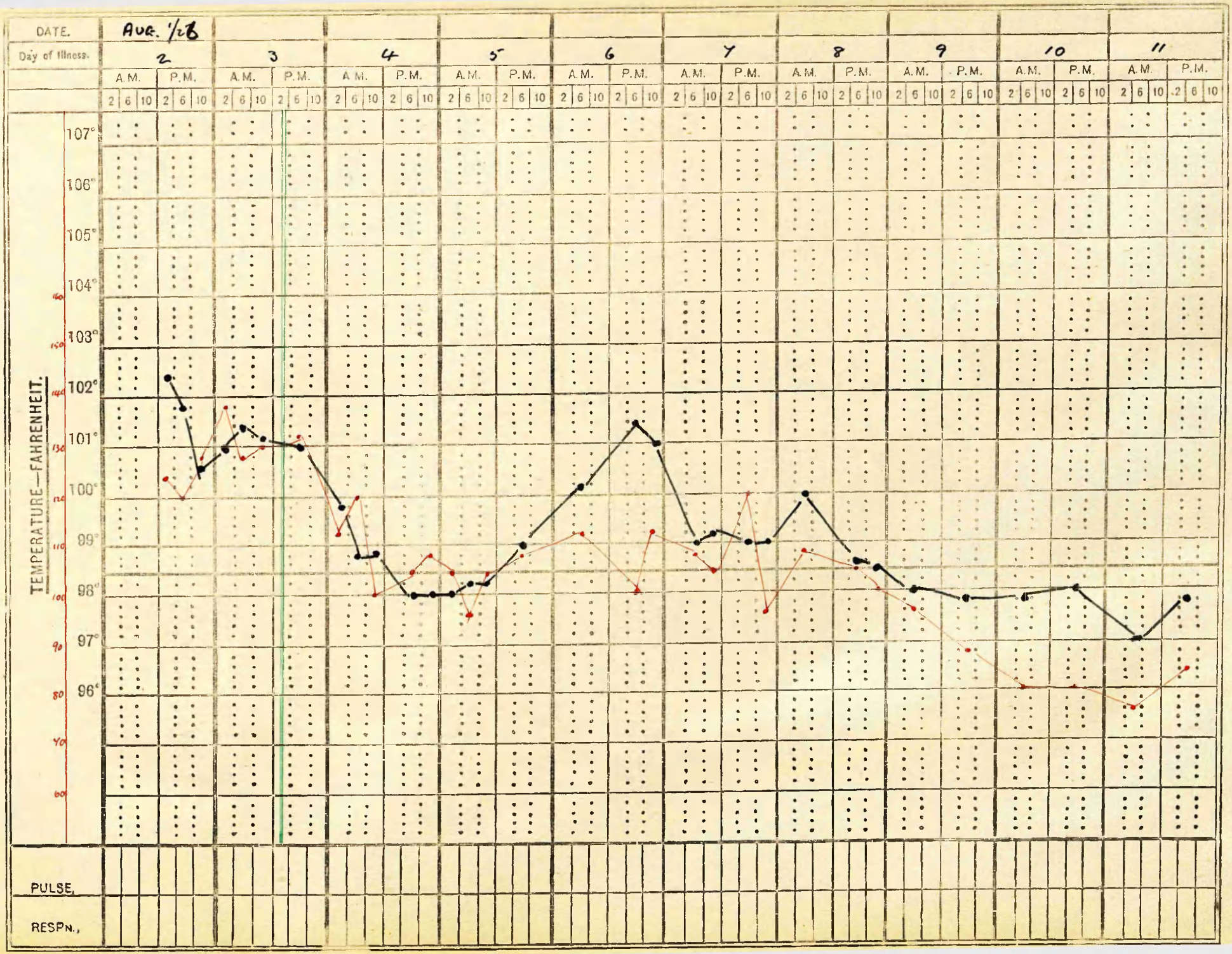
PULSE.

RESPN.


DATE.
July 2/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

72


DATE.
July 22/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
Aug. 1/28
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

14

DATE. SEPT. 6/26

Day of Illness. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

A.M. P.M. — 2 6 10 2 6 10

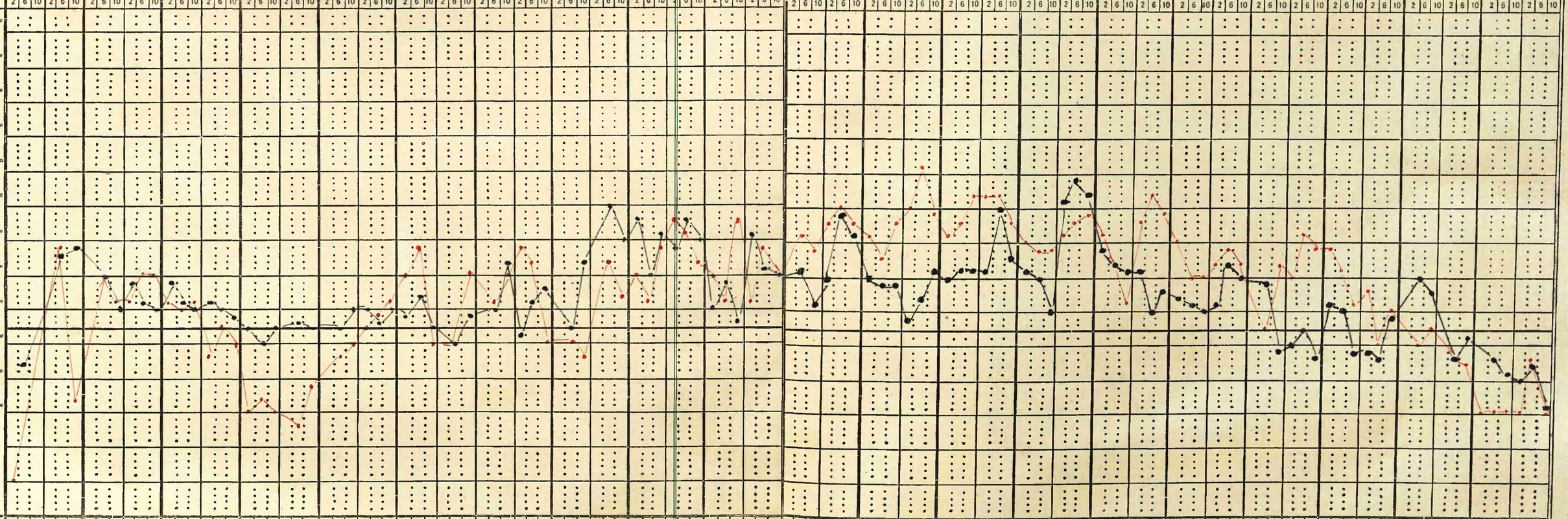
TEMPERATURE—FAHRENHEIT.

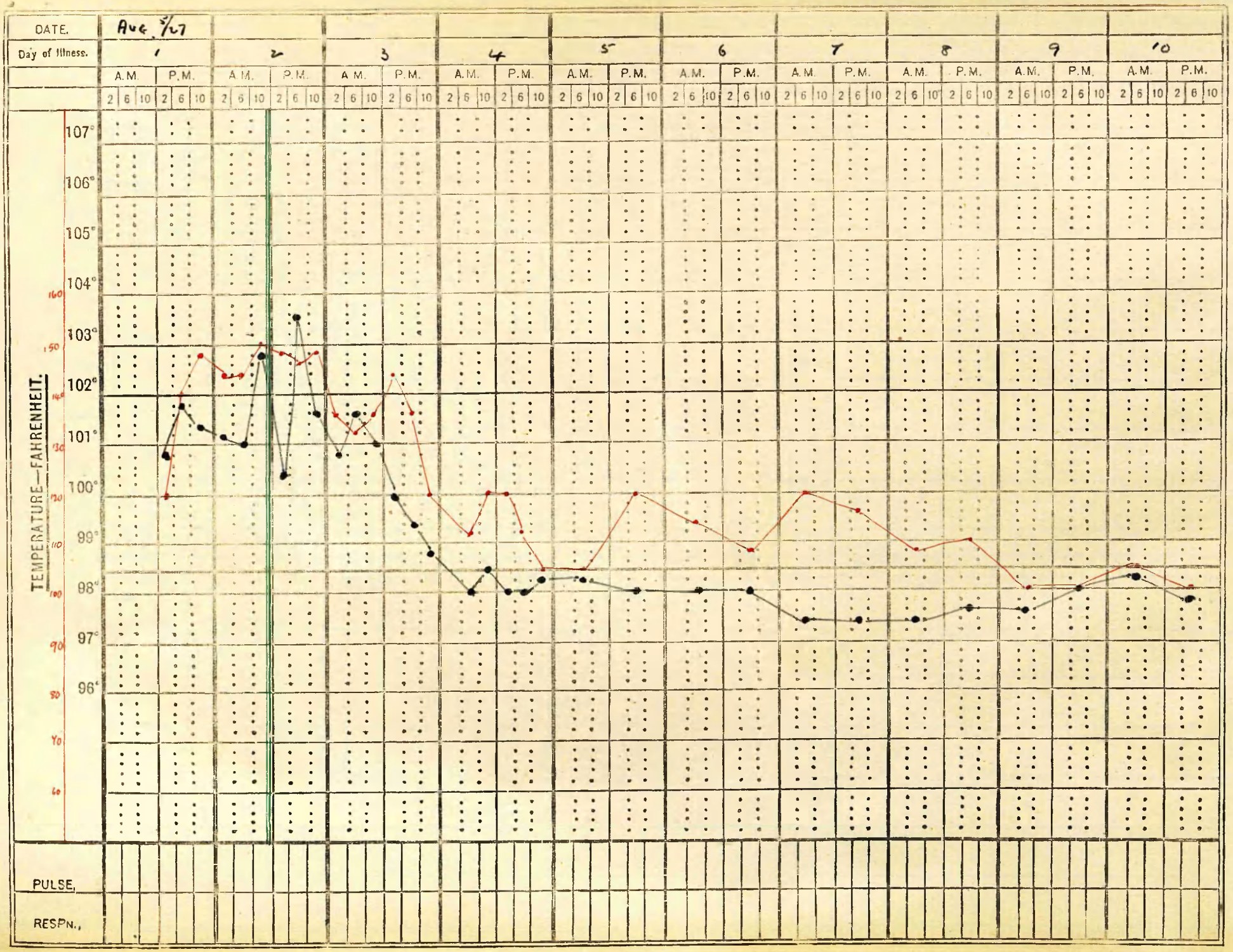
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

160 150 140 130 120 110 100 90 80 70 60

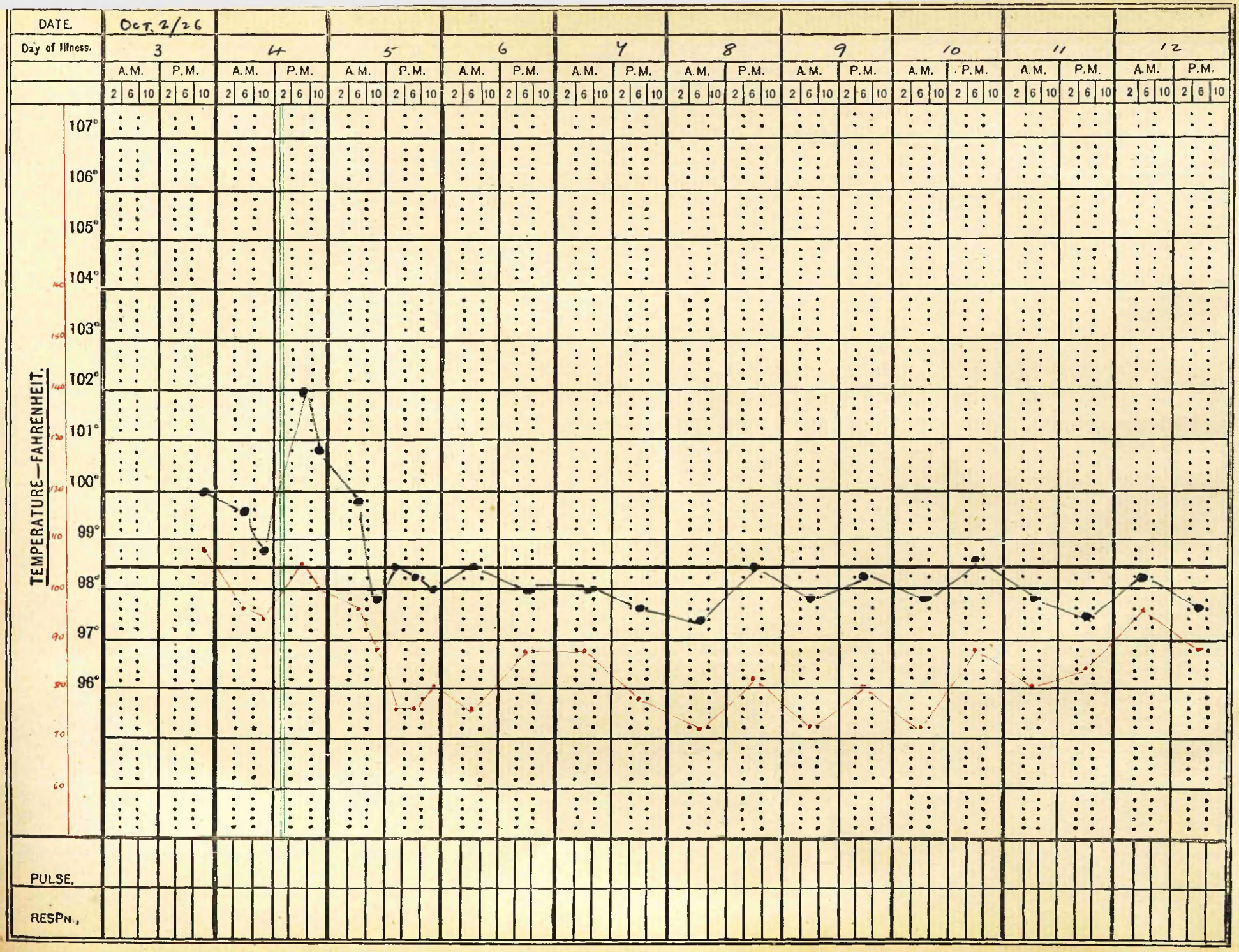
PULSE.

RESPN.,

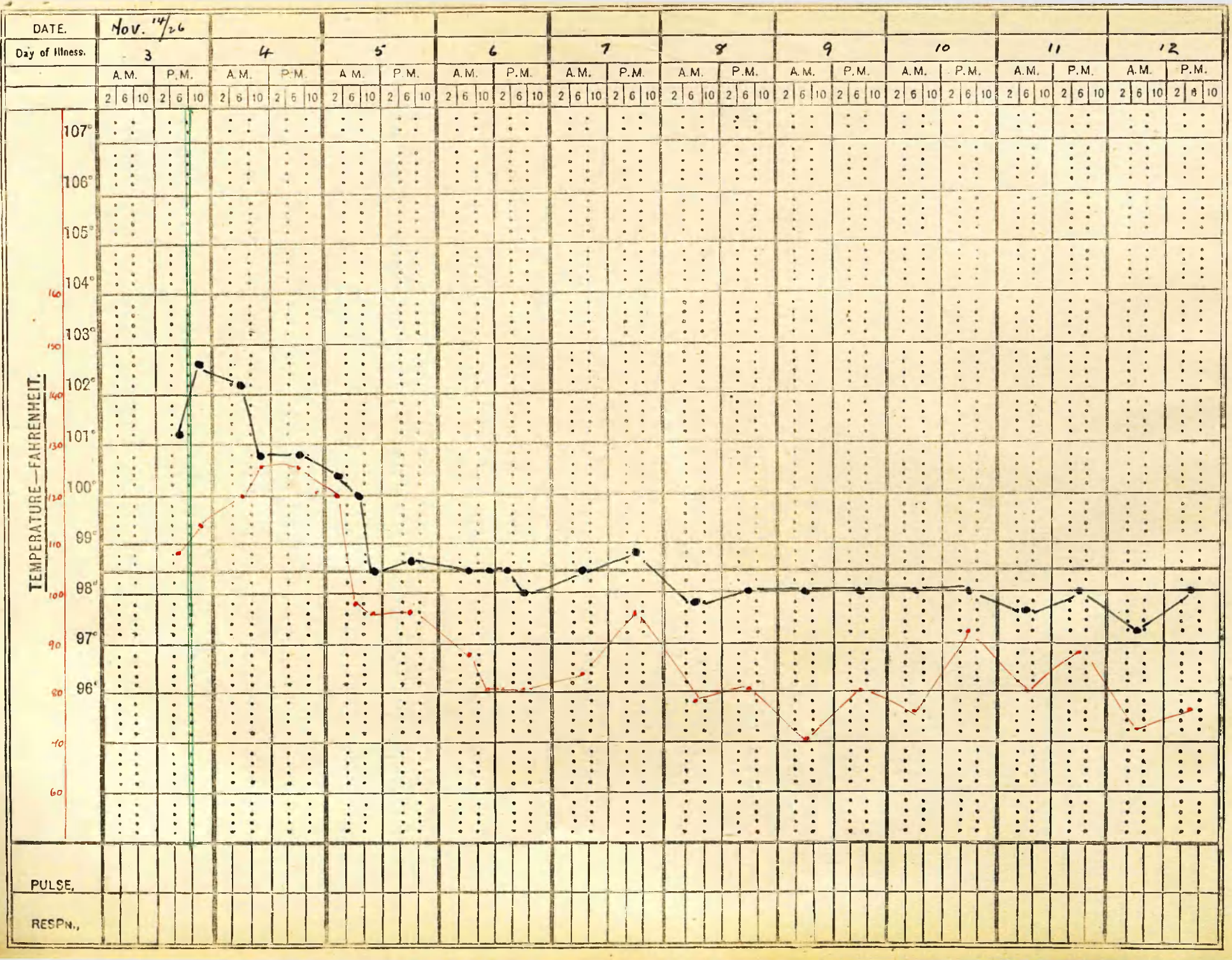



DATE.
Aug 5/07
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

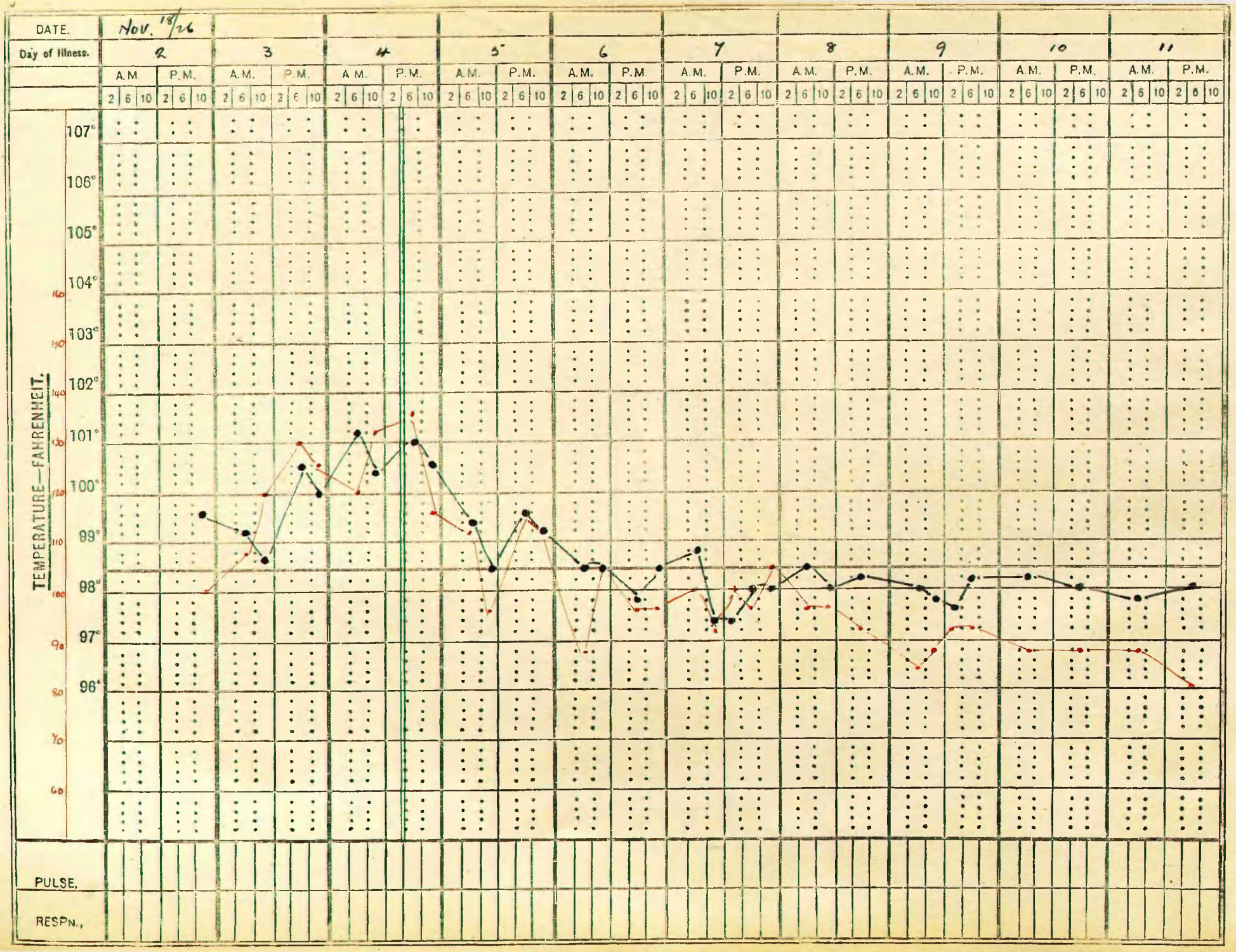
96

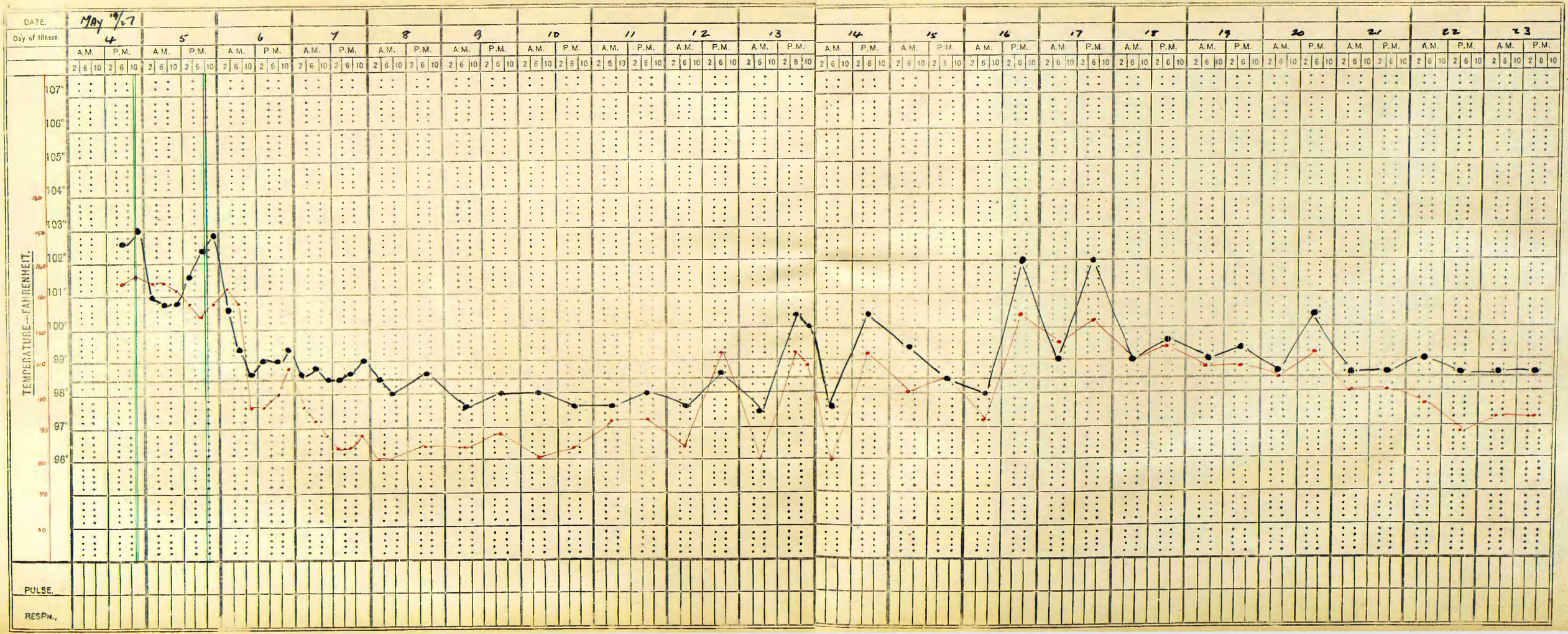

DATE.
Oct. 2/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

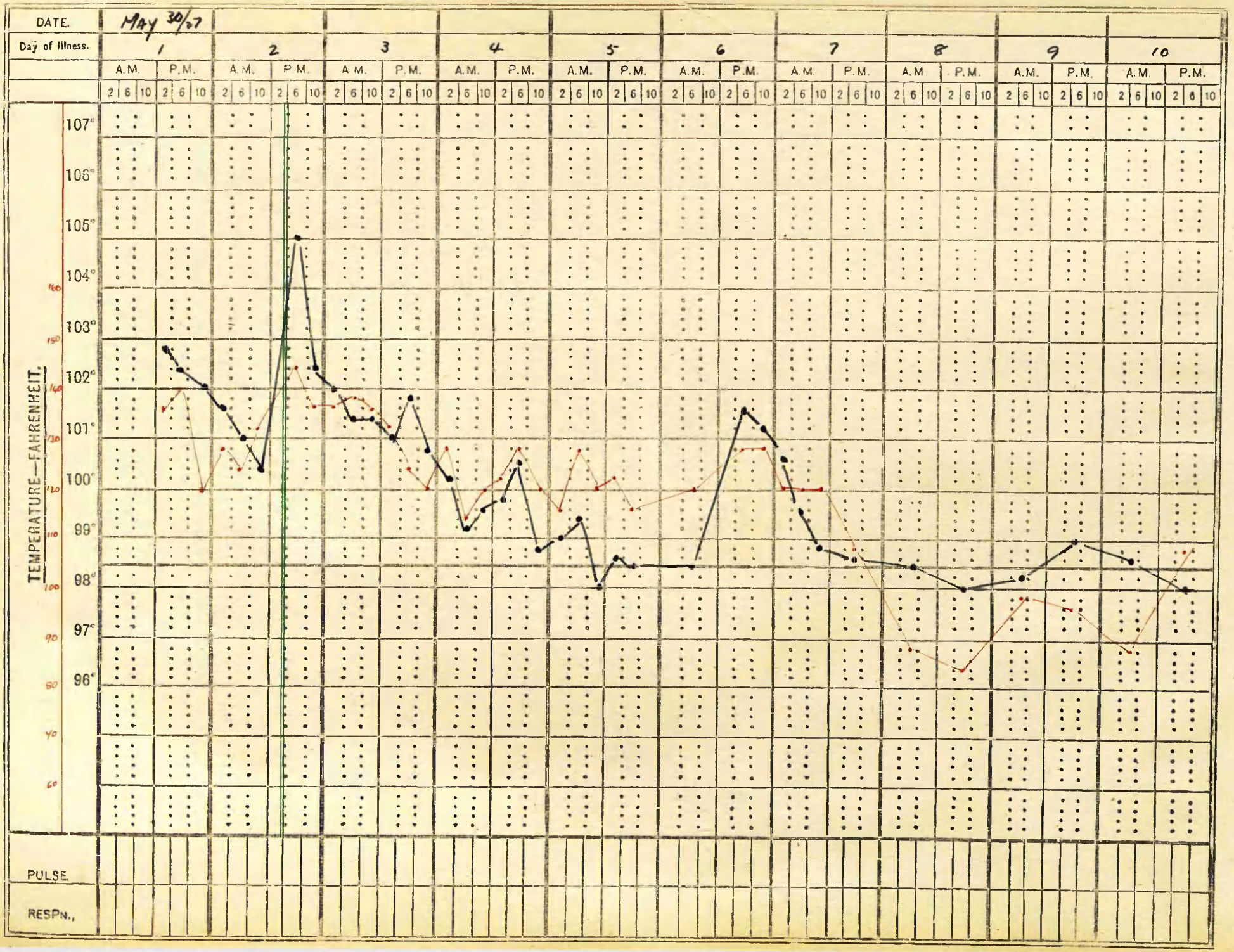
77


DATE.
Nov. 14/26
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

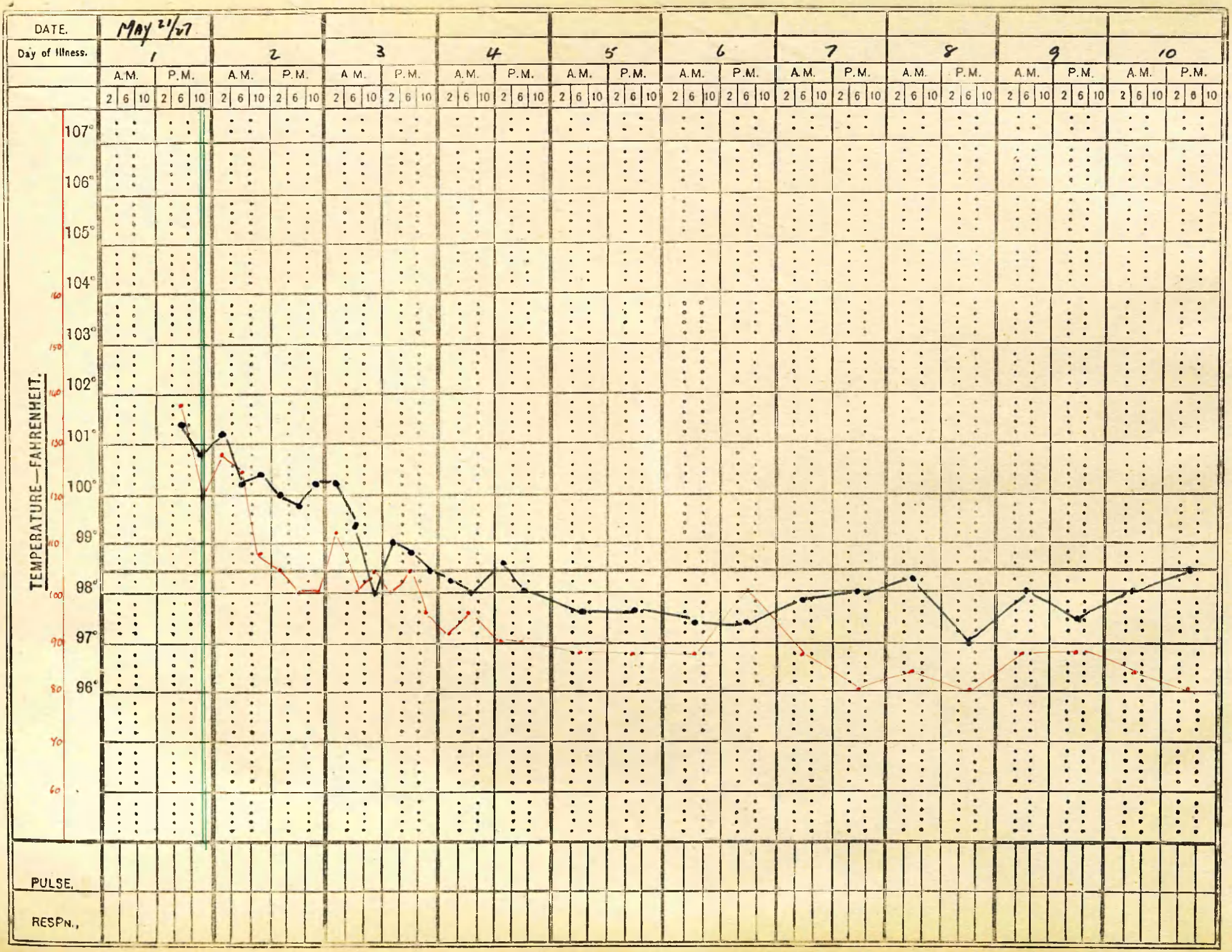
48


DATE.
Nov. 18/26
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
Day of Illness.
MAY 19 27
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
A.M. P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
PULSE.
RESPN.,


DATE.
May 30/07
Day of Illness.
1 2 3 4 5 6 7 8 9 10
A.M. P.M.
2 6 10
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

81


DATE.
MAY 21/07
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

82

DATE. May 21/27

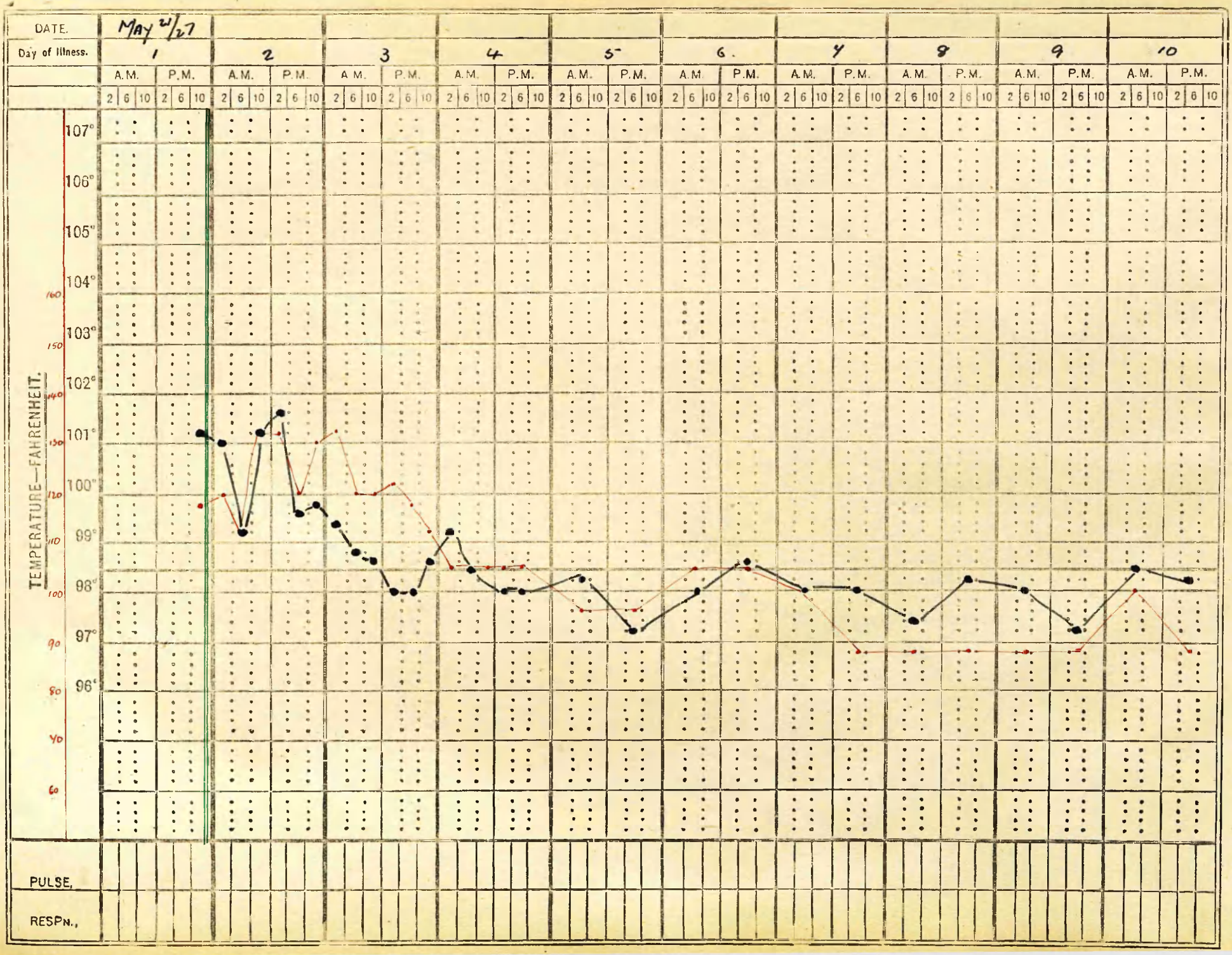
Day of Illness.	2		3		4		5		6		7		8		9		10		11	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

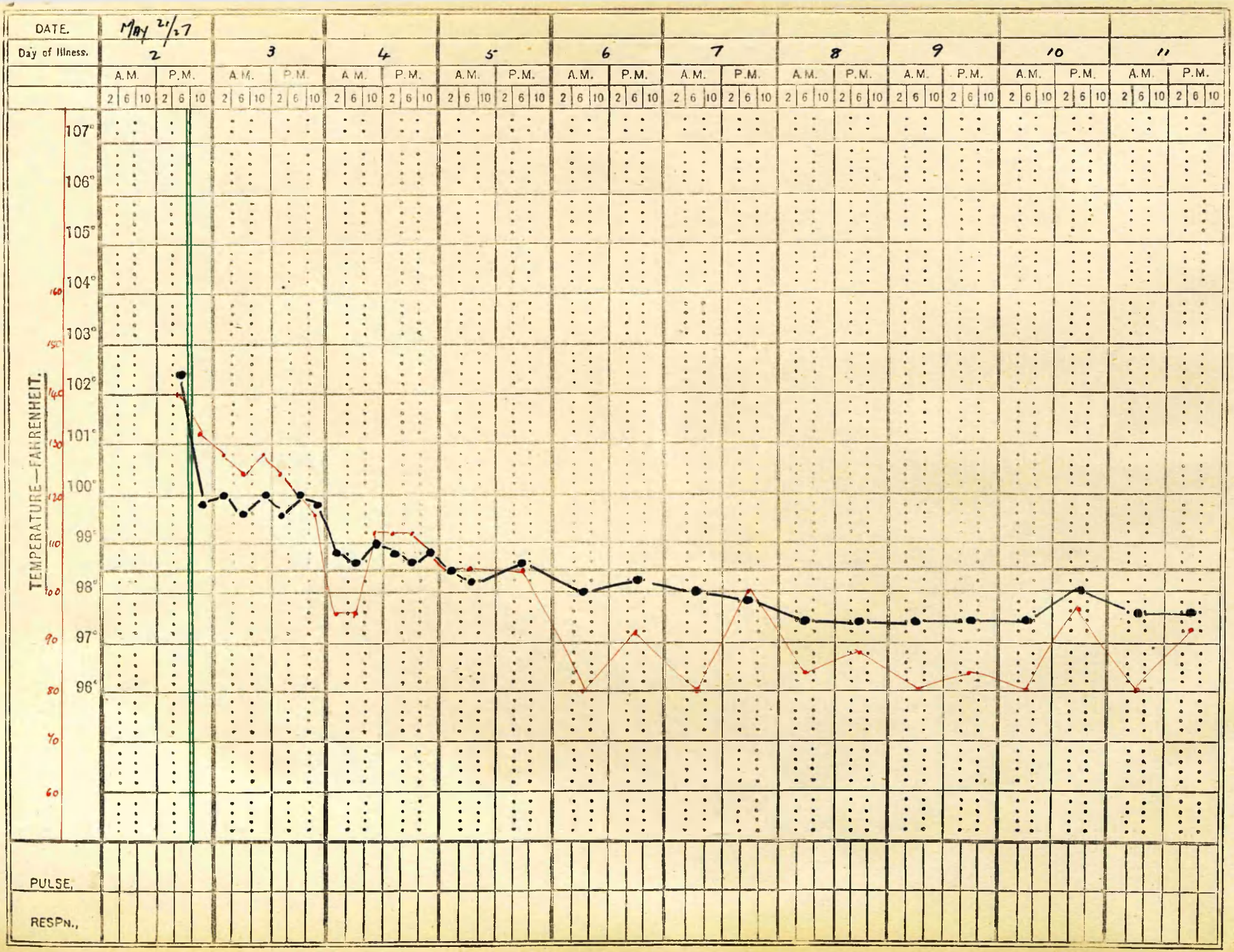
107°	160
106°	150
105°	140
104°	130
103°	120
102°	110
101°	100
100°	90
99°	80
98°	70
97°	60
96°	

PULSE.

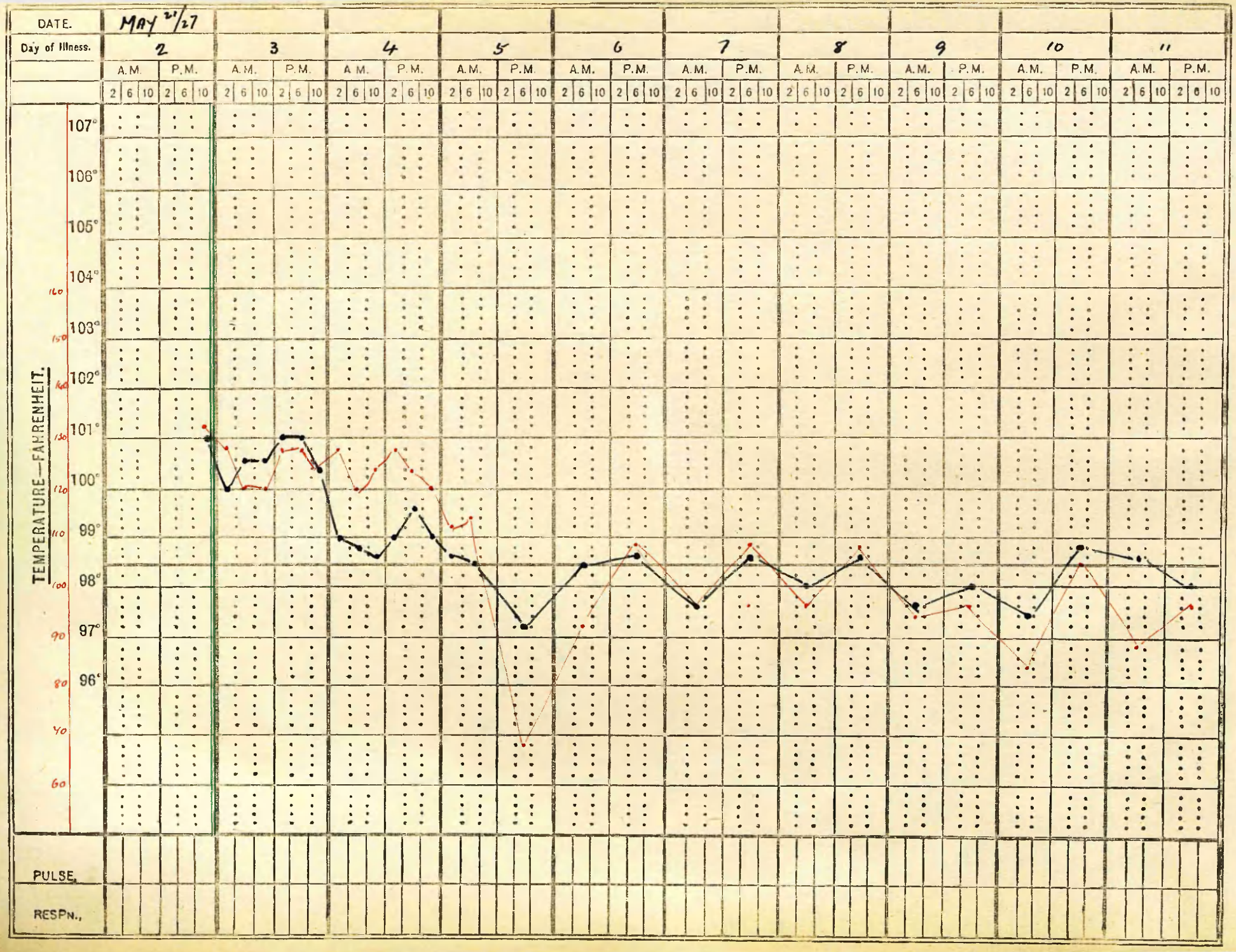
RESPN.,

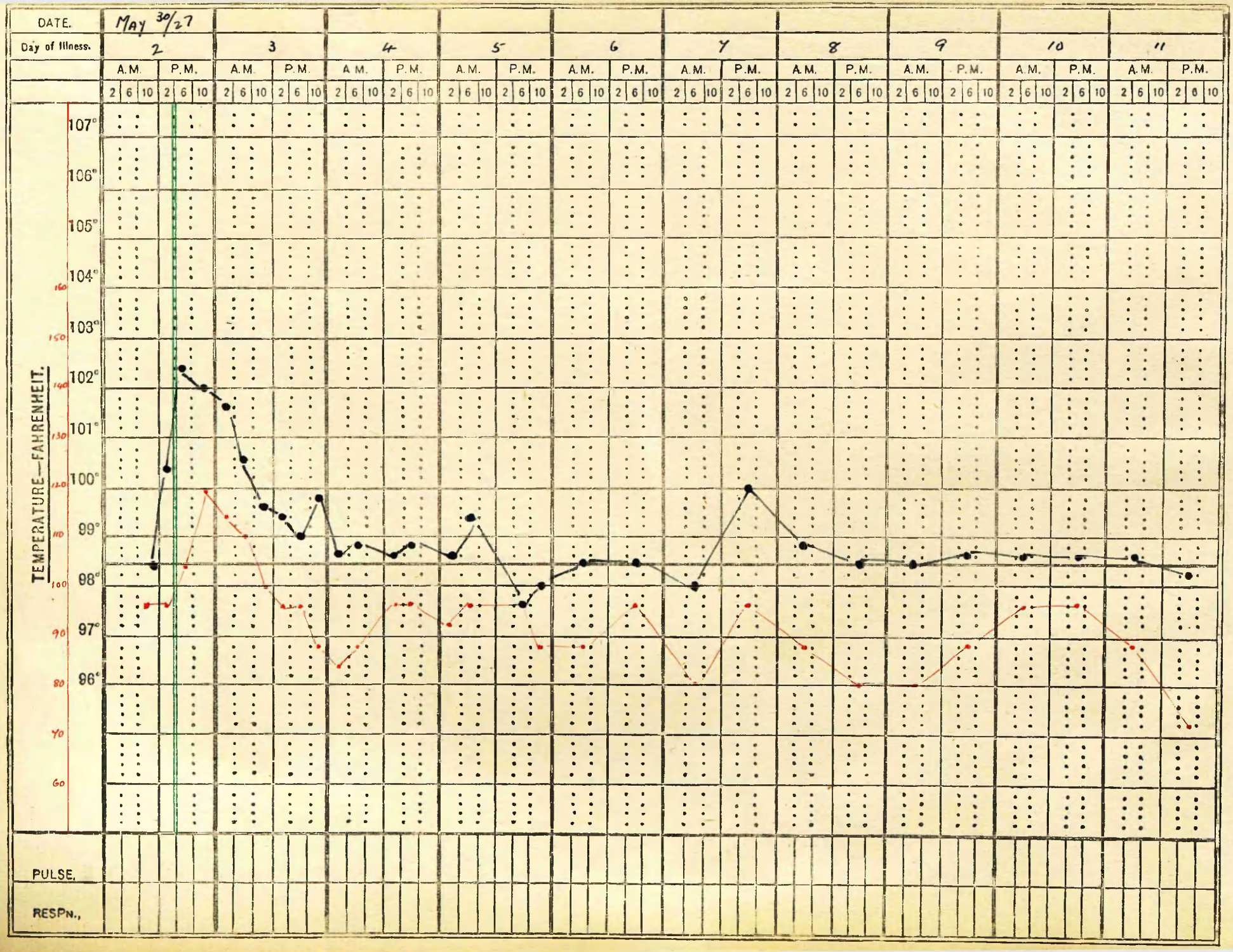

DATE.
May 21/27
Day of Illness.
1
2
3
4
5
6.
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

84


DATE.
May 21/27
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

85


DATE.
MAY 21/27
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
TEMPERATURE—FAHRENHEIT.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.,


DATE.
May 30/27
Day of Illness.
2
3
4
5
6
7
8
9
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

84

DATE. June 3/27

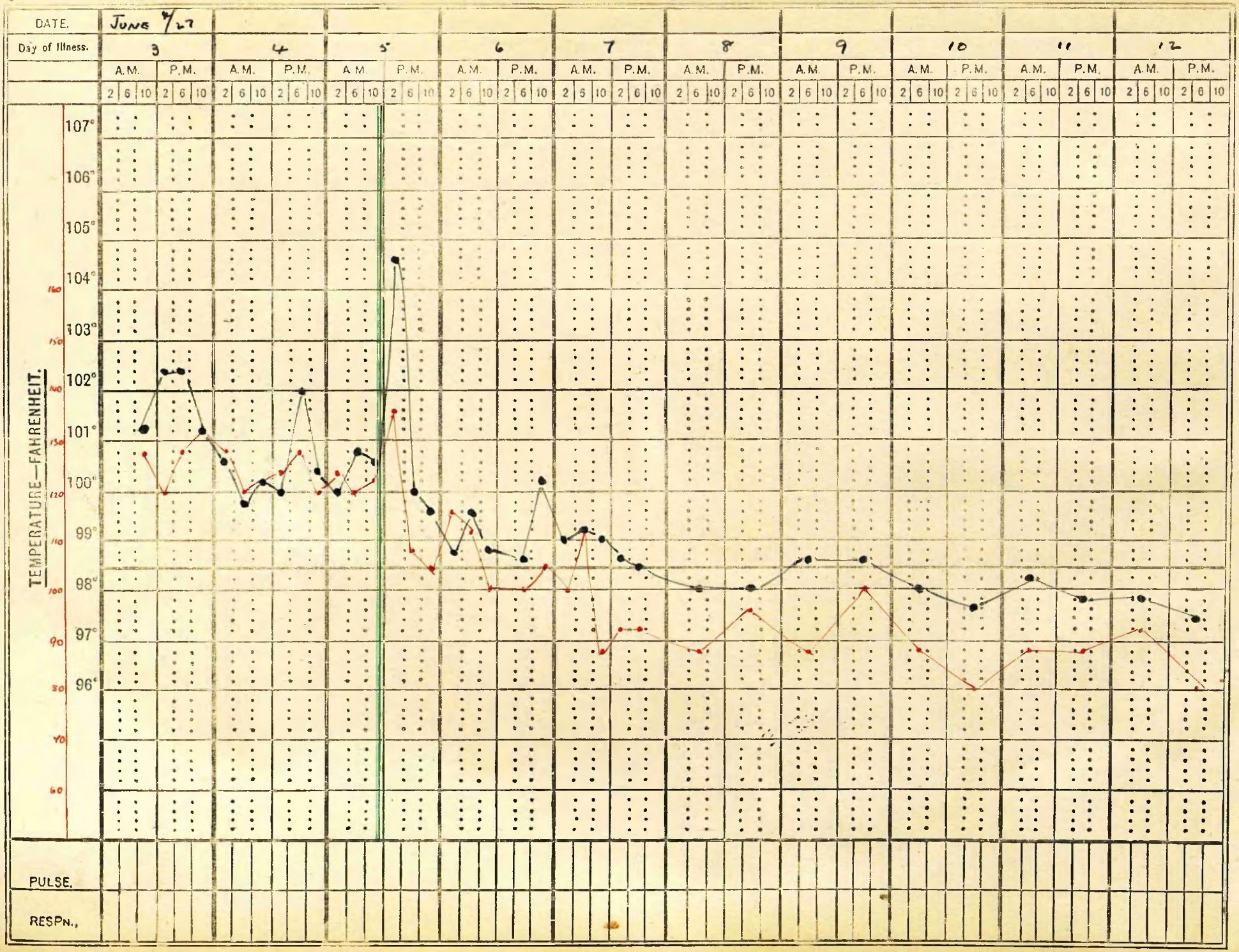
Day of Illness.	3		4		5		6		7		8		9		10		11		12	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

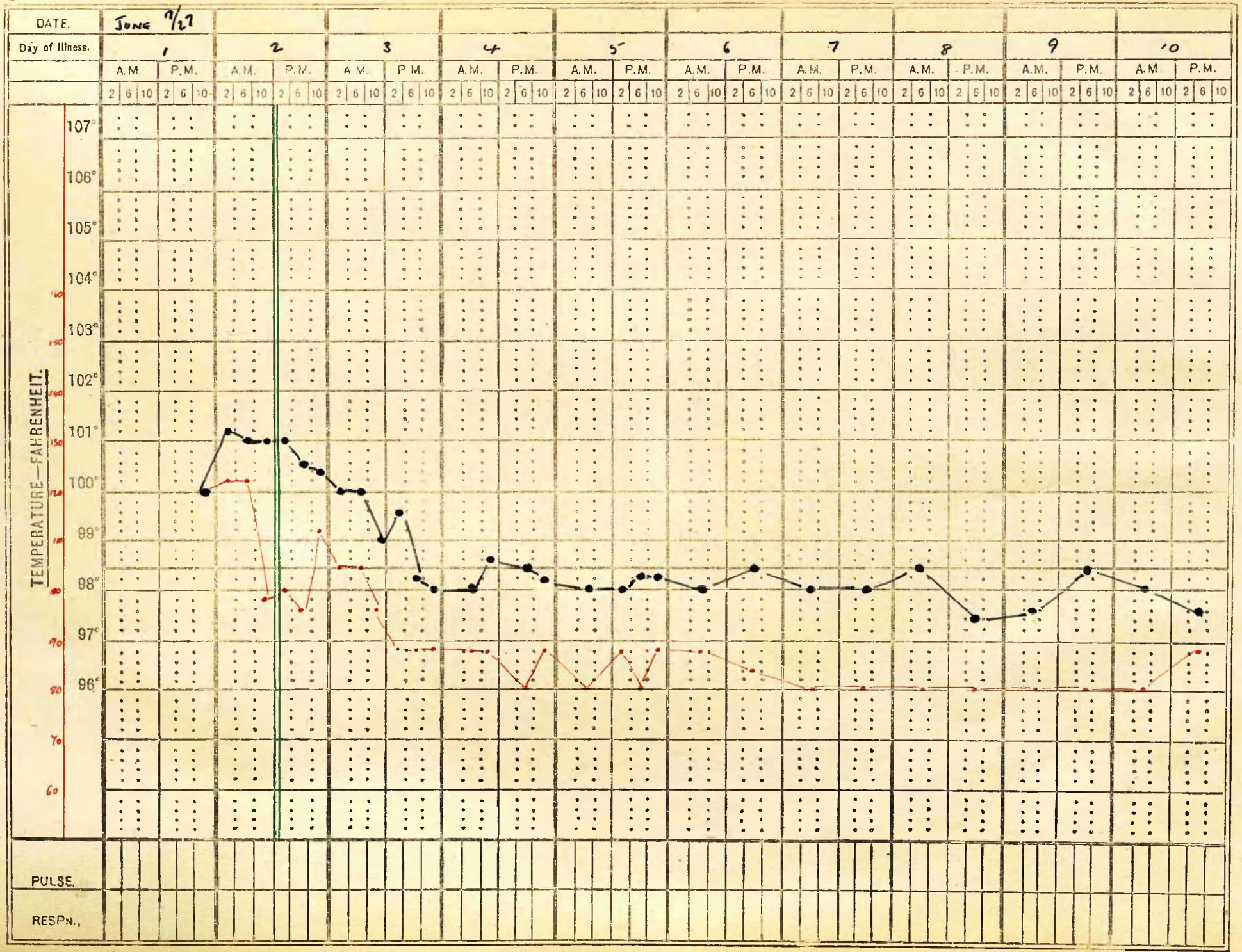
107°	140
106°	130
105°	120
104°	110
103°	100
102°	90
101°	80
100°	70
99°	60
98°	
97°	
96°	

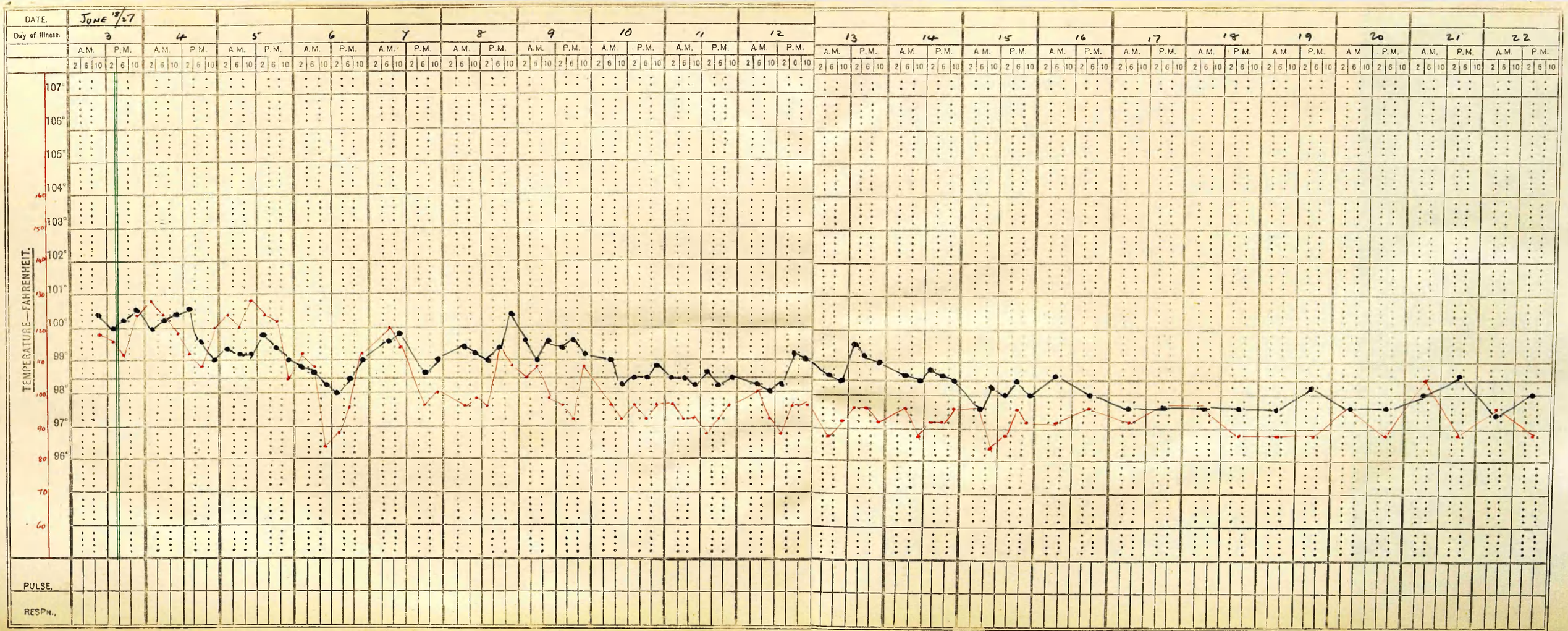
PULSE.

RESPN.,


DATE.
June 4/27
Day of Illness.
3
4
5
6
7
8
9
10
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

89


DATE.
June 9/27
Day of Illness.
1
2
3
4
5
6
7
8
9
10
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
June 13/27
Day of Illness.
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
A.M.
P.M.
2 6 10 2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

DATE. JUNE 21/17

Day of illness: 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

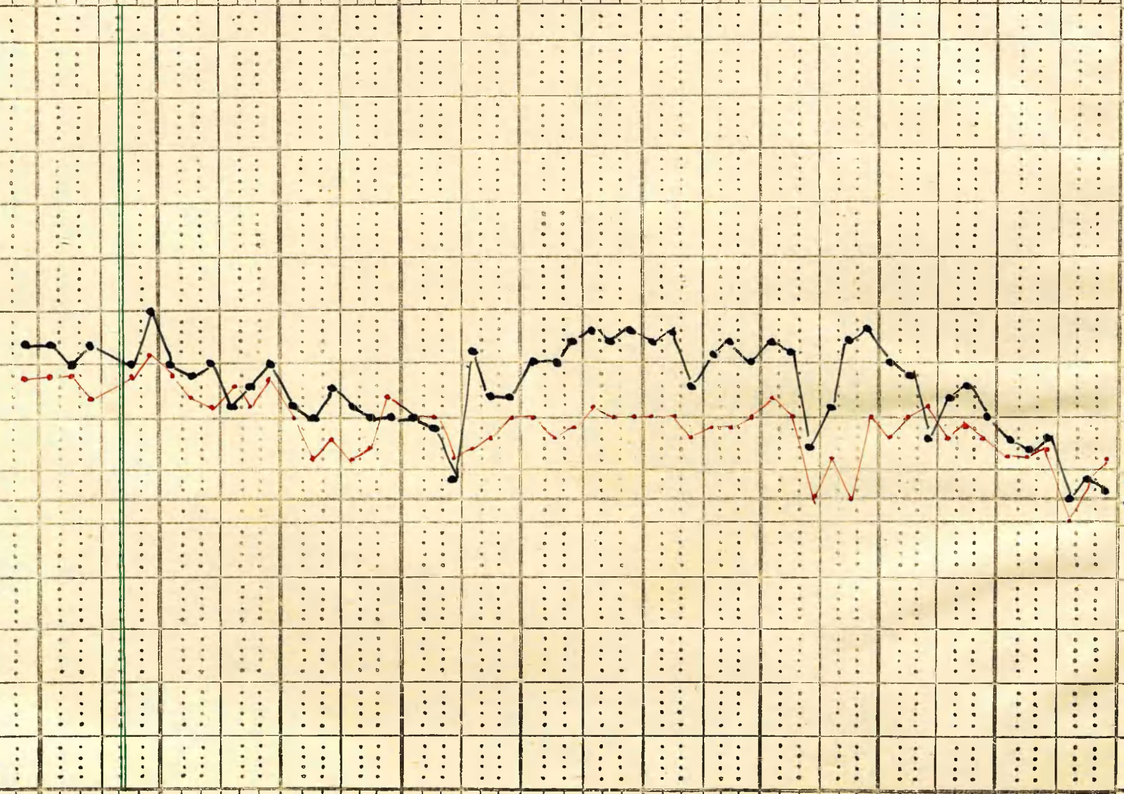
A.M. P.M. — 2 6 10 2 6 10

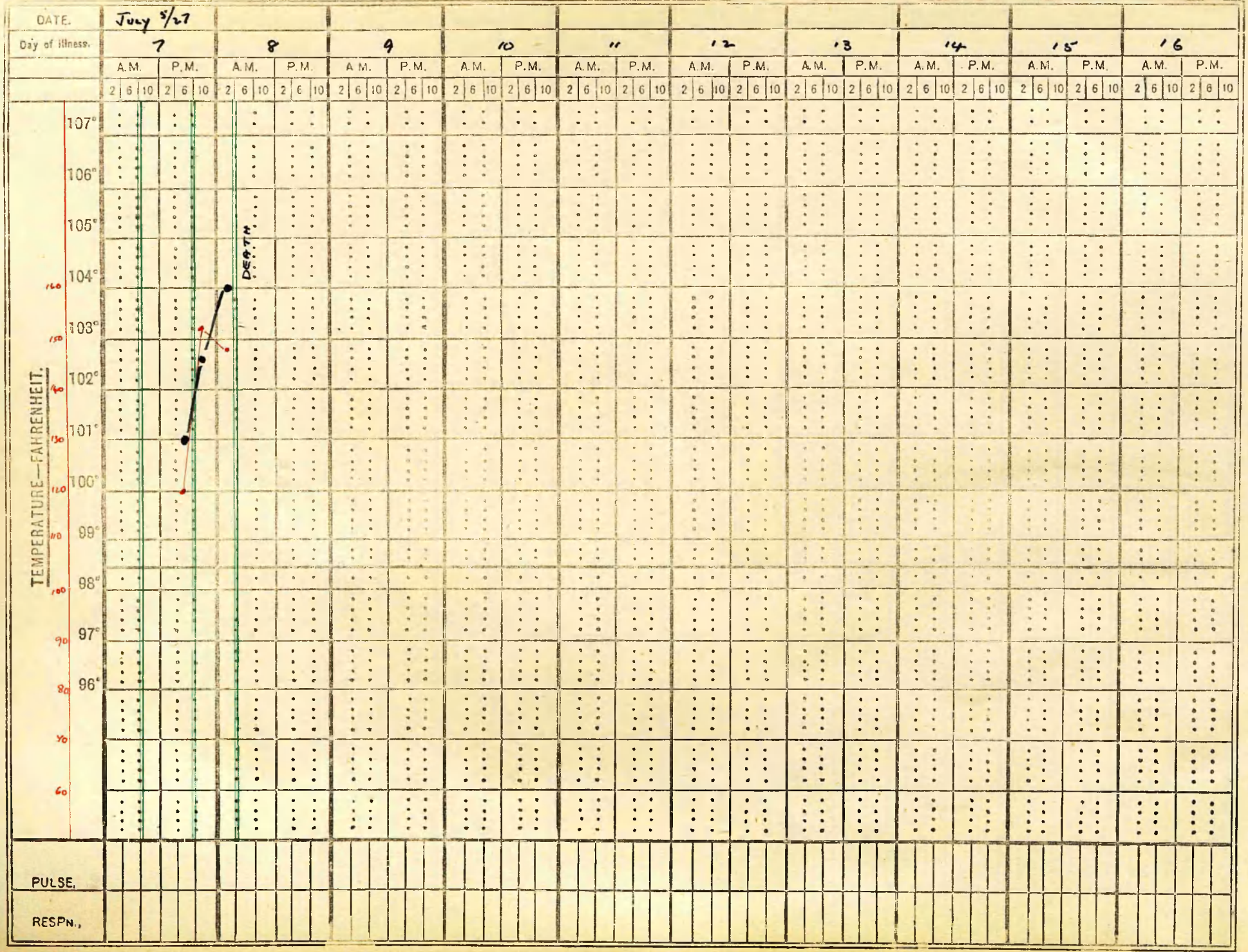
TEMPERATURE—FAHRENHEIT.

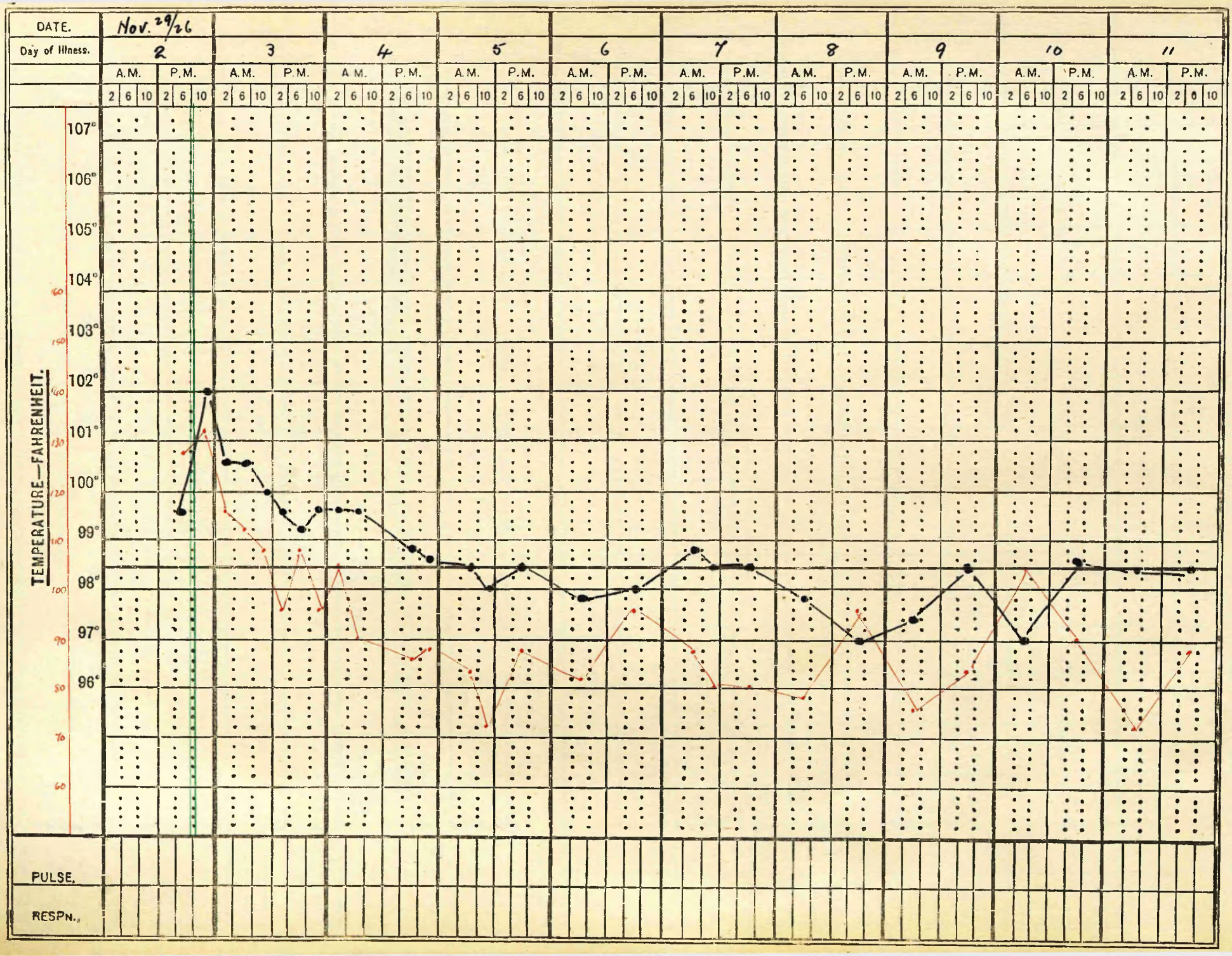
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

PULSE.

RESPN.




DATE.
July 5/27
Day of illness.
7
8
9
10
11
12
13
14
15
16
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
DEATH
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.


DATE.
Nov. 29/26
Day of Illness.
2
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10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

94

DATE.	Dec. 5/26	6	7	8	9	10	11	12	13	14
Day of Illness.	3	4	5	6	7	8	9	10	11	12
	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.	A.M. P.M.
	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10	2 6 10 2 6 10

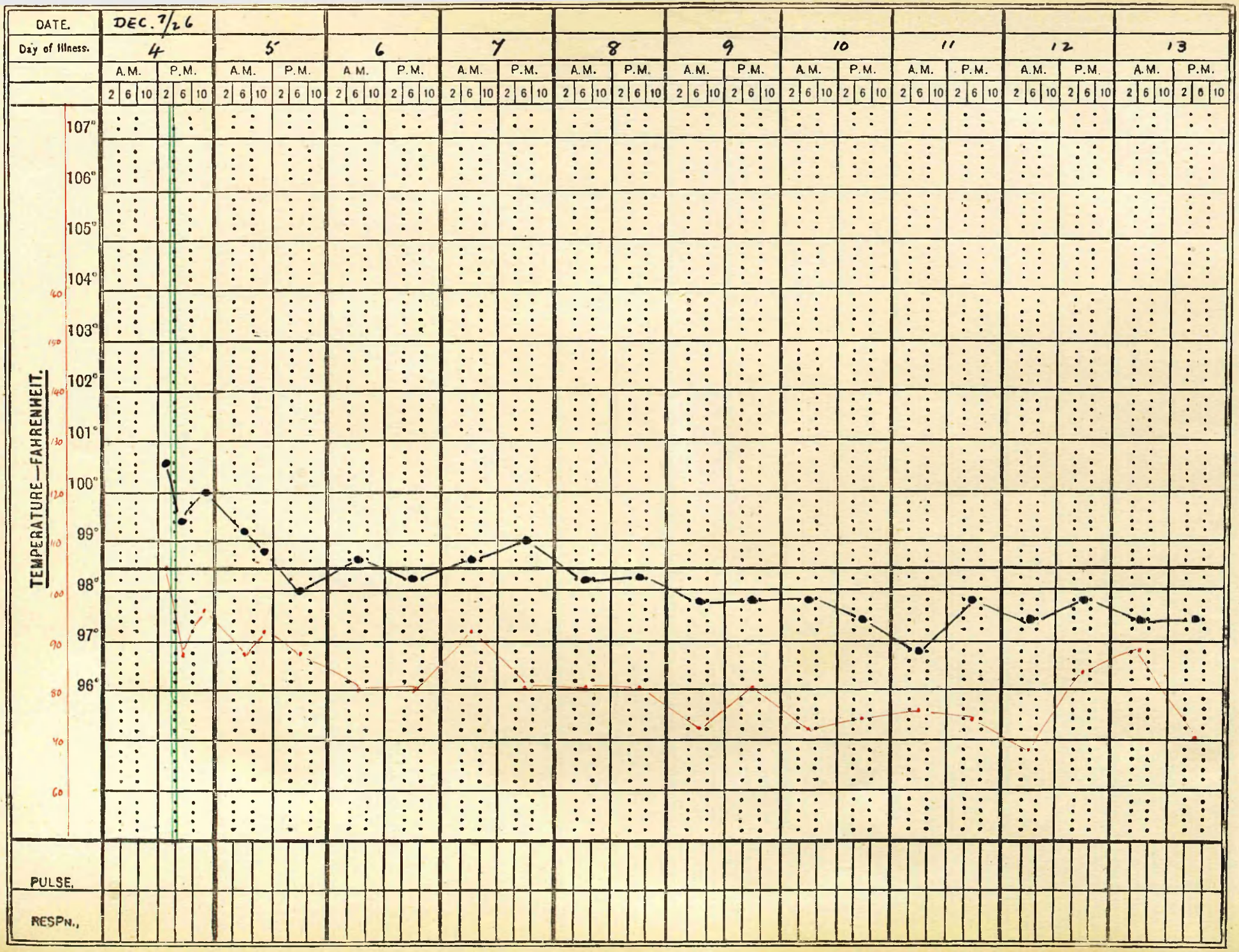
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

DEATH.

PULSE.

RESPN.


DATE.
DEC. 7/26
Day of Illness.
4
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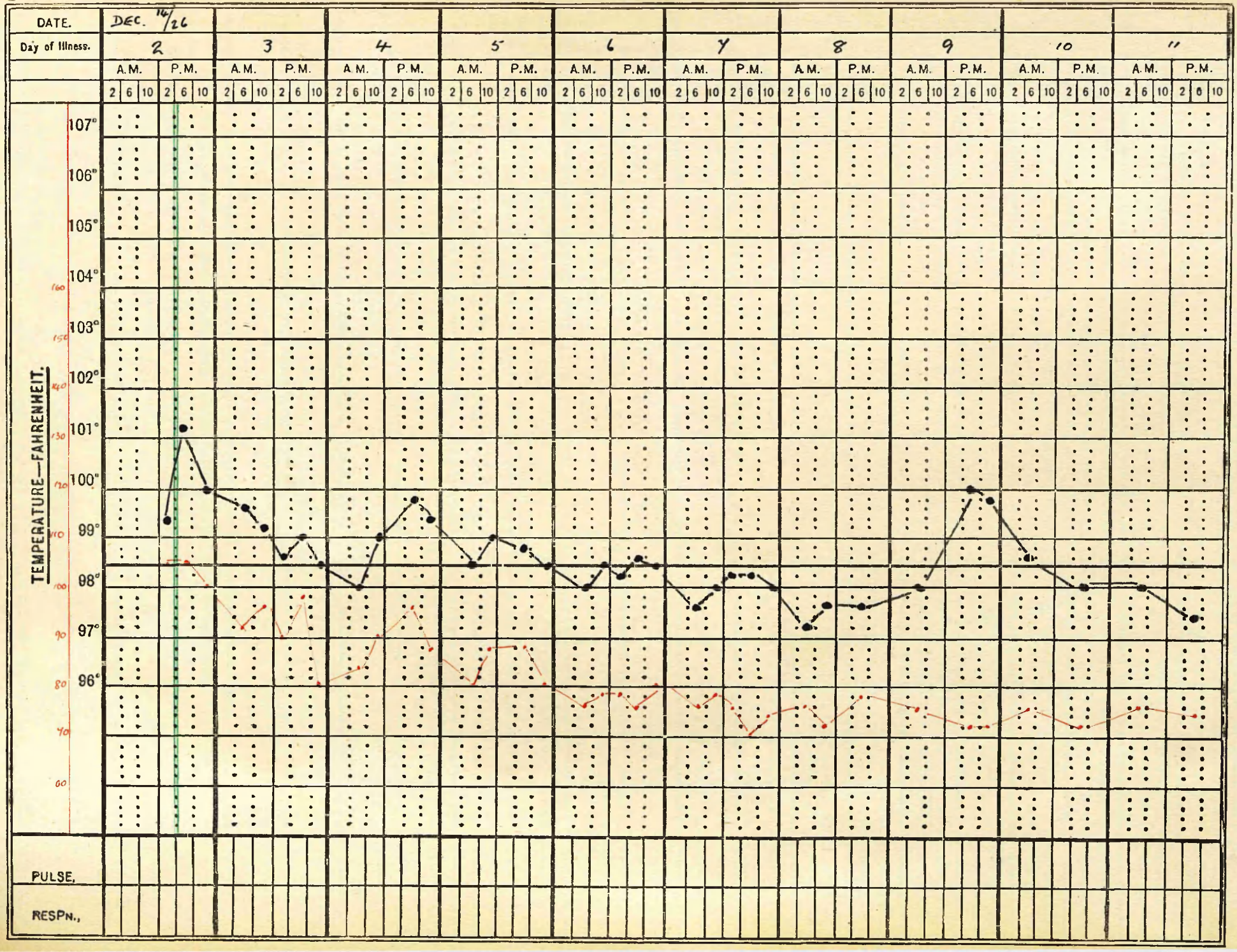
12
13
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

96


DATE.
DEC. 14/26
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
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100
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70
60
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

9 4

DATE.	Dec. 4/26																							
Day of Illness.	4				5				6				7				8				9			
	A.M.			P.M.			A.M.			P.M.			A.M.			P.M.			A.M.			P.M.		
	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10

	10				11				12				13			
	A.M.			P.M.			A.M.			P.M.			A.M.			P.M.		
	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10

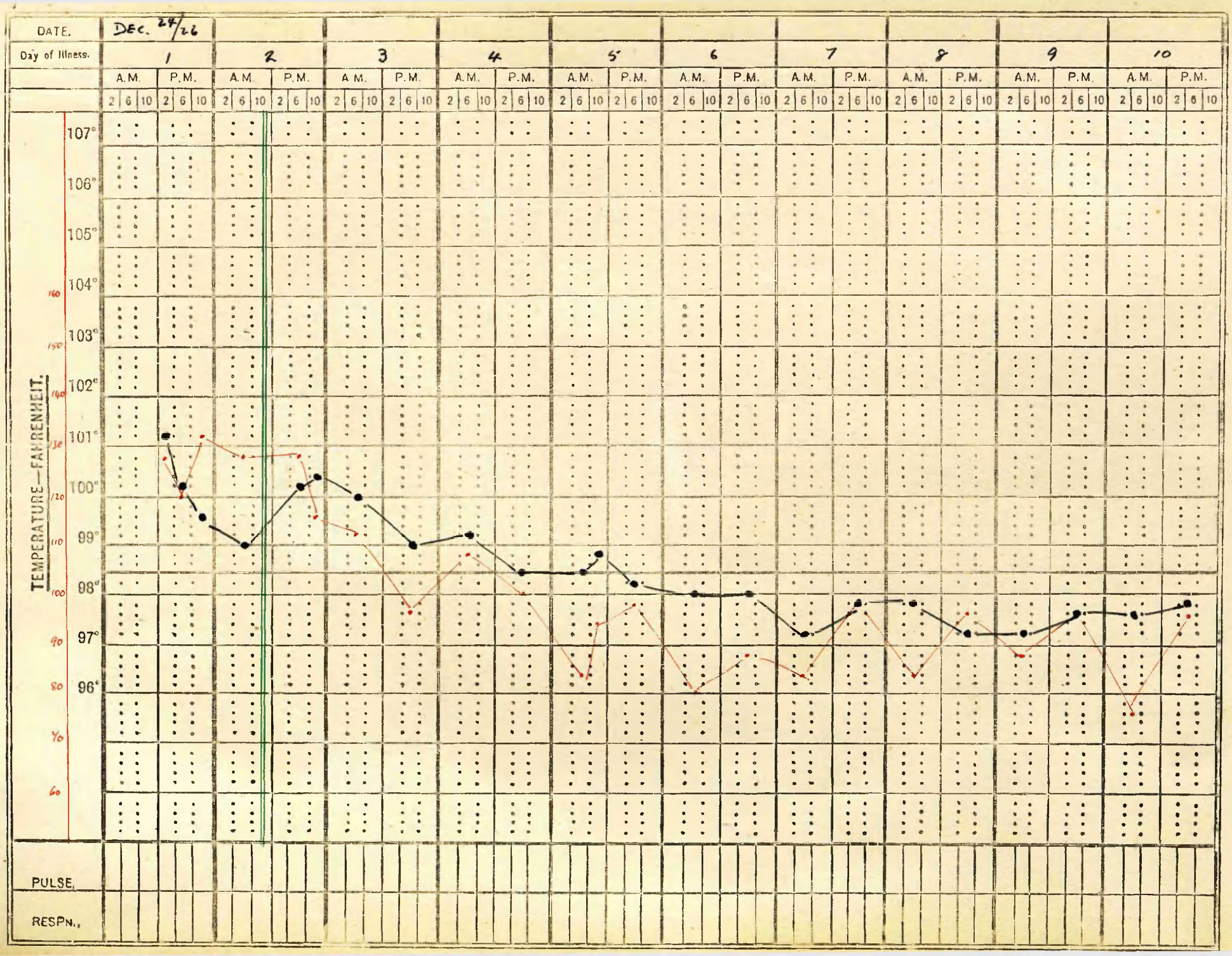
TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

160 150 140 130 120 110 100 90 80 70 60

PULSE.

RESPN.,


DATE.
Dec. 24/26
Day of Illness.
1
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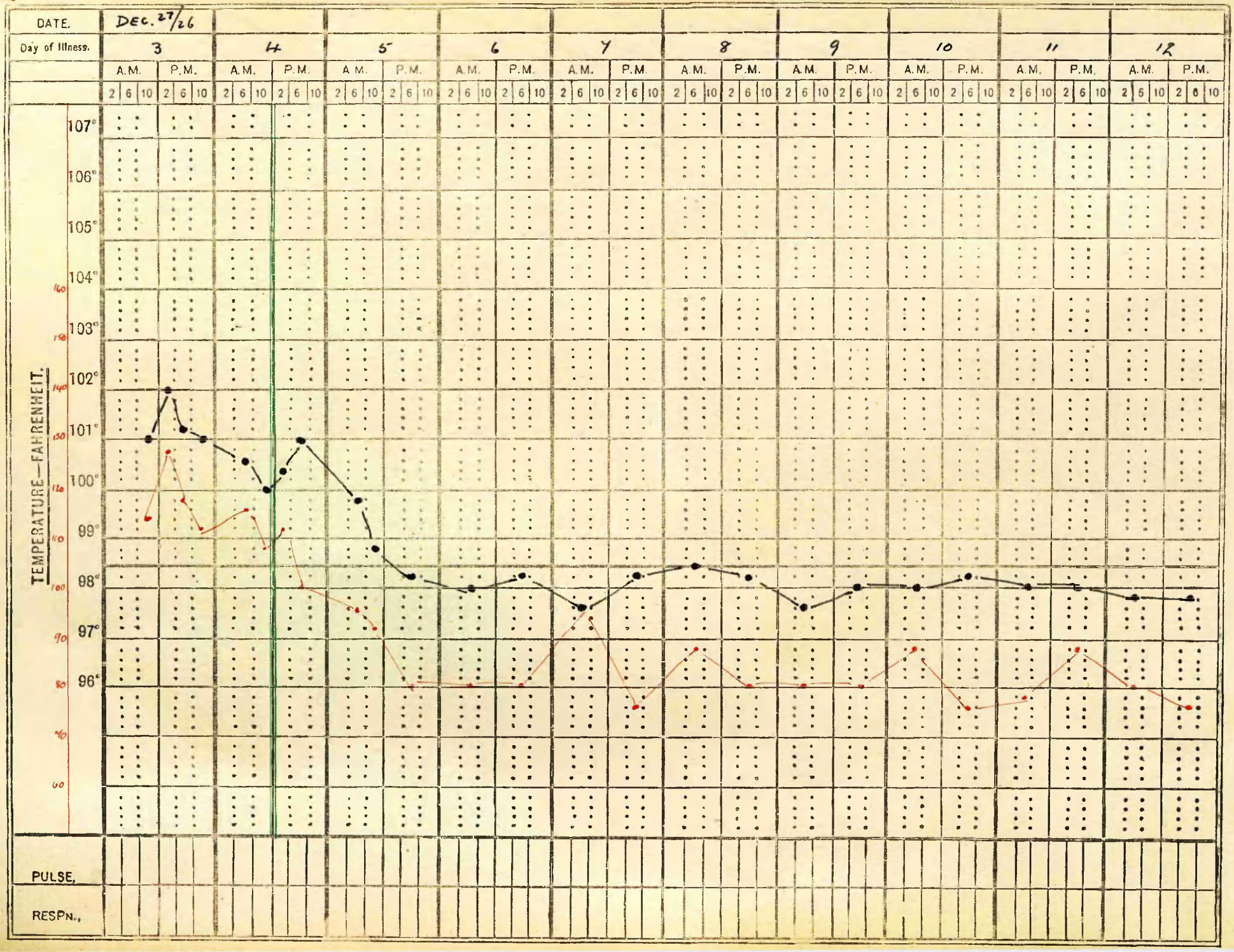
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
Dec. 27/26
Day of Illness.
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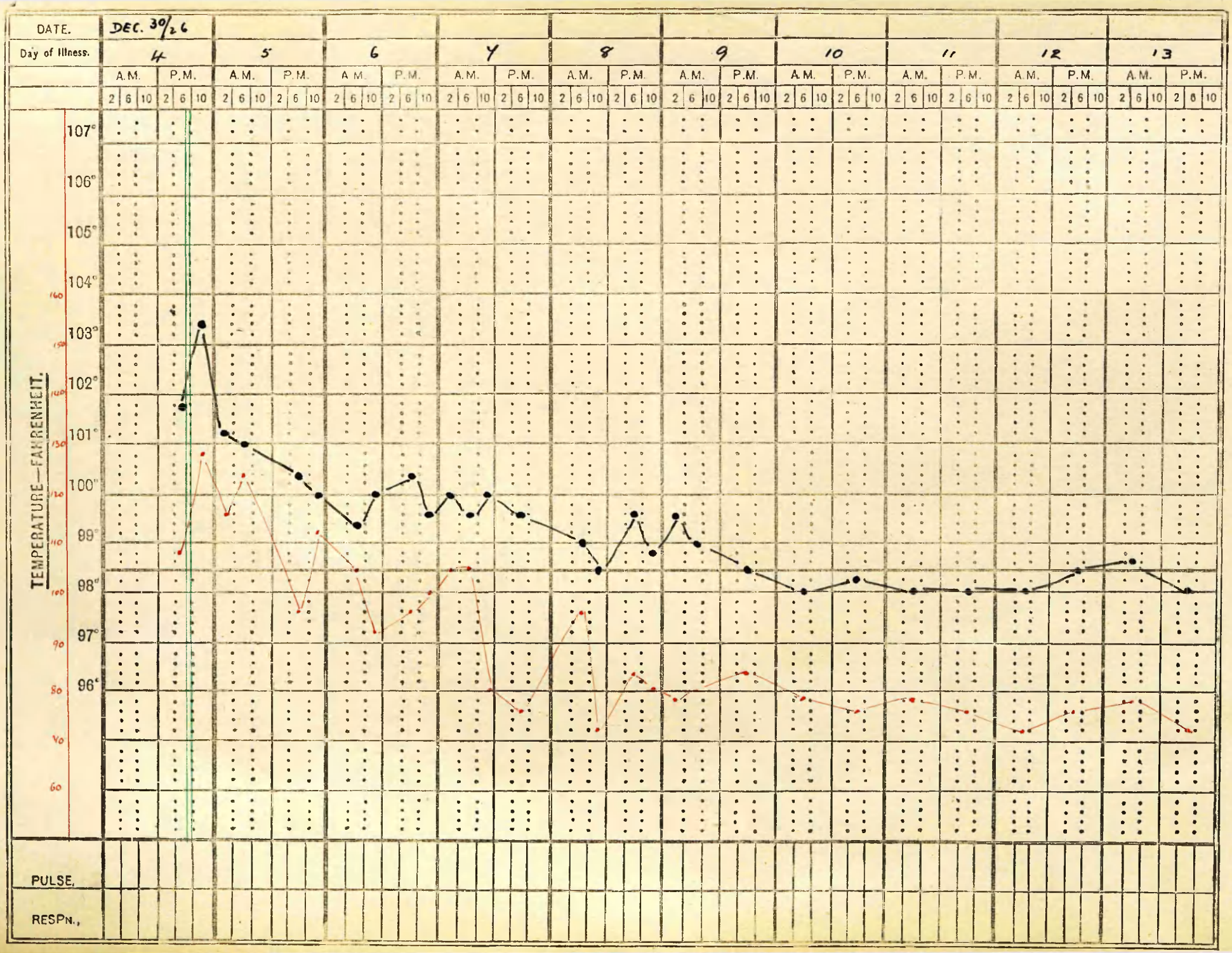
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,
100


DATE.
DEC. 30/26
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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103°
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99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

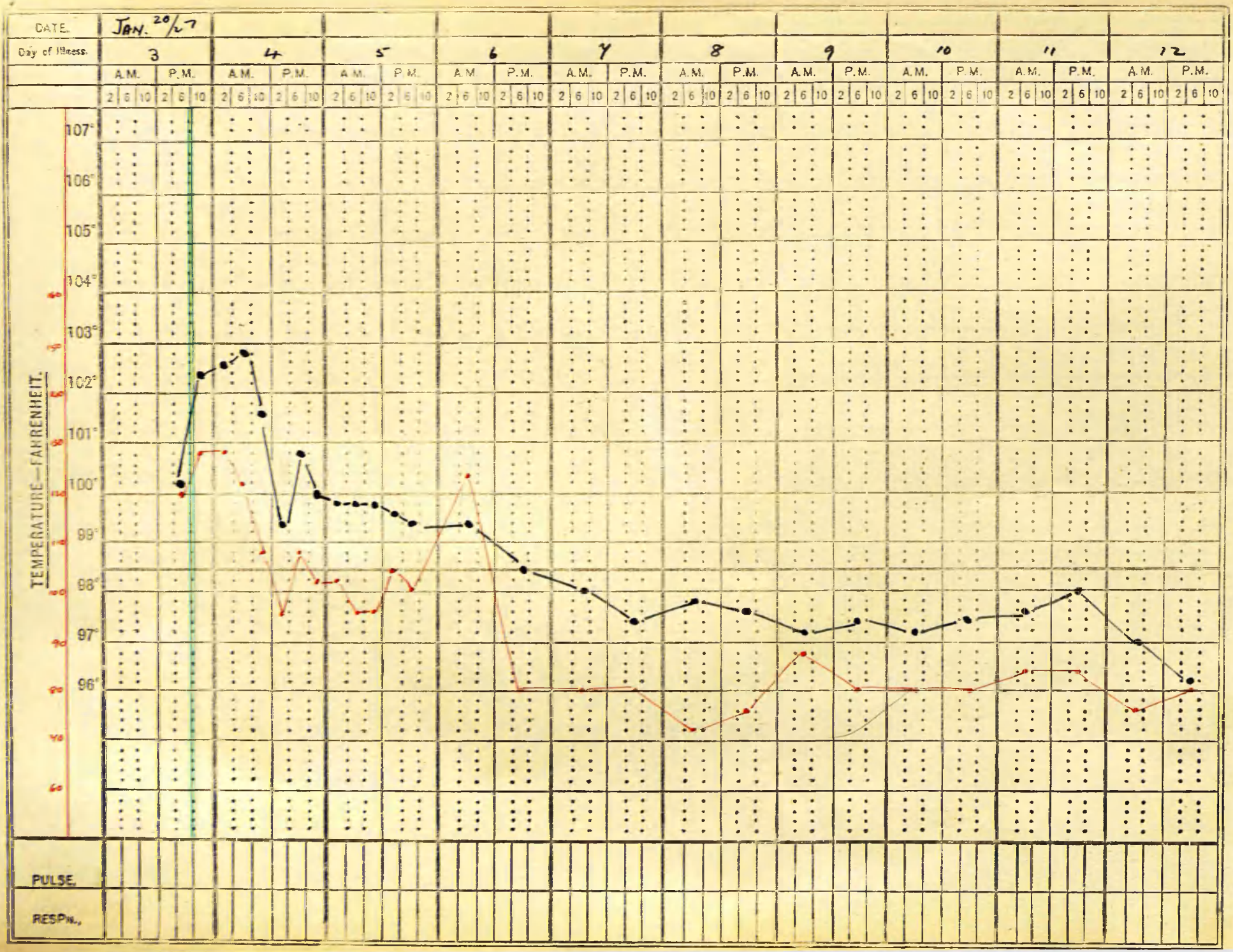
DATE.	DEC. 3/26																							
Day of Illness.	4				5				6				7		8		9		10		11		12		13	
	A.M.			P.M.	A.M.		P.M.		A.M.		P.M.		A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
	2	6	10	2 6 10	2	6	10	2 6 10	2	6	10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10	2 6 10

TEMPERATURE—FAHRENHEIT.

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

PULSE.

RESPN.,


DATE.
JAN. 20/27
Day of Illness.
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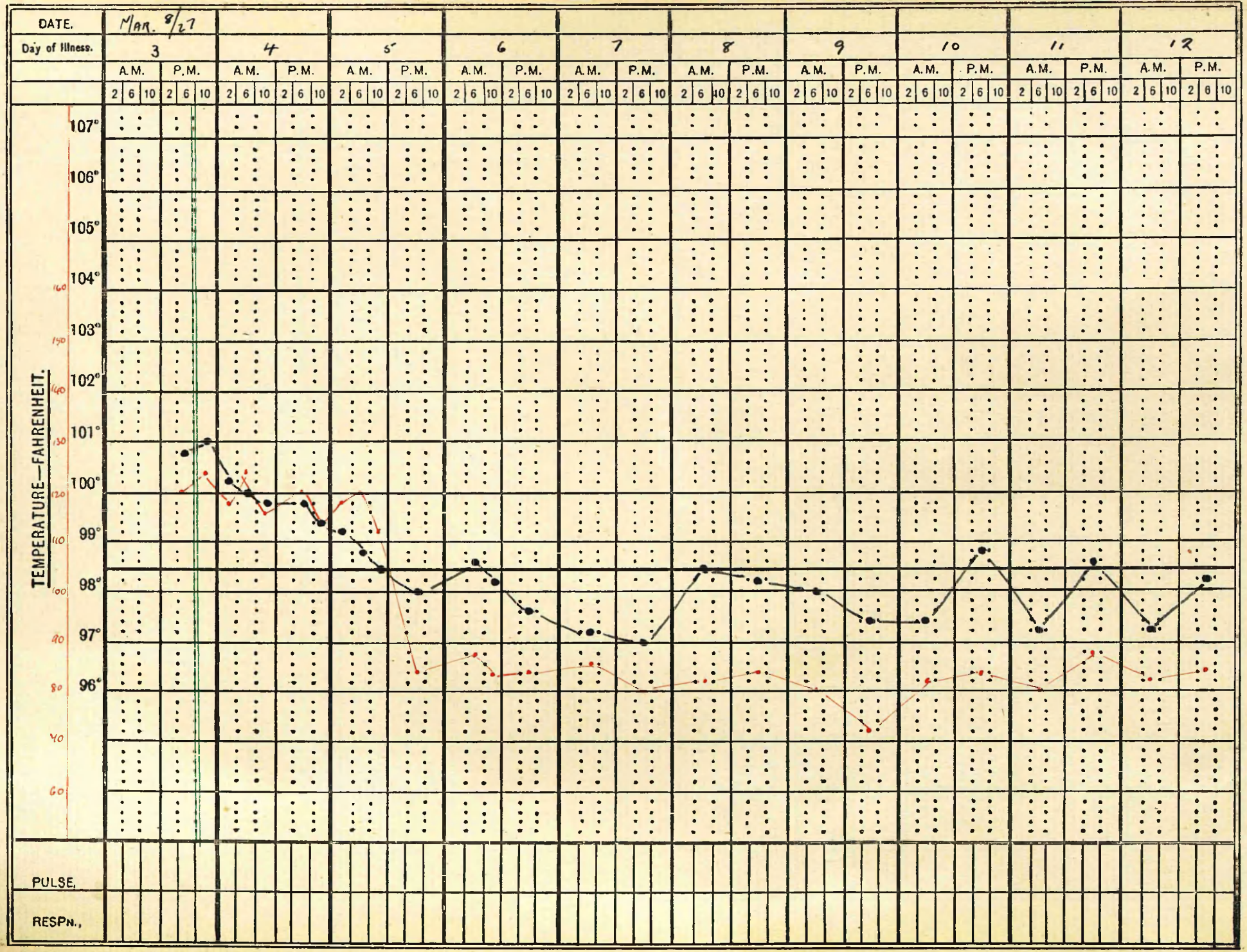
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.

103


DATE.
Mar. 8/27
Day of Illness.
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11
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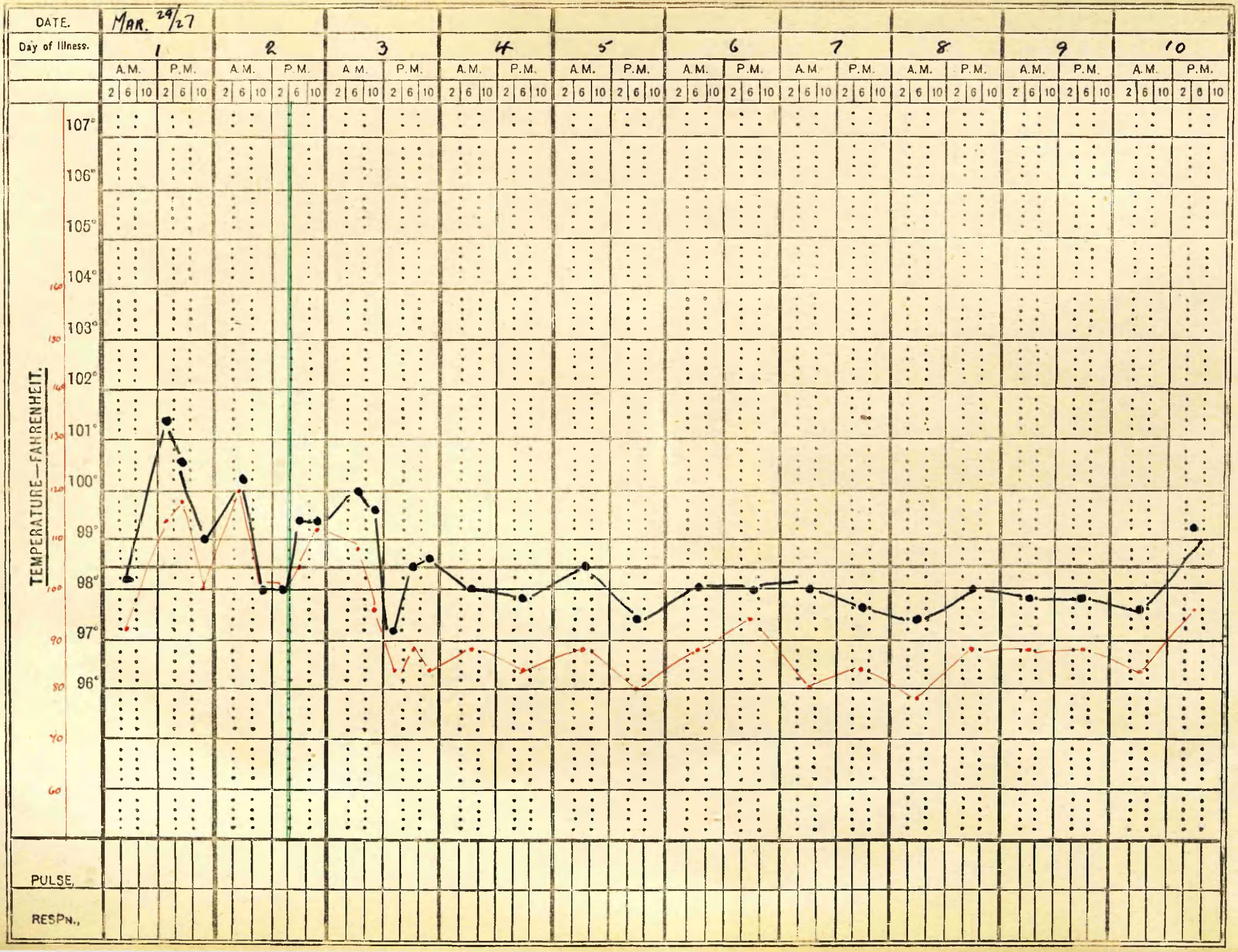
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

104


DATE.
MAR. 29/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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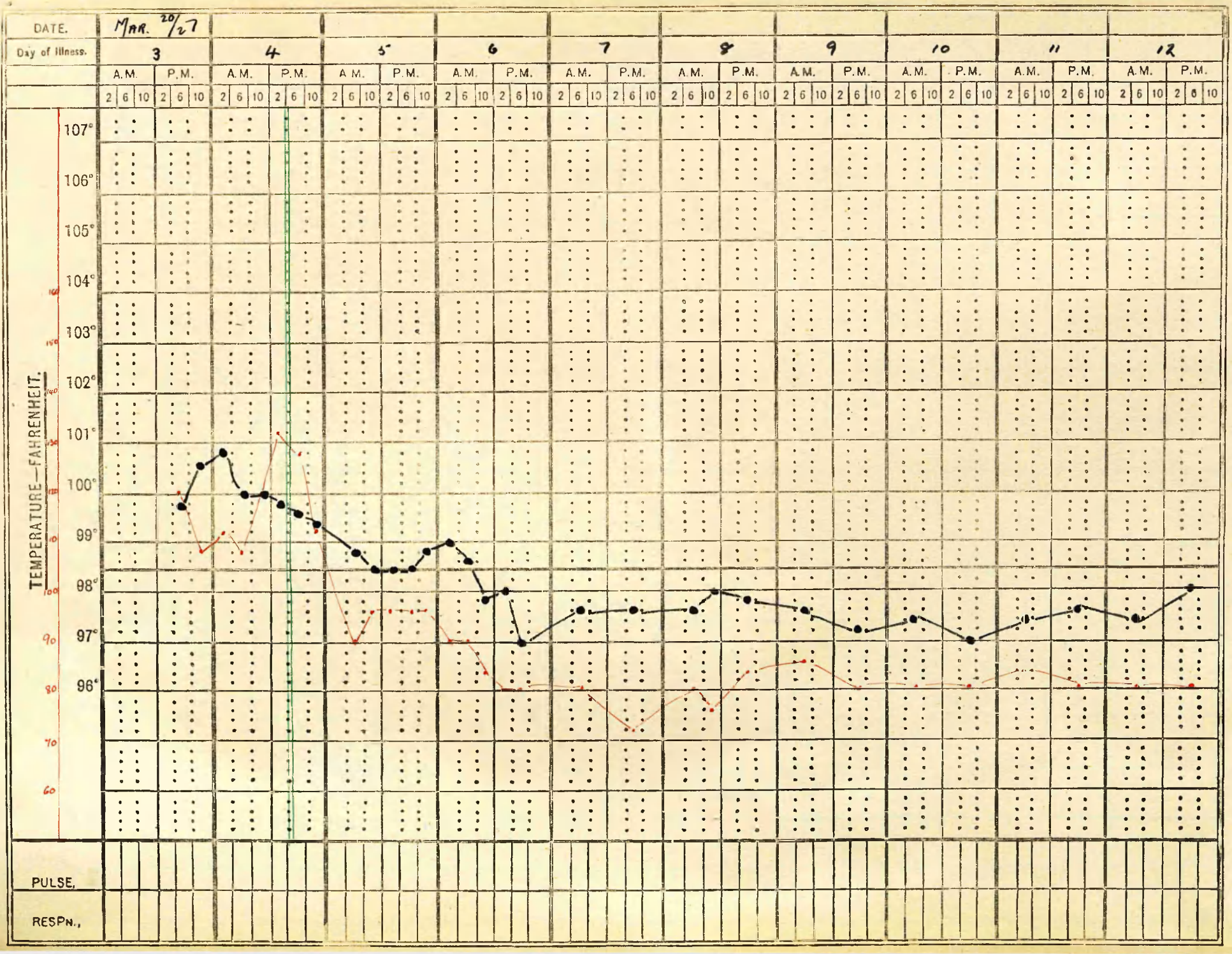
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
MAR. 20/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
105°
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103°
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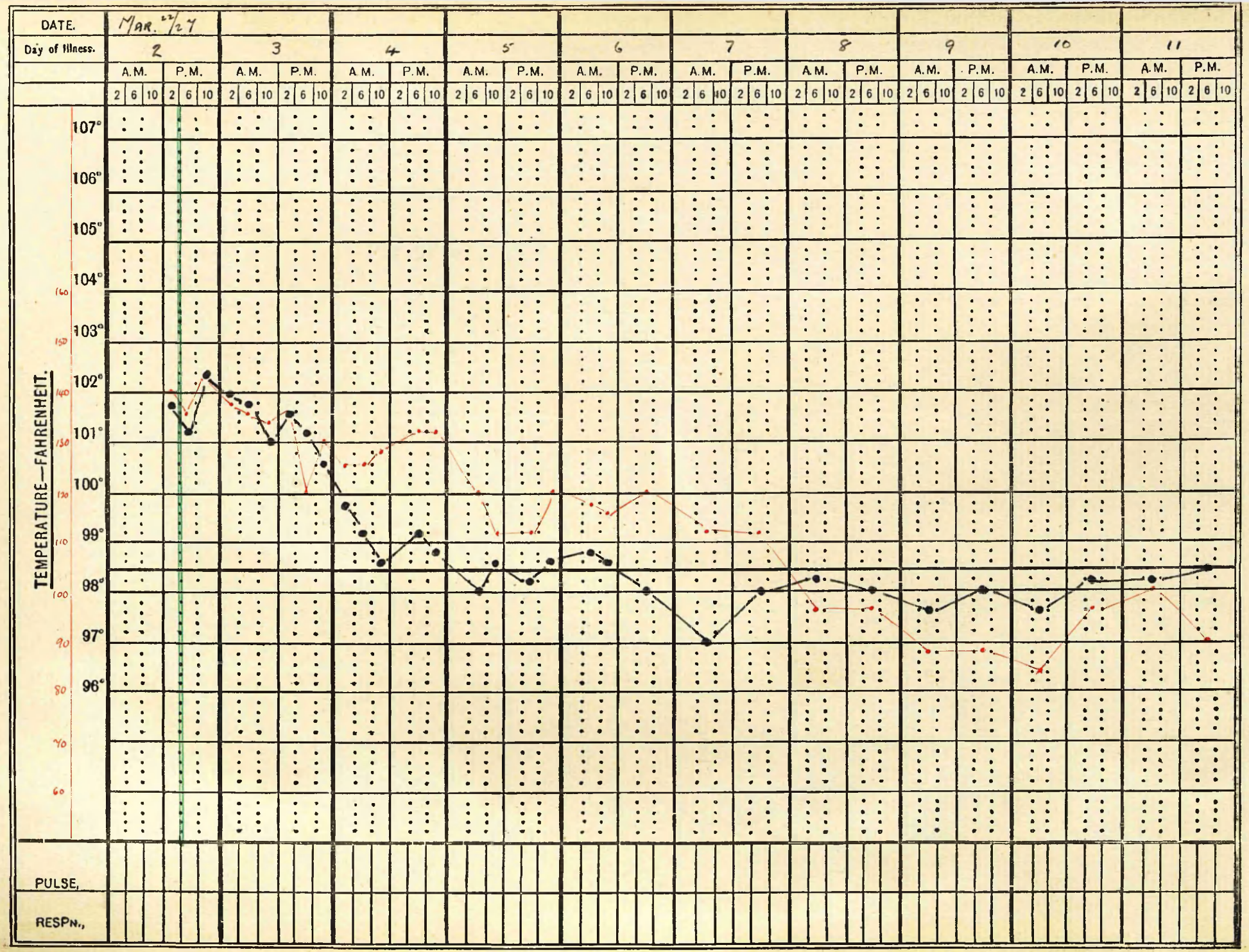
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
Mar. 27/24
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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102°
101°
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97°
96°
160
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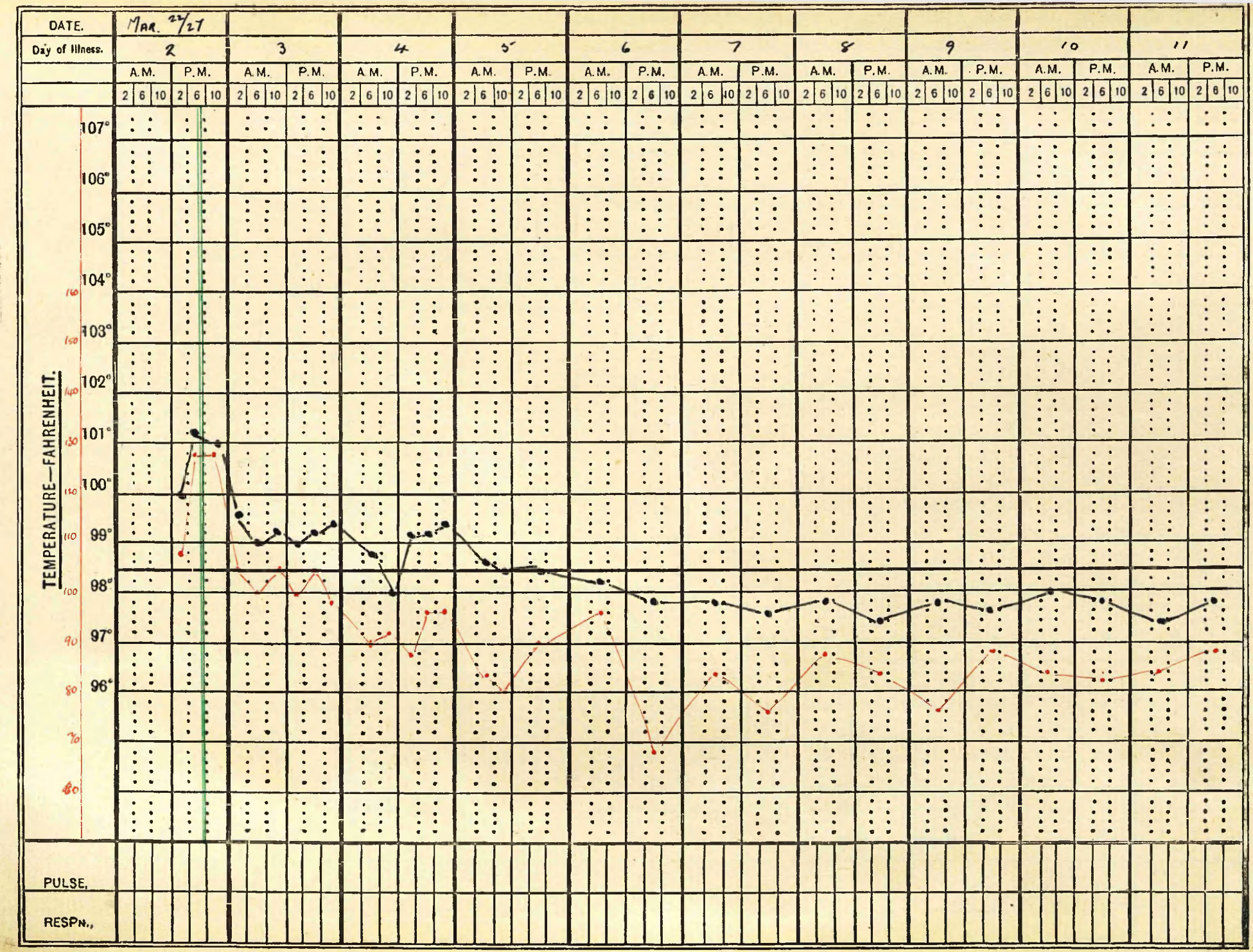
60
TEMPERATURE—FAHRENHEIT.
PULSE,
RESPN.,

107


DATE.
Mar. 27/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
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80
70
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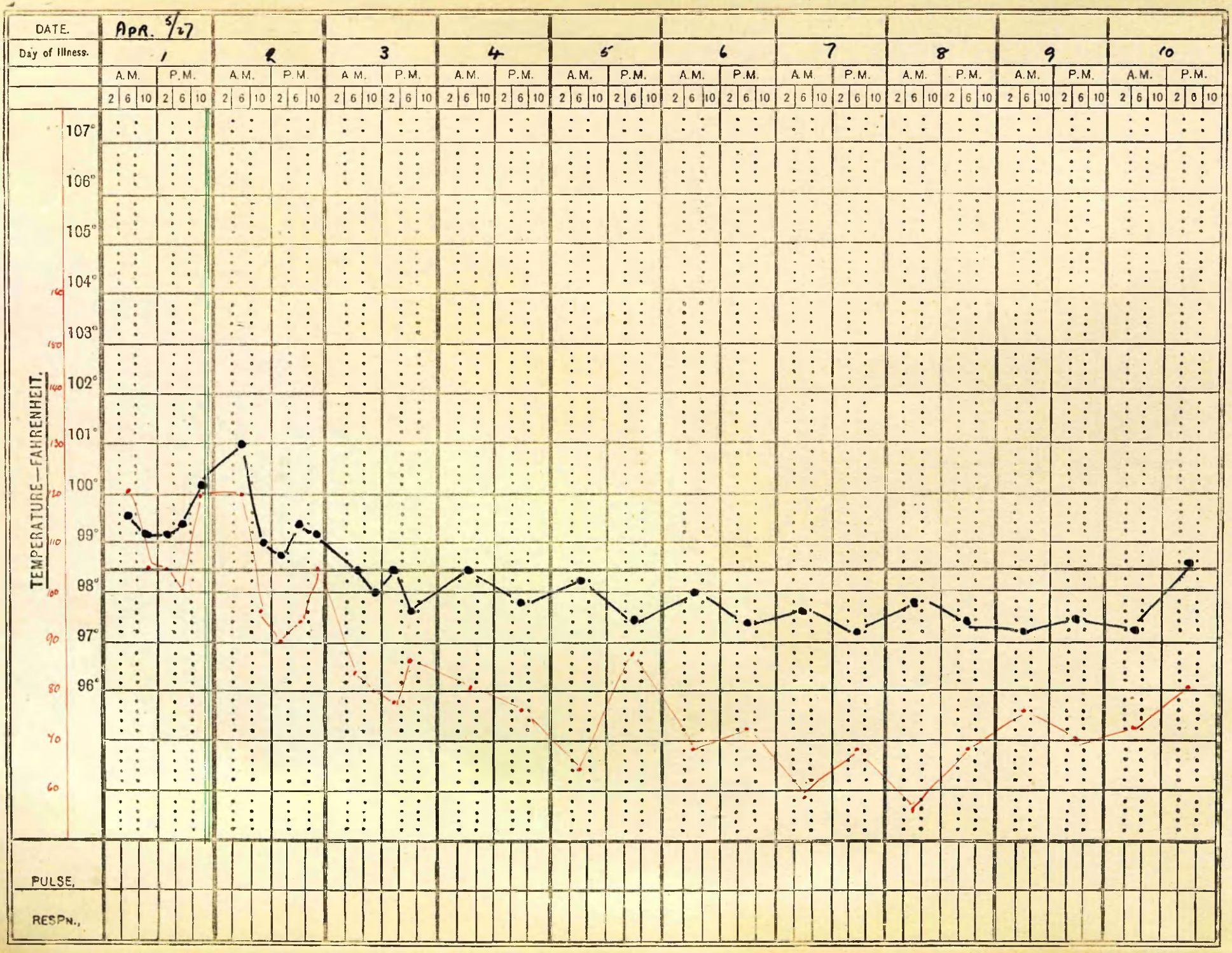
PULSE.
RESPN.,

108


DATE.
Apr. 5/27
Day of Illness.
1
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A.M.
P.M.
2 6 10
107°
106°
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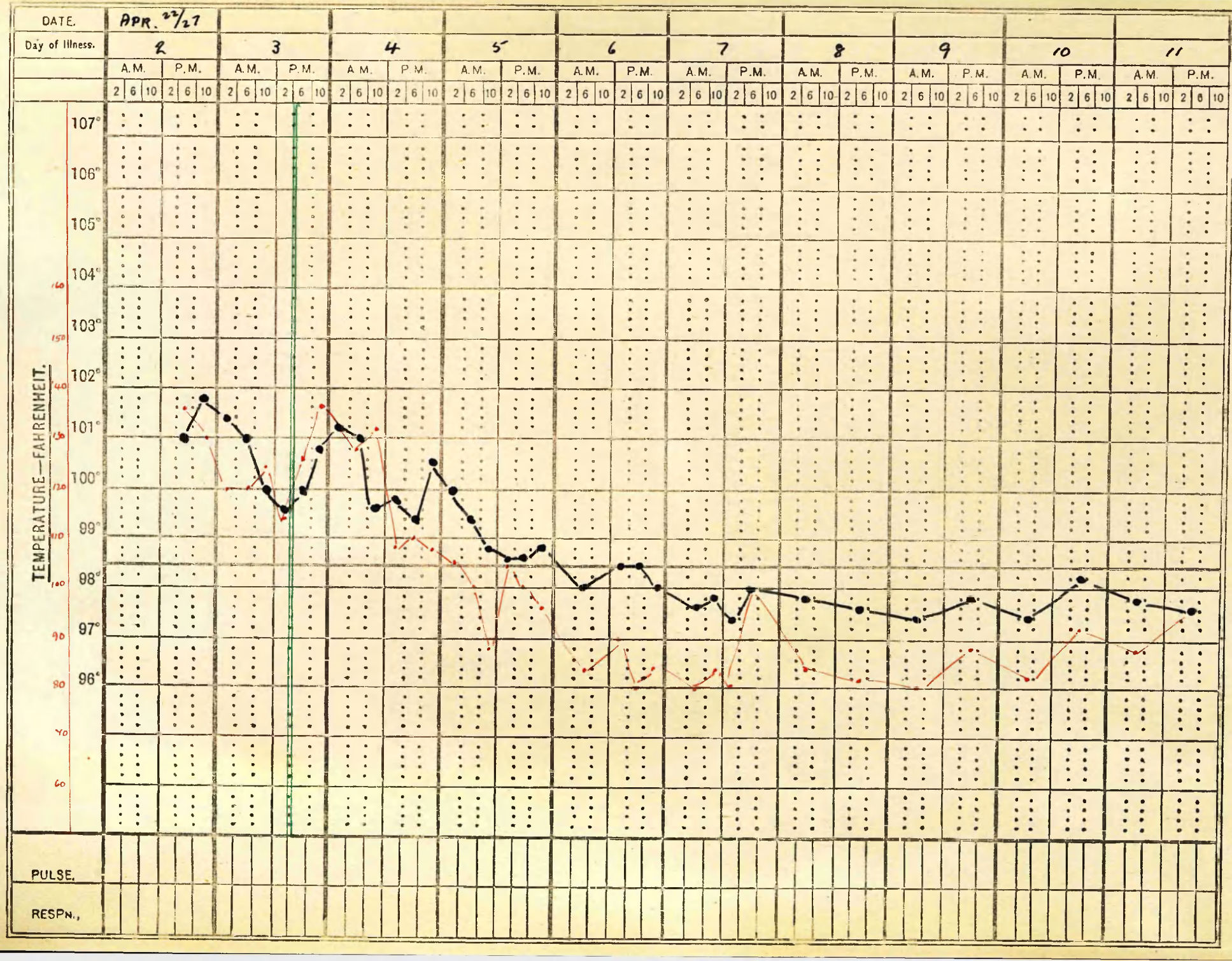
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
APR. 22/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
105°
104°
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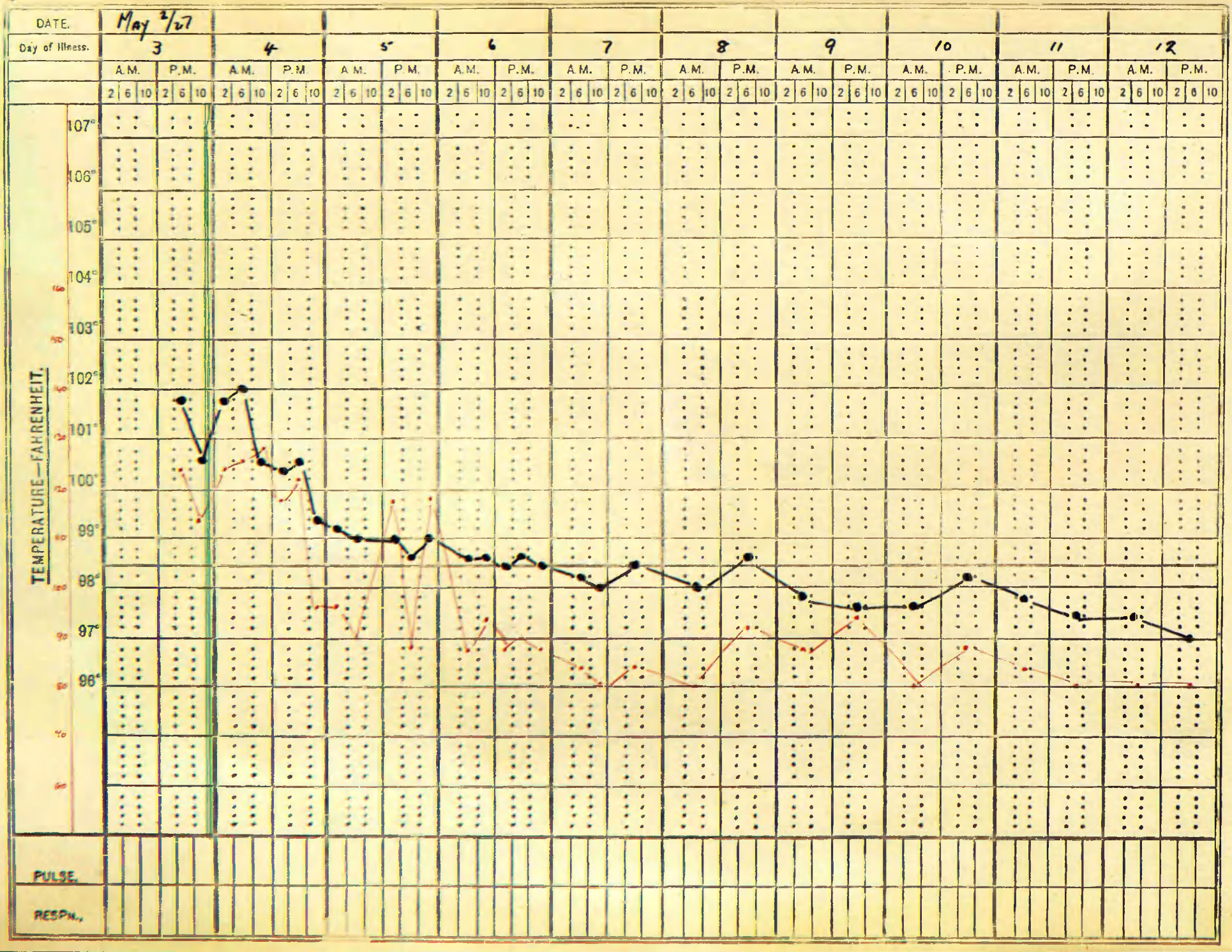
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

110


DATE.
May 2/27
Day of Illness.
3
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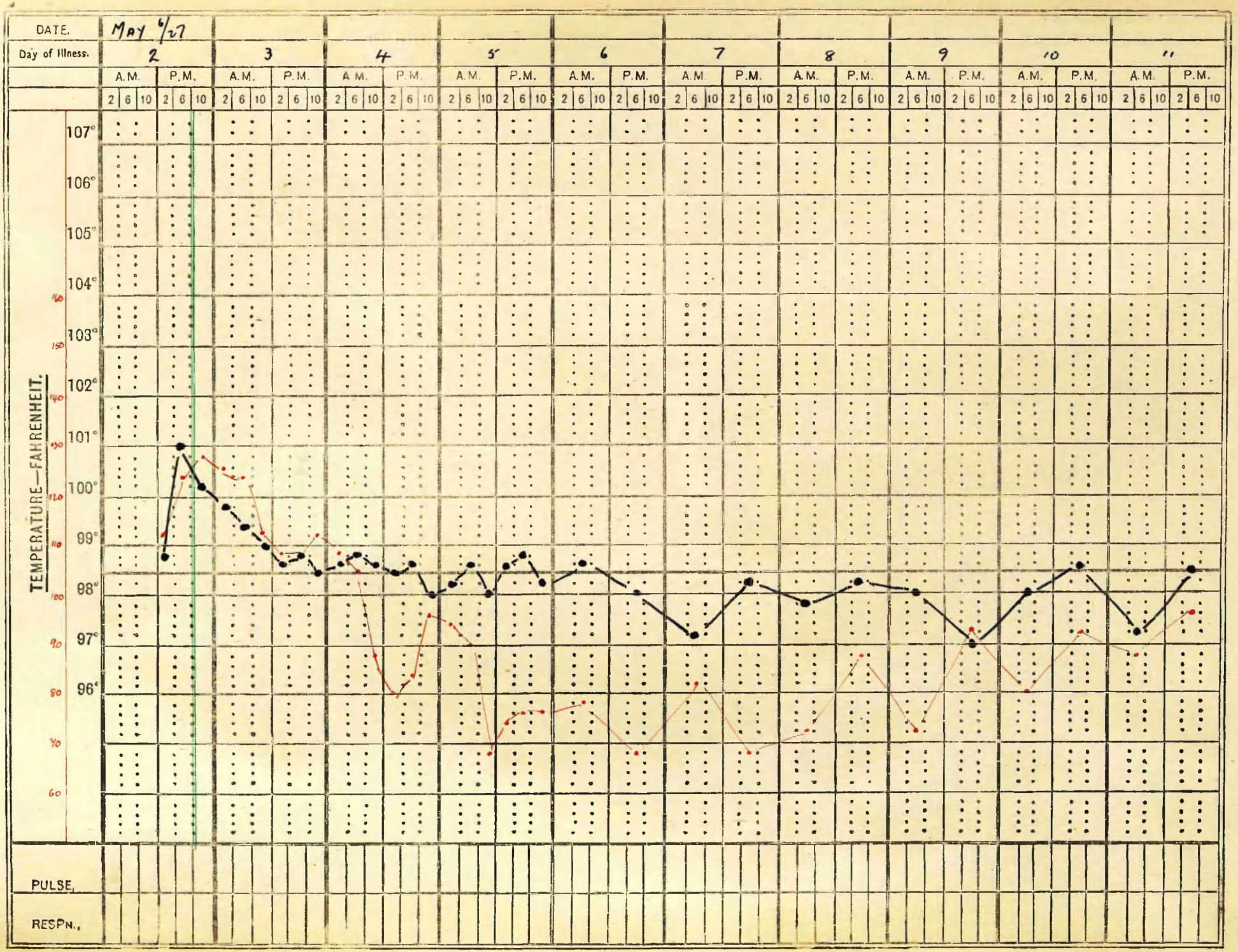
11
12
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
May 6/27
Day of Illness.
2
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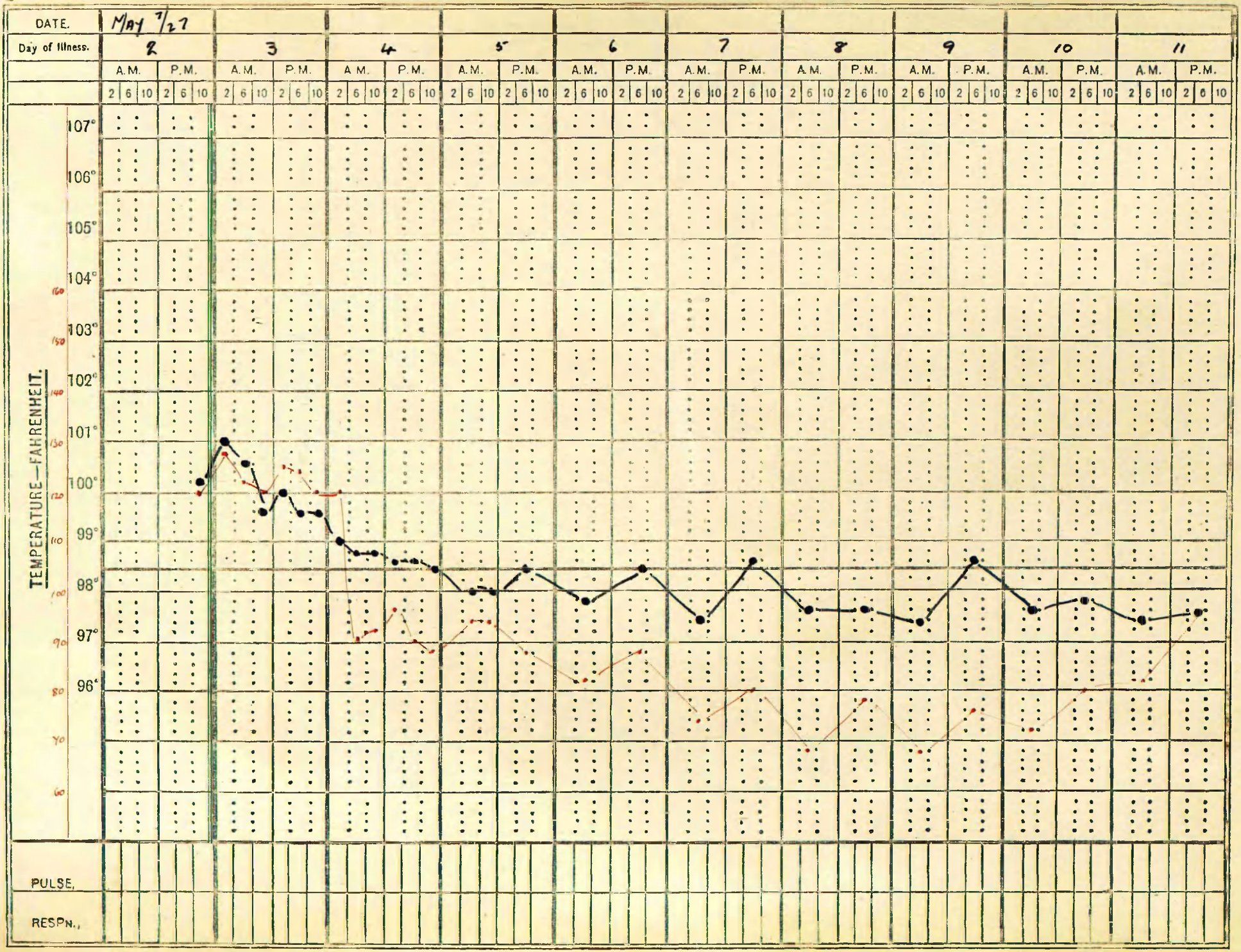
10
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,

112


DATE.
May 7/27
Day of Illness.
2
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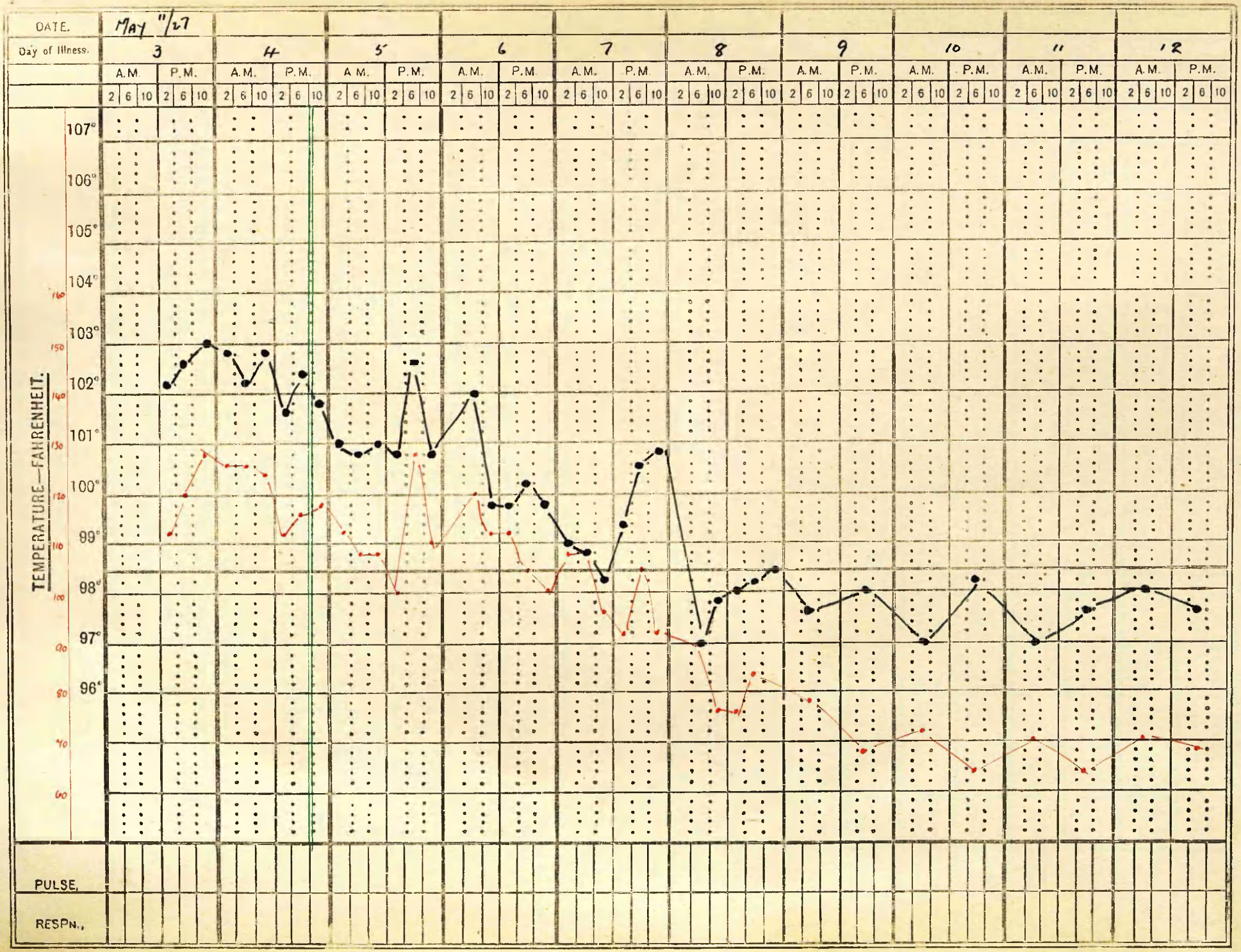
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May "/27
Day of Illness.
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12
A.M.
P.M.
2 6 10
107°
106°
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101°
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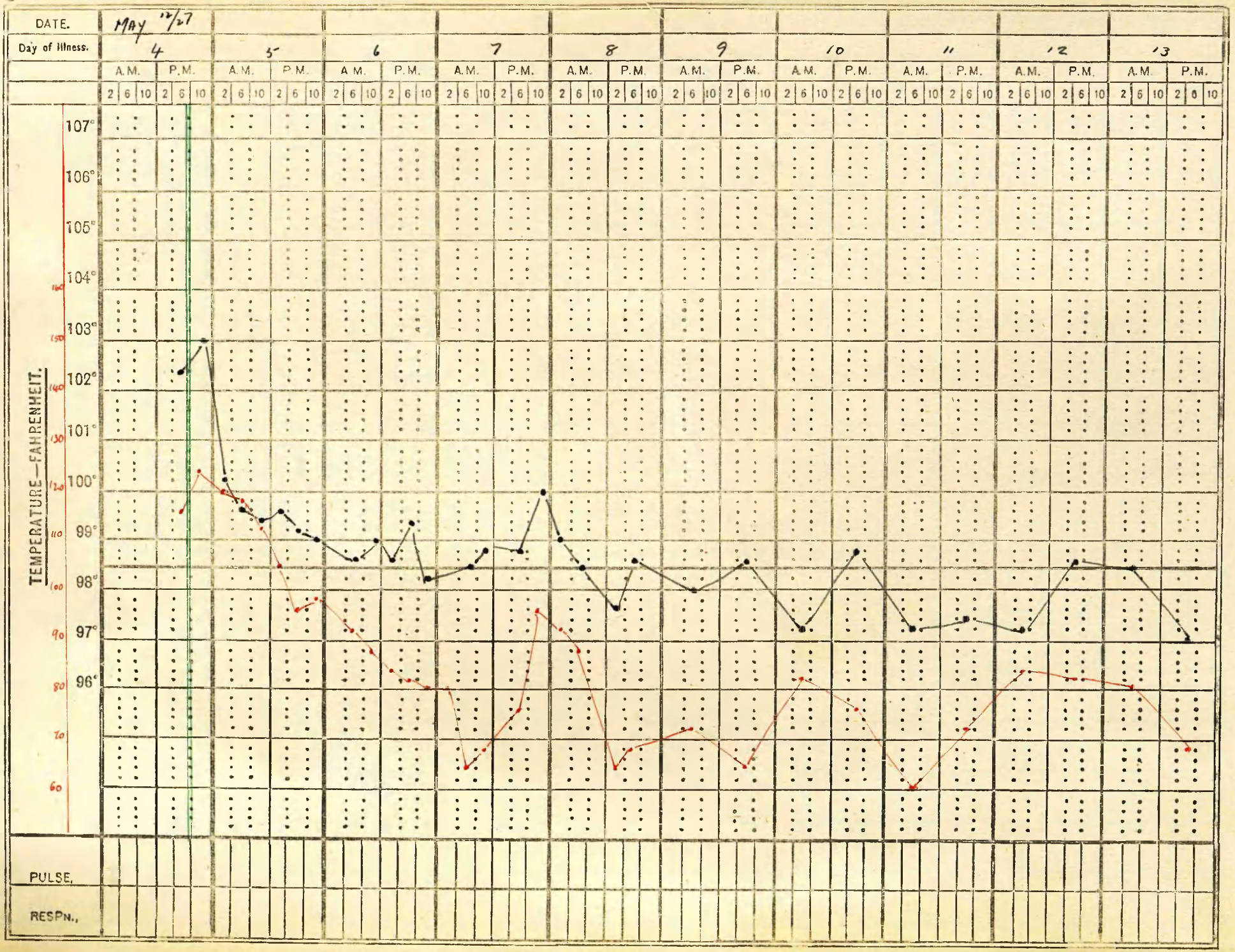
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.


DATE.
MAY 12/27
Day of Illness.
4
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12
13
A.M.
P.M.
2 6 10
107°
106°
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103°
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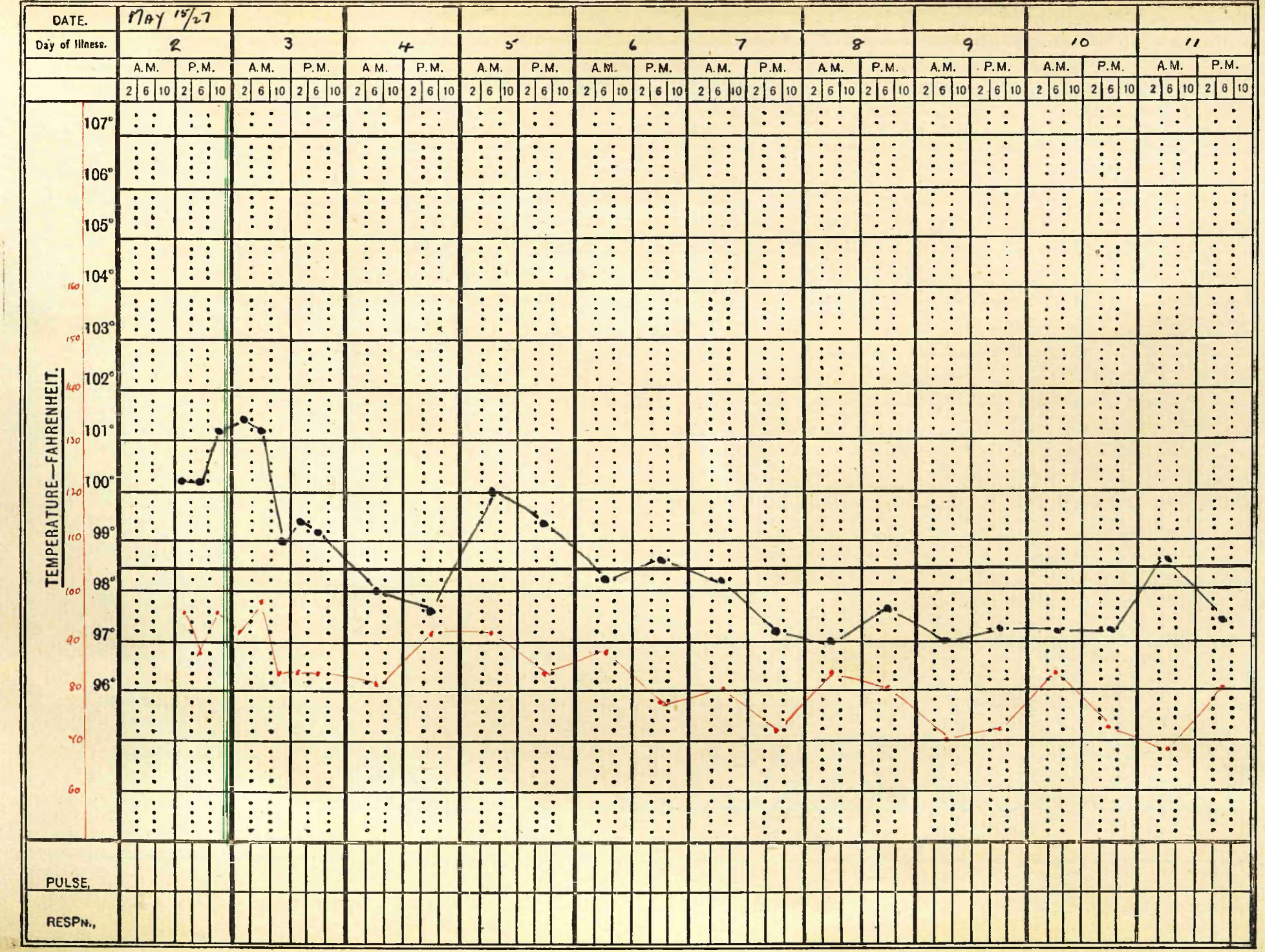
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May 15/27
Day of Illness.
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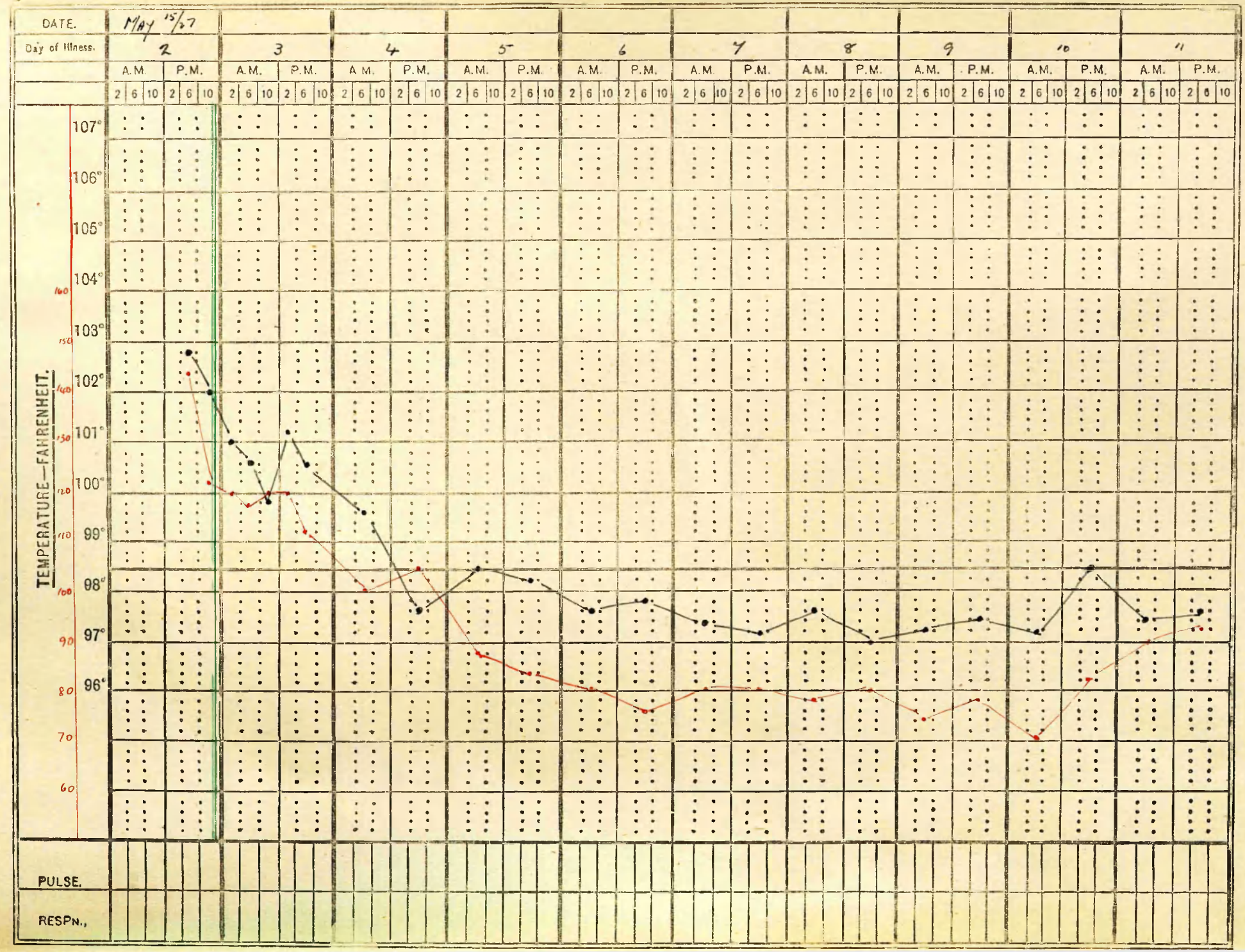
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
160
150
140
130
120
110
100
90
80
70
60
PULSE.
RESPN.,

116


DATE.
May 15/27
Day of Illness.
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A.M.
P.M.
2 6 10
107°
106°
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104°
103°
102°
101°
100°
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97°
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160
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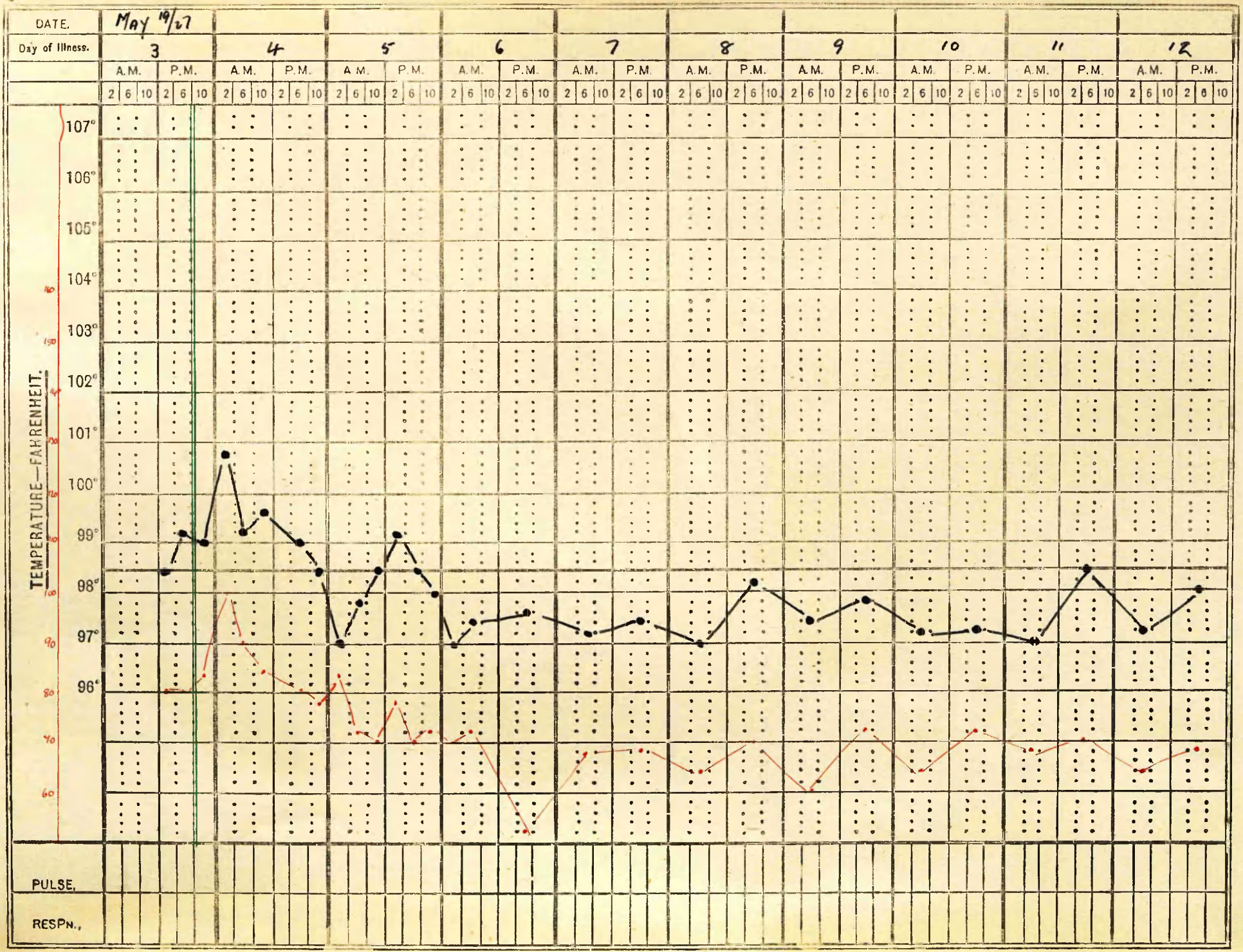
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
May 19/27
Day of Illness.
3
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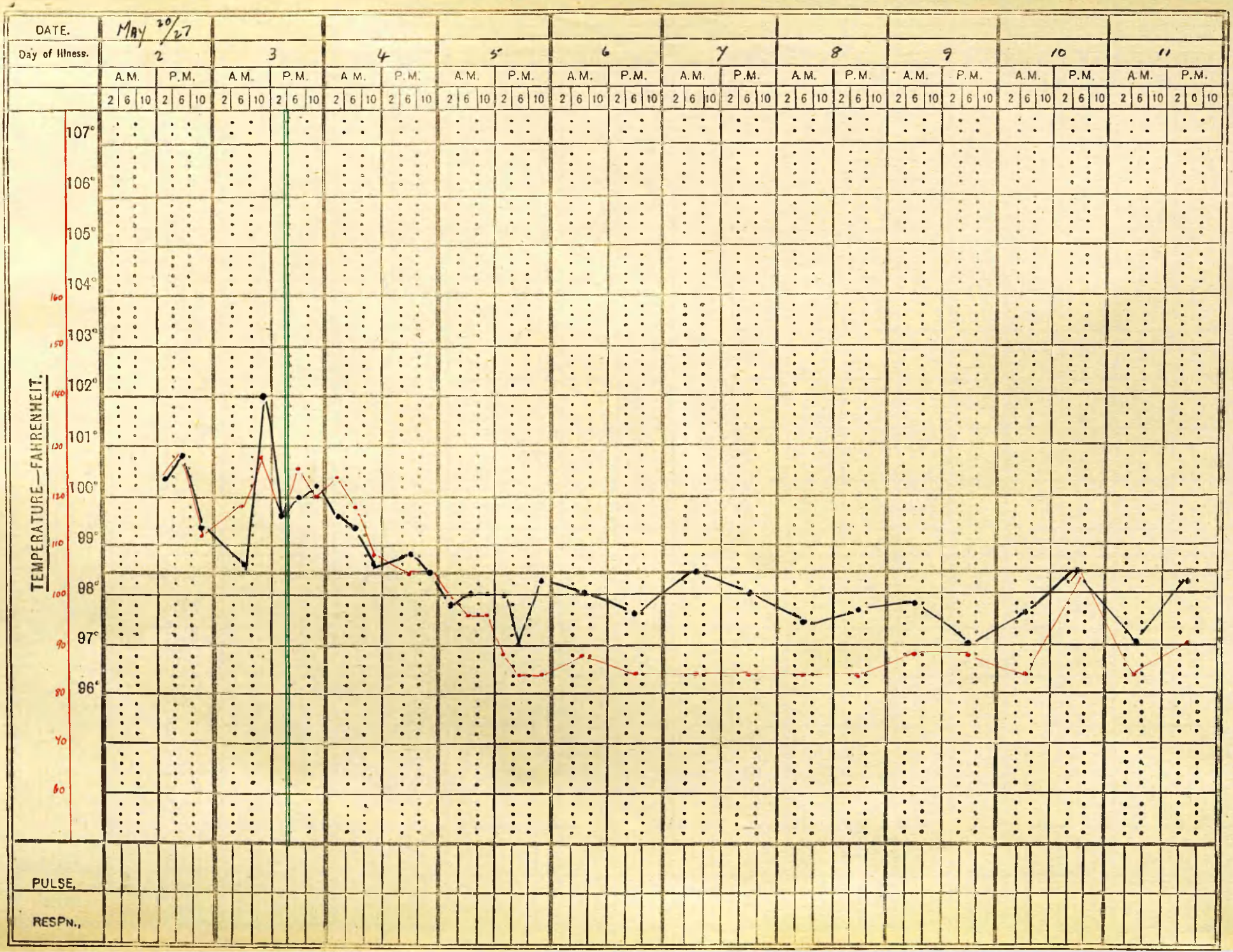
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
TEMPERATURE—FAHRENHEIT.
PULSE.
RESPN.,


DATE.
MAY 20/27
Day of Illness.
2
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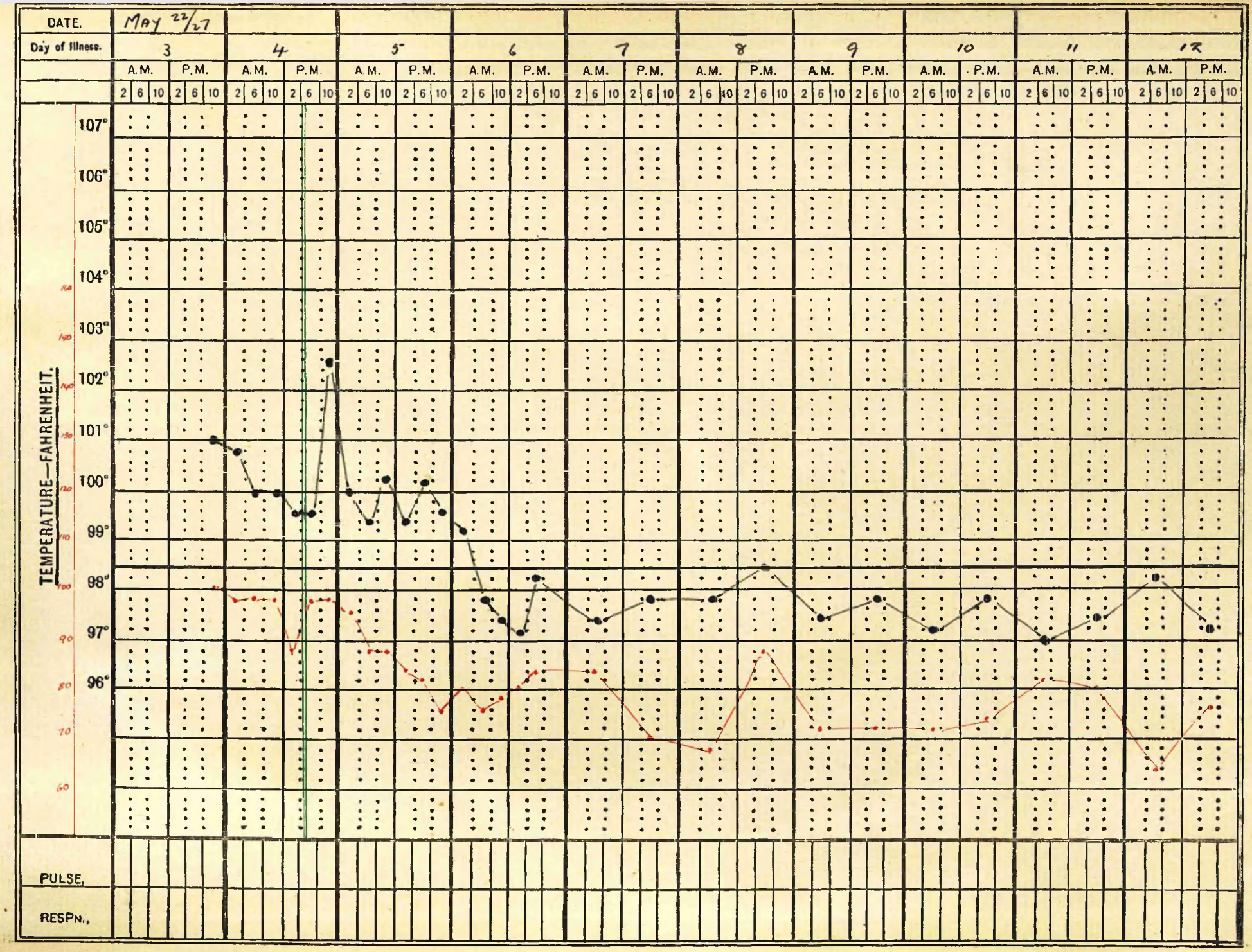
11
A.M.
P.M.
2 6 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
160
150
140
130
120
110
100
90
80
70
60
TEMPERATURE—FAHRENHEIT.
PULSE,
RESPN.,

119



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