THE SERUM FERMENTS AND ANTIFERMENT DURING PNEUMONIA.

STUDIES ON FERMENT ACTION. XXIV.

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Our knowledge concerning the factors that induce the crisis in pneumonia is still unsatisfactory, despite the innumerable attempts which have been made in the endeavor to advance our understanding of the processes by various immunological methods of investigation. There have been demonstrated only slight changes in the serum complement and serum antibodies before or after crisis; the opsonic and leucocyte activity, while increased, shows no striking difference; the infecting organism may show no change in its virulence or its resistance (Rosenow); and yet in a period of a few hours a phenomenon occurs, which in its sharp demarcation more nearly resembles a chemical reaction *in vitro* than a biological process *in vivo*. In so far as we may consider the involved tissue as being isolated from the general circulation, as Kline and Winternitz (1) have recently pointed out, the process must of necessity be largely local in its origin and effect. Recovery is coincident with the destruction not only of bacteria, but also with the removal of the great mass of fibrinous and cellular detritus. It is, therefore, in all of its essentials an autolytic process, and our hope of therapeutic results must be based not only on the idea of overcoming the infecting organism but also of favorably influencing the autolytic changes. The isolation of the lung tissue from the general circulation favors autolysis, for if the tissue were freely supplied with blood serum, with its great concentration of antiferment, no autolysis could take place.

Inception of Autolysis.

In a general way we can consider the factors that influence the inception of autolysis as depending on a balance between the amount of ferment, on the one hand, and the inhibiting elements, on the other, both of which are variables and subject to changes either through chemical or physical alteration. With the disintegration of the accumulated polymorphonuclear leucocytes, a large amount of a powerful polyvalent ferment is liberated, capable of dissolving the fibrin and cellular debris. This ferment is not active in the presence of blood serum because of the excess of antiferment. This inhibiting factor can be influenced either by a change in dispersion, whereby the unsaturated lipoids are rendered less disperse, *i. e.*, when the reaction becomes acid (Opie (2)); by an increased oxidation, as, for example, by iodine (3), whereby the unsaturated bonds of the antiferment are reduced and the antitryptic activity is lessened; by an increased metabolic demand on the lipoids, as, for instance, during starvation, when a marked fall in antiferment occurs (4); and by a saturation with an excess of ferment. During the course of the pneumonia the leucocytes are undergoing disintegration with a resulting liberation of ferment. The blood serum, on the other hand, is subject to various of the above mentioned factors which tend to lower the antiferment power (after the original toxic rise has occurred). We should therefore expect that at some moment the balance would be destroyed and autolysis actively commence. Almagià (5) has recently studied this relation and has called attention to the coincidence of evidences of autolysis with the crisis. He considers the very production of an autolyzing fluid as the factor which inhibits the further multiplication of the pneumococci, for he found that the growth of pneumococci was completely inhibited by autolyzing fibrin. We can thus readily see that the pneumonic process, apart from complications, is actually a self-limited one, for even if the organism is so virulent that it will readily kill the leucocytes this very property will set free a large amount of ferment in a short space of time and thus will shorten the course of the disease.

We must, however, take cognizance of another possible factor; *i. e.*, the question whether or not the blood serum itself may contain an increased amount of ferment derived from the tissue cells of the

body, which, mobilized, would be brought to bear on the diseased organ. That during the course of a pneumonia serum ferments may be found which digest lung tissue and placenta has repeatedly been noted.[1] These ferments are not specific; experiments which might be so interpreted are based on the fact that ordinary immunity reactions occur which by means of adsorption phenomena permit proteolysis of the serum proteins. Guggenheimer (6) has studied the problem in another way, in that he has determined the inhibitory or accelerating effect of the pneumonic serum on liver autolysis. He noted that pneumonic sera occasionally acted in an auxiliary way and regards this as evidence of a mobilization of cellular ferments. Other sera, however, showed a marked inhibiting effect, as did the normal serum.

Early during the course of antiferment investigations Ascoli and Bezzola (7) studied the conditions obtaining during pneumonia. With the Gross-Fuld method they noted an early rise in antiferment titer, with a decline after the crisis.

The serum investigations so far reported have lacked any quantitative basis, because the methods used to determine the amount of ferment and antiferment are largely qualitative. In order to obtain a more definite insight into the ferment-antiferment balance of the serum we have undertaken a study of a number of patients during the course of pneumonia.

The serum protease has been estimated by the amount of non-coagulable nitrogen formed per cc. of serum when emulsified with chloroform (8); the lipase by the usual ethyl butyrate method; and the antiferment titer by determining the amount of casein digestion by means of the Folin method, instead of the unreliable estimation by inspection of the precipitate. In the majority of the cases the type of organism has been determined by agglutination by means of specific sera.[2]

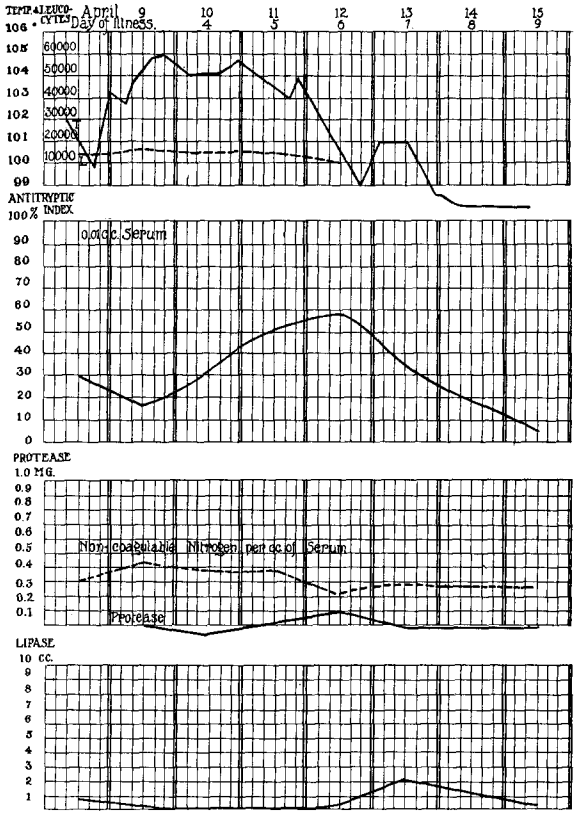
[1] Falls (Falls, F. H., *Jour. Infect. Dis.*, 1915, xvi, 466) has recently demonstrated such ferments in a series of cases. He concludes that the source of the ferments is not to be found in the leucocytes.

[2] These specific sera were kindly supplied by Dr. Cole of The Rockefeller Institute. We wish furthermore to express our appreciation to Drs. McCabe, Manier, and Weaver, and the members of their respective staffs of the City, Vanderbilt, and Industrial School Hospitals, who have placed their patients at our disposal for study and have facilitated our work in every way.

Case Records.

The following case records and their accompanying text-figures are typical of the relations.

Case 1 (19).—(Text-fig. 1.) J. H., male, colored, aged 28. Became sick Apr. 6, 1915, when he had a chill lasting a half hour, together with severe pain in both sides of chest. Entered hospital Apr. 7, 1915.



TEXT-FIG. 1. Serum changes during pneumonia (Case 1).

Physical Examination.—Well nourished colored man. Mucous membrane of mouth red, tongue coated, pharynx engorged. Pulse rapid. Lungs: diminished expansion on the left side, distinct tubular breathing, also vocal fremitus and dullness on percussion. Apr. 8, 1915. Urine negative except for a few granular casts.

The case progressed normally. On the 6th day the temperature began to decline and after a slight increase the following day reached normal the same evening.

The following facts will be noted from Text-fig. 1. The antiferment curve reached its maximum on the sixth day of illness, following which it showed a progressive decline. The protease reached a maximum on the sixth day; *i. e.,* when the temperature began to decline. At this time also the non-coagulable nitrogen showed a considerable drop. Following the fall in temperature the protease remained at a low level. The serum lipase declined progressively until immediately after the crisis when it increased almost to the strength of normal serum, with a following decline. The proteoses contained in the serum gave the following results (per 5 cc. of serum):

Date.	*mg.*
Apr. 8, 1915	0.25
" 10, "	0.21
" 13, "	0.13

The organisms isolated from the sputum agglutinated with serum of Type I.

Case 2 (16).—(Text-fig. 2.) J. W., male, colored, aged 18. Present illness began about 2 p. m., Mar. 16, 1915, with a chill and headache, aching of limbs and body, pain in left side and chest below the heart, accompanied with shortness of breath and expectoration of a dark brown sputum, and sometimes fresh blood. Admitted to the hospital Mar. 20, 1915.

Physical Examination.—Strong, well developed young negro. Head examination negative. Heart rapid; pulse rather weak and running in character. Blood pressure, systolic 98. Lungs: increased voice and breath sounds in both lower and middle lobes of right lung; grunting at the end of expiration; some bubbling râles over right lung anteriorly. Abdomen soft and slightly tender. Liver and spleen negative.

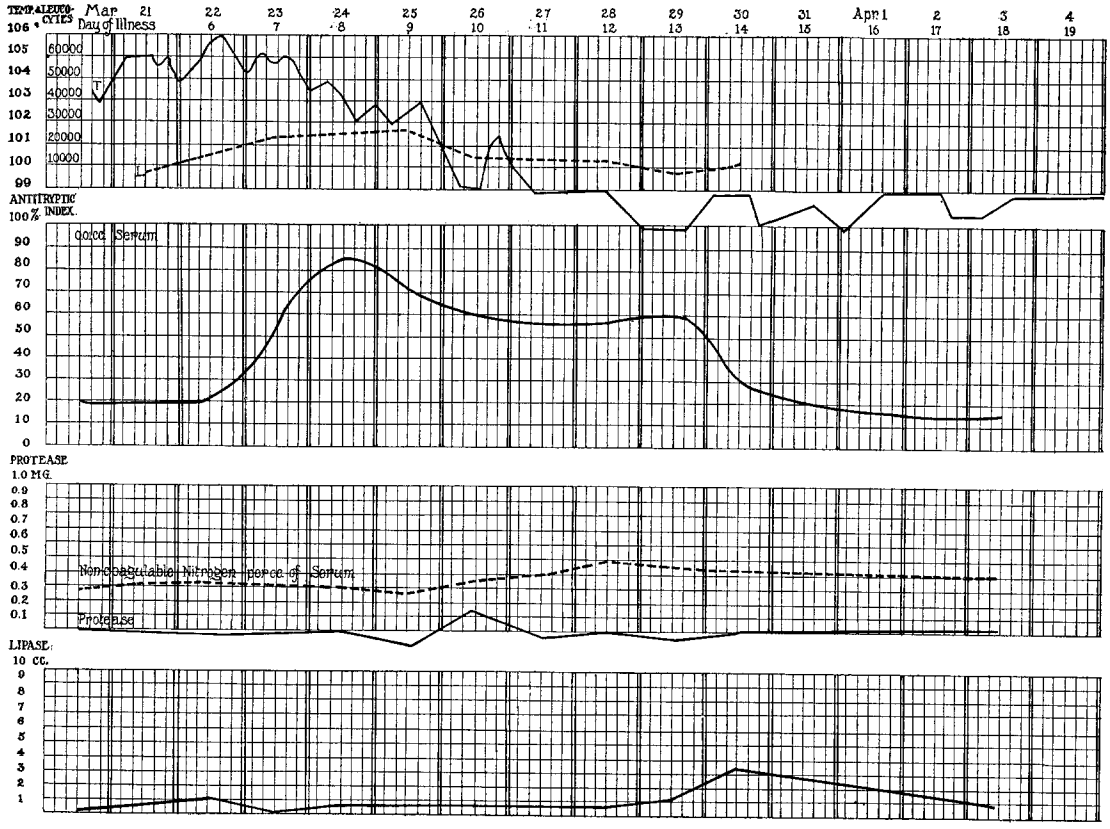
Pneumococcus isolated from the sputum agglutinated with serum of Type I.

On Mar. 23 the patient became delirious and remained irrational for the following 6 days, during which time it was necessary to restrain him in bed.

Text-fig. 2 shows that the greatest rise in antiferment occurred after the 6th day of illness and remained high until the 13th day. The non-coagulable nitrogen reached the maximum on the 12th day; after that it declined slowly. The protease change is quite striking. There was a lack of protease action during the entire time before the crisis. On the day before the crisis the total non-coagulable nitrogen of the serum incubated under chloroform

decreased from 0.27 to 0.17 mg. per cc. of serum. A control made by means of the Van Slyke method gave the following result, thus checking very well with the Folin determination:

	mg.
Amino nitrogen, 2 cc., direct	0.872
" " after incubating, 2 cc., direct	0.692
Loss	0.180 mg. per 2 cc.



TEXT-FIG. 2. Serum changes during pneumonia (Case 2).

On the following day, however, we noted a marked protease action, after which the ferment was again practically negative. The lipase reached the lowest titer on the 7th day, after which there was a gradual increase until the 14th day.

Case 3 (12).[3]—O. B., male, white, aged 18. Mar. 23, 1915, patient had a chill followed by a headache; pain in chest, especially on the right side; coughed a good deal, expectorated colored sputum. Admitted to the hospital Mar. 25, 1915.

Physical Examination.—Strong, robust boy. Head, heart, arteries, and pulse negative. Lungs: increased fremitus and voice sounds, marked increase over the right lobe, breath sounds also increased, percussion very flat. Abdomen slightly tender. Liver and spleen not palpable. Blood pressure, systolic 128. Urine contained albumin and granular casts. Clinical course was uneventful. The temperature fell by lysis, reaching normal on the 8th day.

The antiferment titer, which was relatively low, reached a maximum on the 6th day after which it declined progressively. The maximum of non-coagulable nitrogen was reached on the 6th day, declining slowly after that time. The protease was strongly positive on the 6th and 8th days of illness, corresponding to the period of lysis. The lipase reached the maximum on the 6th day, after which it increased almost to normal.

Case 4 (17).—G. T., male, white, aged 18. Patient was well and at work when without seeming cause he had a hard chill about 3 p. m. on Apr. 3, 1915. The chill continued through the night and until about 9 o'clock the next morning, together with pain in axillary region. After the chill he states that he perspired; had dyspnea; developed a cough at the time of the chill which became worse after the chill. Admitted Apr. 5, 1915.

Physical Examination.—White boy, fairly well nourished. Head negative; throat somewhat engorged. Heart normal; P. M. I. in the fifth interspace, nipple line; pulmonic second accentuated; arteries in good condition. Inspection shows decreased expansion on the left side and lower lobe both in front and behind; increased tactile fremitus; vocal resonance and tubular breathing on auscultation. Vocal fremitus is at first absent over the lower lobe on the left side, but is noted on change of position and after coughing. Abdomen normal. Urine negative. The crisis occurred on the 7th day.

In this case the antiferment did not reach a maximum until the day following the crisis, after which it declined. The non-coagulable nitrogen was never very high and showed little change. The protease before the crisis was negative; at the time of the crisis it became normal. The lipase showed the usual change. Proteoses per 5 cc. of serum:

Date.	*mg.*
Apr. 6, 1915	0.14
" 9, "	0.0

[3] This case was from the City Hospital.

Case 5 (20).[4]—R. M., male, colored, aged 20. Present illness commenced the last week in March with pain in the right side. He had no chill but vomited the next day. Since he became ill he has been in bed at a railroad camp; is somewhat constipated; has coughed a good deal, expectorating much sputum, sometimes blood tinged; has pain, now worse than at the onset on each inspiration and when he coughs, more especially over abdomen and lower chest on right side; never had a chill.

Physical Examination.—Negro, poorly nourished. Head negative. P. M. I. inside of nipple line in fifth interspace; sounds are regular, no murmurs; second pulmonic accentuated; pulse regular and full, and of good volume. Blood pressure, systolic 103, diastolic 60. Lungs: respiration rapid, decreased expiration on the right side; tactile fremitus increased over right lower lobe together with decreased voice sounds, dullness, and tubular breathing. There is a friction sound behind and over the right lower lobe. The middle lobe of the right lung is quite flat with some tubular breathing, increased voice sounds, and fremitus. The left lung is normal. The abdomen is rigid and tender and the lymph glands especially are enlarged. Apr. 9, 1915. Urine examination: albumin negative; numerous casts. Apr. 14, 1915. Some hyaline and granular casts. Apr. 8, 1915. Blood examination: red cells 4,800,000; hemoglobin 70 per cent. Apr. 9, 1915. Condition worse; temperature has risen to 103° F., and pulse to 140. Examination shows no change over right middle lobe; right lower lobe still shows impairment with bronchovesicular breathing and increased voice sounds, except the lower part in posterior axillary line, where there is flatness with diminished breath and voice sounds. The upper right lobe shows slight impairment with a tendency to bronchovesicular breathing; posterior shows nothing as yet definite. Left lung clear throughout. Heart sounds rapid and of only fair quality, though the second pulmonic is still accentuated. Needle was inserted next to right inner area but no fluid obtained. Blood pressure, systolic 116. Apr. 10, 1915. Patient much improved, temperature having fallen this morning to 99.4° F. and pulse to 110. Patient expectorated yesterday considerable brownish material. Examination to-day shows much less impairment over middle lobe except in region of anterior axillary line where it is still flat with tubular breathing and exaggerated voice sounds; many moist râles over whole lobe. Lower lobe is clearing up except at base where there are still diminished breath sounds and voice sounds. Blood pressure, systolic 105, diastolic 60. Apr. 11, 1915. General condition excellent. Temperature is normal and pulse 100. Examination shows but little impairment over middle lobe, with only slight voice sounds and breath changes. Apr. 12, 1915. Blood pressure, systolic 95.

As will be noted, the patient entered the hospital practically at the end of his illness, the antiferment and non-coagulable nitrogen declining very rapidly, while the protease tended to rise. 5 cc. of serum contained 0.2 mg. of proteoses on April 11, 1915.

[4] This case was from the Vanderbilt Hospital.

Case 6 (*21*).[5]—H. H., male, white, aged 18. In 1913 patient had rheumatism in both arms and legs; was ill in bed about a month. Present illness began Apr. 6, 1915, with pain on left side in nipple region. Apr. 7, 1915. Had chill and high fever, expectorated, cough was dry and hacking. Since then cough has been deep seated and he has expectorated more than at first. Entered hospital Apr. 9, 1915.

Physical Examination.—Fairly well nourished. Head negative. P. M. I. normal, arteries soft and compressible, accentuated pulmonic second sound. Lungs: deficient expansion on left side, decreased fremitus over left upper lobe in front, dullness and feeble breath sounds over left upper lobe, tubular breathing in the left axilla. Blood pressure, systolic 95. Crisis on the 8th day. General condition excellent throughout.

The antiferment titer reached a maximum on the 6th day, after which it declined until the day following the crisis. The non-coagulable nitrogen reached its maximum on the 5th day, at which time the protease was lowest. The protease reached + 0.02 mg. per 1 cc. on the day following the crisis. The lipase showed the usual curve. Proteoses per 5 cc.:

Date.	*mg.*
Apr. 9, 1915	0.19
" 13, "	0.12
" 14, "	0.13

Pneumococcus of Type I was isolated from the sputum.

Case 7 (*18*).—T. A., male, colored, aged 30. Present illness began with headache about a week ago. On Apr. 5, 1915, 3 or 4 days following headache, he had chill about 10 a. m., which lasted for about 3 hours; no vomiting, but fever following chill; pain in the right side. Admitted Apr. 6, 1915.

Physical Examination.—Well nourished colored man. Head negative; some pyorrhea; pulse 120, but full in volume. P. M. I. fifth interspace mammary line; no murmurs. Increased fremitus and voice sounds on the right side in front, no dullness on percussion. Abdomen rigid, otherwise negative.

The patient showed a rather irregular course. On the 7th day the temperature dropped to normal, but he complained of a severe sore throat the same evening and a marked tonsilitis was noticed. This continued for 3 days. After this time the temperature again reached normal. Apr. 17. Pulse 118, respiration 30. Tonsils engorged, with some exudate. Lungs: fremitus increased over upper and middle right lobes; very dull; occasional moist râle. Breath sounds bronchial. This case is rather interesting because of the period on the 7th day when it appeared clinically that the patient was having a crisis.

At this time the non-coagulable nitrogen had decreased and the protease reached + 0.05 mg. per 1 cc. The antiferment also

[5] This case was from the City Hospital.

showed a slight fall from the height reached on the previous day. Then, however, the tonsilitis set in and we found the antiferment continuing at a high titer, while the non-coagulable nitrogen increased again and the protease fell. The resolution seems to have been delayed, for the clinical signs began to clear only after April 17, when the protease again reached + 0.05 mg. per 1 cc. of serum. The proteoses determined per 5 cc. of serum gave the following figures:

Date.	*mg.*
Apr. 6, 1915	0.125
" 14, "	0.26
" 16, "	0.13
" 18, "	0.00

Case 8 (14).[6]—W. A., male, colored, aged 35. Present illness began Mar. 31, 1915, with pain in the left side, coughing, and expectoration of a bloody sputum; he lost his appetite but has not been nauseated; there was diarrhea; no chill. Admitted to hospital Apr. 1, 1915.

Physical Examination.—Well nourished young man. Teeth bad. Heart normal; second pulmonic accentuated. Lungs: tactile fremitus normal on both sides, except in front on left side where it is increased downward and outward from the left nipple line. Percussion is normal except for the above mentioned area, which is very dull. On auscultation, vocal fremitus is normal except over the same area where it is increased; there is bronchophony and tubular breathing on inspiration and expiration, together with coarse râles. Abdomen is negative. Blood pressure, systolic 90 and diastolic 50. Urine shows few hyaline and granular casts. Apr. 1, 1915. Red blood cells 5,000,300. Apr. 4, 1915. Condition good. Temperature dropped suddenly to normal at 9 a. m., pulse and respiration dropping with it. Signs over original area practically cleared up, beyond moist râles. No impairment and no tubular breathing; no signs over rest of lower lobe, beyond a few râles. Over left upper lobe there is flatness, with exaggerated tactile and voice frictions and bronchial breathing; moist râles are heard over this area. Blood pressure, systolic 80, diastolic 50. Apr. 5, 1915. Temperature went up again last evening to 101° F. Examination this morning shows complete consolidation of the upper lobe with exaggerated tactile fremitus, vocal resonance, and bronchial breathing; original area shows no change in signs. Abdomen quite distended. Apr. 6, 1915. Temperature down around 99° F., pulse slow and of better volume. Patient is resting better. Pain in side not severe; signs still present on left side. Blood pressure, systolic 95, diastolic 60. Apr. 7, 1915. Blood pressure, systolic 80. Apr. 8, 1915. General condition good. Temperature has been practically normal for last 2 days. Signs over lower left lobe have practically cleared up; there is some slight impairment over left upper lobe with bronchovesicular breathing and a few râles. Apr. 11, 1915. Condition good. Temperature has been normal

[6] This case was from the Vanderbilt Hospital.

now for almost 4 days. Examination of lung to-day shows no impairment or evidence of previous trouble except occasional râles at end of inspiration.

The antiferment curve reached its maximum at the time the temperature first fell to normal. It is quite evident, however, that at this time the patient had no crisis, for the leucocytes continued to rise until the following day. The non-coagulable nitrogen, however, was much lower after the fifth day of illness. The protease was positive on the sixth and ninth days of illness; after that time the patient made an uneventful recovery. The lipase was rather high throughout.

Case 9 (29).[7]—H. G., male, colored, aged 35. Illness began Apr. 6, 1915, when he began to cough a great deal, which caused pain in left side; expectorated much thick brownish sputum; had no chill. Entered the hospital Apr. 11, 1915.

Physical Examination.—Icteric; mucous membrane of mouth red; tongue coated; heart and arteries normal. Lungs: left lung shows deficient expansion, tactile fremitus increased, and large râles and spoken voice sounds heard in both upper and lower lobes, together with dullness on percussion. Abdomen negative. Reflexes normal.

This patient is the only one in the series that we have studied who showed a constant amount of protease in the serum during the disease and showed no change during the crisis, unless it was a slight fall. The antiferment remained high even after the crisis. The lipase remained low throughout. Proteoses per 5 cc. of serum:

Date.	*mg.*
Apr. 16, 1915	0.21
" 17, "	0.12

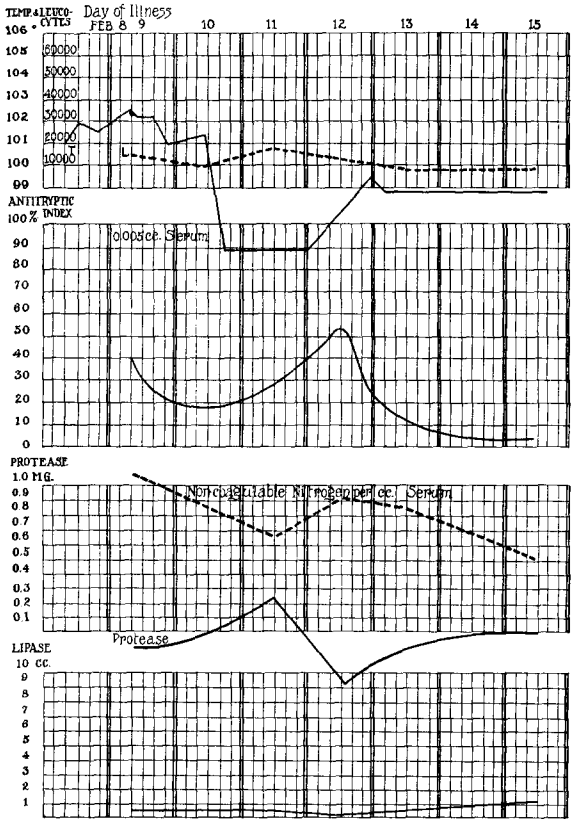
Case 10.[8]—(Text-fig. 3.) J. M. J., male, white, aged 40. Became ill Jan. 31, 1915, when he had a chill. Entered hospital Feb. 5, 1915.

Physical Examination.—Typical right lower lobe involvement. Urine contained numerous casts. White blood count 10,200. Sputum contained numerous pneumococci (type not determined). The patient showed evidence of profound intoxication, was stuporous, with rapid pulse and respiration. On the 10th day the temperature dropped by crisis, but the physical condition, especially the pulse rate, continued unfavorable. From the 9th to the 12th day the patient was delirious. After the 12th day the recovery was rapid.

[7] This case was from the City Hospital.

[8] This case was from the City Hospital.

The course of the disease was marked by a rather low leucocytosis and a large amount of non-coagulable nitrogen in the serum. The temperature fell as the amount of protease increased, but there was considerable intoxication for the three days following, as evidenced



TEXT-FIG. 3. Serum changes during pneumonia (Case 10).

by the increase in antiferment, the drop in protease, and the rise in non-coagulable nitrogen. The lipase began to return toward normal after this second period of intoxication.

Case 11 (22).[9]—E. H., male, colored, aged 30. Patient came to hospital because of pain in lower right chest, which increased on deep inspiration; this was first noted Apr. 4, 1915, when coughing accompanied pain. Apr. 7, 1915.

[9] This case was from the City Hospital.

Had a chill and headache since that time. Admitted to the hospital, Apr. 9, 1915.

Physical Examination.—Head negative. Heart: apex slightly down and out from the normal point; no murmurs; second pulmonic increased; pulse full, rather hard but regular. Lungs: right, slight dullness of lower lobe in front; no increase in voice sounds and tactile fremitus; left lung normal. Blood pressure, systolic 110, diastolic 65.

There was a progressive rise in the serum protease, reaching a maximum on the seventh day of illness, at which time the non-coagulable nitrogen had largely decreased. The antiferment decreased after the seventh day. Proteoses per 5 cc. of serum:

Date.	*mg.*
Apr. 12, 1915	0.13
" 13, "	0.30
" 14, "	0.29
" 15, "	0.15

Pneumococci from sputum agglutinated with serum of Type I.

Case 12 (23).[10]—G. F., male, colored, aged 20. Apr. 4, 1915. Pain in back and left side on breathing; no chill; has had some fever and expectorates blood tinged sputum; some coughing; shortness of breath. Entered hospital Apr. 11, 1915.

Physical Examination.—Eyes and head negative. Arteries soft, heart normal. P. M. I. fifth interspace inside of nipple space. Lungs: dullness, tubular breathing, increased voice sounds, tactile fremitus over left lower lobe, friction sound heard over left lower chest. Abdomen rigid. Liver and spleen not palpable, otherwise normal.

The patient became irrational and delirious the second day after admission to the hospital. On the 11th day of illness the pneumonic process involved the upper lobe on the same side, evidenced by area of tubular breathing and dullness. The patient died on the 15th day. No autopsy was obtained. A pneumococcus agglutinating with serum of Type II was obtained from the sputum.

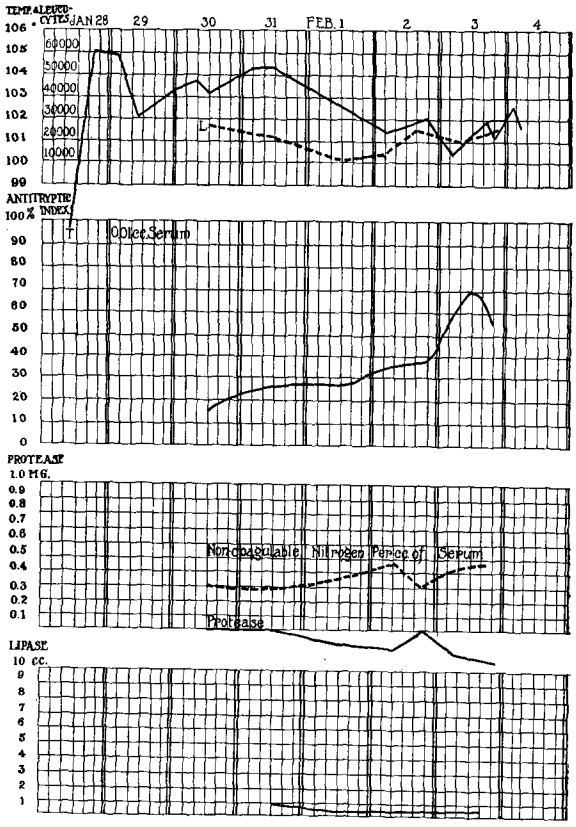
There was a rather constant increase in antiferment, which reached a maximum on the eleventh day and remained high after that time. The protease was low during the course of the disease but showed a gradual rise. The non-coagulable nitrogen remained relatively low throughout. Proteoses per 5 cc. of serum:

Date.	*mg.*
Apr. 12, 1915	0.1
" 16, "	0.0

[10] This case was from the City Hospital.

Case 13.[11]—(Text-fig. 4.) J. H. D., male, colored, aged 14. Jan. 28, 1915, 3 a. m. Became suddenly ill with a severe chill and pain on the right side of chest. Has coughed for the past few days. Admitted to hospital 9 a. m., Jan. 28, 1915.

Physical Examination.—Well nourished negro boy. Physical findings negative. No evidence of consolidation. White blood count 40,000. Jan. 29. Dullness and bronchial breathing were noted over entire right lung. The patient became very restless and coughed considerably. Jan. 30. All evidences of a complete consolidation of the entire right lung were present. There was con-



TEXT-FIG. 4. Serum changes during pneumonia with fatal termination (Case 13).

siderable pain and restlessness. Feb. 3. In the morning the patient showed definite signs of improvement, was quiet, and numerous large râles were noted over the involved area. During the following night, however, he became much worse and died at 5.30 a. m.

[11] This case was from the Vanderbilt Hospital.

Data from the Postmortem Protocol.—Body is that of a negro boy 14 years old, 172 cm. in length, well developed, and well nourished.

Lungs.—The right lung weighs 1,080 gm. The surface is smooth with the exception of the posterior part of upper lobe. There are many soft, friable adhesions. There is a small amount of amber-colored fluid in the pleural cavity. The lung when removed from the chest maintains its form. There are definite areas of consolidation in the lower part of the upper lobe. The middle lobe is free. On section through these consolidated areas the surface yields very little fluid and the lung tissue is definitely consolidated, of a grayish appearance, and around the margins of each there is a red zone. The left lung weighs 740 gm. The pleura is smooth. The upper lobe is normal. The lower lobe shows areas of consolidation similar to those described in the right.

Anatomical Diagnosis.—1. Lobar pneumonia of both lower lobes and bronchopneumonia of the right upper lobe. 2. Fibrinous pleuritis. 3. Acute splenitis. 4. Fatty changes and cloudy swelling of the liver, kidneys, and myocardium.

It will be seen from Text-fig. 4 that there was a progressive increase in the non-coagulable nitrogen until the evening of February 2, when a fall occurred. At this time there was also a distinct change in the ferment, so that on incubation a loss of non-coagulable nitrogen no longer occurred, although the serum did not actually become proteolytic. Instead, the non-coagulable nitrogen again increased and the ferment fell while the antiferment increased markedly. It will be observed that clinically the patient was in good condition during the night and morning after the temporary fall in non-coagulable nitrogen and the rise in ferment. The lipase showed simply a continued decrease.

Case 14.[12]—H. M., male, colored, aged 30. Became ill with chill and thoracic pain on Dec. 11, 1914. Entered hospital Dec. 15, 1914.

Physical Examination.—Breath sounds diminished on left side, with vocal fremitus increased over right upper lobe posteriorly. Pulse rate 108 to 120. Heart normal. Patient continued to run a typical course and the temperature dropped to normal on the 9th day, the respiration dropping from 38 to 24, and the pulse rate from 132 to 108 from the afternoon of the 19th to the morning of the 20th day. The temperature, however, again rose and continued to be irregular. Dec. 28, 1914. Patient developed meningeal symptoms. Lumbar puncture at this time yielded a small amount of turbid fluid. The pressure was not increased, nor were organisms obtained on examination. Dec. 31, 1914. Patient died.

Autopsy.—Dec. 31, 1914.

Heart.—Weight 450 gm. The tricuspid valve measures 14 cm. The pulmonary valve measures 7 cm. The cusps of the mitral valve contain vegetations measuring from 2 cm. in diameter to others which are smaller. These vegeta-

[12] This case was from the City Hospital.

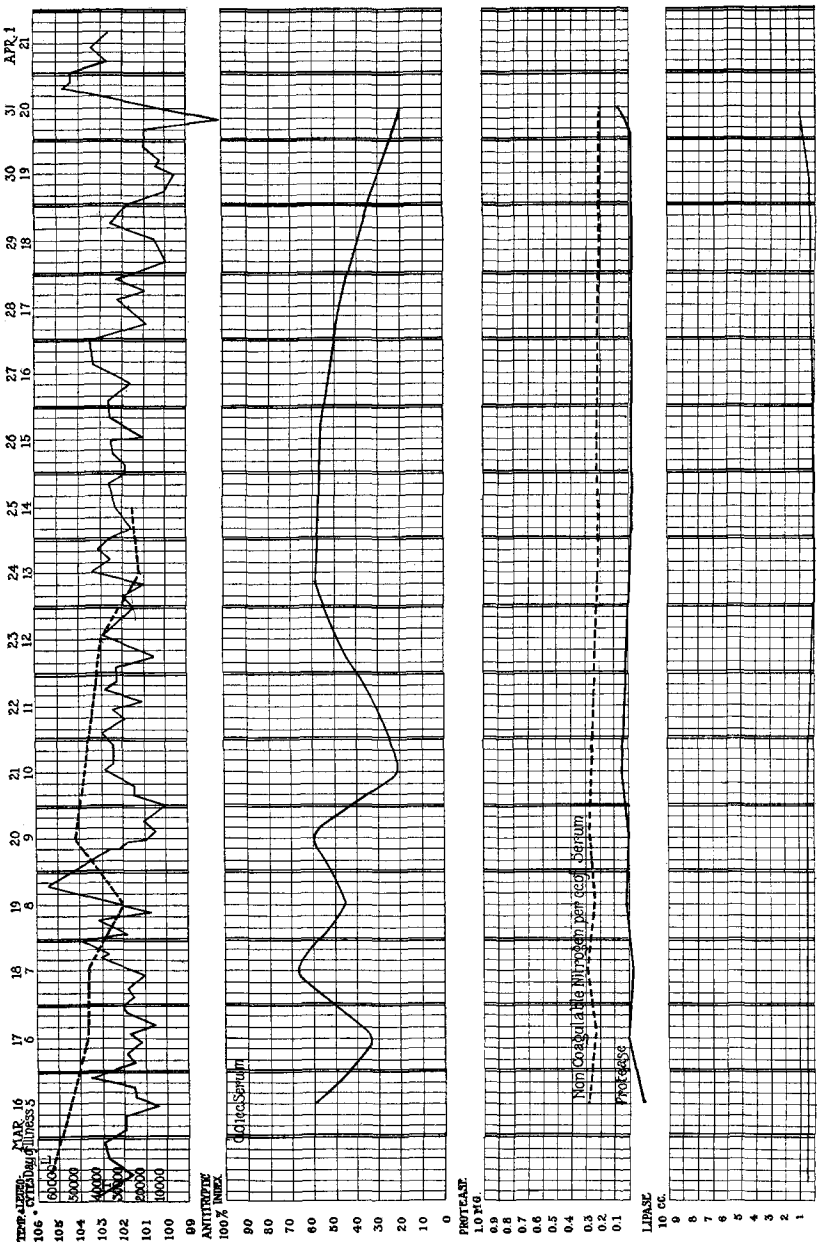
tions are firmly attached to the cusps. The distal surface is roughened and corrugated; otherwise they present a smooth surface. The cusps of the aortic valve are smooth and shining. The myocardium is brownish red in color and presents several grayish white patches, which are evidently fibrous in character. The left ventricle measures 17 mm., the right ventricle 7 mm. in thickness.

Lungs.—The left lung weighs 840 gm. The lung is entirely covered with a fibrous and fibrinous exudate, which binds it to the chest wall. It is bluish black in color. The consistency is increased and the organ contains no air except in the apex. The bronchi are bright red in color and contain a mucopurulent exudate. On section the surface is dark gray in color. In the lower lobe the process is diffuse. In the upper lobe it is nodular in character. The centers of the nodules present a grayish color and the peripheries are red. The cut surface is rather smooth. The right lung weighs 500 gm., and is bluish black in color. The edges are rounded. The surface is smooth. The upper and lower lobes are bound together by old fibrous adhesions. The lung is markedly emphysematous. On section the surface is pinkish gray in color and dry.

Brain.—On removing the dura the cortex is seen to be covered with a greenish, cloudy, fibrinous exudate. This involves the frontal and parietal lobes of the cortex. Occiput shows more congestion than the other two named. The fluid is increased along the sulcus and especially along the Rolandic fissure. In the fluid are flakes of a purulent material. The intima is firmly adherent to the convolutions of the brain and the exudate extends between the convolutions. The base of the brain shows the same condition as the cortex but apparently more marked in the infundibulum and the medulla oblongata. The lateral ventricle contains a thick, cloudy fluid. The choroid plexus is covered with an inflammatory exudate. The third ventricle is filled with the above described fluid. Upon section the blood vessels in the cerebellum are engorged and in many places there are many small petechial hemorrhages. The blood vessels medially to the external capsule are very much engorged. The purulent exudate is also found in the fourth ventricle.

Anatomical Diagnosis.—1. Lobar pneumonia of the left upper and lower lobes. 2. Pneumococcus meningitis. 3. Vegetative endocarditis. 4. Acute parenchymatous nephritis. 5. Cloudy swelling of the myocardium, liver, and spleen. 6. Fatty changes of the liver. 7. Fibrous and fibrinous pleuritis. 8. Emphysema of the right lung. 9. Fibrous myocarditis.

Microscopical Diagnosis.—Heart shows an increase in fibrous tissue, the muscle fibers are pale, enlarged, and some of them, especially beneath the pericardium, show fatty degeneration. One lung showed congestion, anthracosis, and compensatory emphysema; in the other lung the pleura was thickened, and many of the alveoli of the lung were collapsed, some of them showing fibroblasts and fibrous tissue. There was intense congestion and the bronchi were filled with an acute inflammatory exudate. Liver showed congestion, a few areas of necrosis, and some cloudy swelling. The capsule of the spleen is thickened; there is much congestion; and an increase in parenchymatous tissue. The capsule of the kidney is thick, glomeruli are swollen, the epithelium of the tubules is swollen, granular, and contains fat. Pancreas is negative. Stomach shows no definite change. The cerebrum is covered with an inflammatory exudate, rich in polymorphonuclear leucocytes. The pia mater is markedly thickened,



TEXT-FIG. 5. Serum changes during secondary pneumonia with fatal termination (Case 15).

the cortex is edematous, and there is marked perivascular infiltration of polymorphonuclear leucocytes.

This case showed the usual progressive rise in antiferment to the seventh day of illness, and the temperature reached normal on the ninth day. The protease was only determined three times, showing a progressive rise, however, about the time of improvement of the condition clinically. No signs of resolution were noted, however; the antiferment again rose, as did also the non-coagulable nitrogen. The lipase, except for an early rise, remained low. The high antiferment index may possibly be associated with the lack of autolysis in the lung described above.

Case 15.[13]—(Text-fig. 5.) J. T., female, colored, aged 14. Mar. 6, 1915. Abortion of 3 months' fetus, followed by fever 3 days later, together with dyspnea, cough, and general malaise. Entered hospital Mar. 12, 1915.

Physical Examination.—Young mulatto girl, well nourished. Heart action vigorous and rapid; second pulmonic sound accentuated; slight systolic thrill; no murmurs. Lungs: diminished expansion on left side; increased tactile fremitus over left upper lobe; dullness over lower portion of left upper lobe posteriorly and in axilla; increased voice sounds, bronchial breathing; and a few râles over lower portion of upper left lobe. Mar. 16. The entire left lobe became involved, with more numerous râles over the upper lobe. Mar. 17. There was distinct evidence of involvement of the lower right lobe, and the pulmonic second sound was found less accentuated. Mar. 18. Some signs of resolution were noted in the left lower lobe. Mar. 19. Hemorrhage. Mar. 20. Heart sounds very weak; patient in poor condition. The following days showed considerable resolution, but the cough continued, and the sputum became rather offensive. Apr. 1. Patient in a very critical condition. Patches of bronchial breathing and bronchophony over posterior part of both upper lobes, and in front on left side, with a patch in the right axilla. Great amount of offensive sputum. Died in the evening after a rather profuse hemorrhage.

In this case of septic pneumonia the fluctuating involvement of the lungs finds its reflection in the constantly changing antiferment curve, and the non-coagulable nitrogen also shows an almost daily variation. The protease remained low throughout, despite the clinical evidence of resolution in part of the involved areas. An autopsy was not obtained.

Analysis of Cases.

On examination of Text-figs. 1 to 5 there will be noted a very constant increase in the serum protease about the time of crisis, together

[13] This case was from the Vanderbilt Hospital.

with a decline in the antiferment titer. These two factors would indicate that at this time conditions for autolysis would be most favorable, and we must remember that the sera are after all only an index of the condition that obtains in the local areas involved.

It will be noted that the non-coagulable nitrogen decreases, as a rule, after the crisis, as Rzetkowski (9) has already pointed out, and the proteoses also diminish markedly.

When we average the various changes that have occurred in the eight cases that ended by crisis we obtain the figures given in Table I.

TABLE I.

Average Antiferment Titer.

Day before crisis.	Day of crisis.	Day following crisis
per cent	*per cent*	*per cent*
57	50	46

Average Total Non-Coagulable Nitrogen per Cc.

mg.	*mg.*	*mg.*
0.50	38	40

Average Protease Action per Cc. (Autolysis under Chloroform).

mg.	*mg.*	*mg.*
— 0.05	+ 0.05	+ 0.02

Average Lipase per Cc.

0.45 cc. $\frac{N}{100}$ NaOH	0.7 cc. $\frac{N}{100}$ NaOH	0.9 cc. $\frac{N}{100}$ NaOH

The protease activity which is demonstrated is probably not derived from the leucocytes undergoing autolysis in the pneumonic lung. If that were true we would expect that the ferment would continue to be present after the autolysis had once begun. That this is not the case is best illustrated in Text-fig. 5, when clinically all signs of resolution were present while the protease curve remained negative. The ferments are probably mobilized from the tissue cells in general.

DISCUSSION.

In a paper discussing the crisis in pneumonia, Hektoen (10) has recently reviewed the present status of our knowledge and concludes that the crisis is the effect of the prompt destruction of the infecting organism at a time when the antipneumococcal reaction reaches a certain height. But the mere concentration

of antibodies can hardly explain the whole picture, for in pneumonia, as in typhoid, such immune reactions may be quite marked, but the organism nevertheless may remain viable. He remarks that the crises cannot be wholly dependent on resolution, for, while they usually concur, the crises may precede resolution. But autolysis may take place in a lung without affording immediate evidence by physical finding, just as readily as the early infection may be well established in the lung before signs of consolidation can be elicited.

Dick (11) and Rosenow (12) have studied specific proteases both in the immune animal and in clinical material, Dick determining an increased proteolytic power for pneumococcus protein at the time of the crisis, and associating it with an increase in the complement strength. Even if such proteolysis were specific, rather than based on colloidal changes following in the wake of the usual immunity reactions, it would have no influence on living pneumococci, for proteolytic ferments, as is well known, are without action on intact organisms (13).

That autolysis plays a large share in the pneumonic picture has been shown by Müller (14). Flexner (15) has discussed more especially the conditions present in unresolved pneumonia.

Before entering into a discussion of the relation of autolysis to the crisis, we believe that our ideas concerning the factors that produce the intoxication must be amplified. Quite naturally the entire emphasis has so far been placed on the pneumococcus. Kruse (16) and Cole (17) have discussed the work so far accomplished in the study of pneumococcus toxicity. Vaughan (18) has shown that pneumococcus proteins are relatively less toxic than those of other organisms. The toxicity is manifested on simple solution, to which the pneumococcus is rather liable, *e. g.*, with bile salts (Neufeld), and soaps (Lamar); by freezing (Cole); lipoid solvents (Jobling and Strouse); and also during autolysis, as Rosenow has demonstrated (19). Rosenow determined the rate of autolysis by means of the Sörensen method.

Using the Folin method and coagulating by means of heat and acid, we have not been able to convince ourselves that the pneumococcus undergoes autolysis more readily than other organisms. In one experiment the following rate of autolysis to non-coagulable forms of nitrogen was noted:

	hrs.	*per cent.*
Pneumococcus	24	6
"	48	11
Typhoid	24	4
"	48	25
Staphylococci	24	30
"	48	45

It is possible that other strains might show some difference. The organisms used contained from 3.6 to 4.7 per cent of total lipoids; the degree of unsaturation was not determined because the amount of lipoids obtained was too small. If the pneumococcus at the time

of crisis was subject to extensive lysis and was the sole factor in the causation of the toxemia, we should expect an increase rather than a lessening in intoxication, for during lysis toxic material is liberated from the organism.

The fact which we wish to emphasize is the great mass of fibrin and leucocytic debris which dominates the pneumonic picture. This to all intents and purposes represents foreign proteins as far as the lung is concerned and while undergoing solution must give rise to toxic split products. While the inhibitory factors are in the ascendency, this material is undergoing a very slow autolysis with the splitting proceeding only to the higher and toxic products which are absorbed as such. The balance being once destroyed, and the autolytic process allowed full sway, the splitting proceeds much farther to non-toxic products. This period is characterized clinically by the greatest excretion of nitrogen following immediately upon the crisis. We believe that it is this factor (to which Cole (20) has already referred) that must be taken into consideration when we seek to define the various potentially pyrogenic sources.

We regard the amount of proteoses present in the serum as an indication that such a condition actually obtains. It will be noted from the various determinations made that these reach two or three times the amount present in the early serum samples and fall off quite markedly after crisis. These must be derived either from the resolving lung tissue, or the tissue cells in general, for their amount is too large for the pneumococcus protein to be considered their source. It is recognized clinically that fibrin and blood clots or aseptic tissue autolysis in general give rise to a febrile condition as readily as an accumulation of leucocytes among which the infecting organism may have completely disappeared. The source of the toxin here is quite palpably the autolyzing homologous proteins. It seems only reasonable, therefore, that the same condition, even in an exaggerated form, should, during the pneumonic process, give rise to an intoxication. Under such circumstances the pneumococcus intoxication proper would be only an accessory factor, and would account for the fact that the rapid destruction of the organisms which must occur during and after the crisis is accompanied by no further evidence of intoxication.

CONCLUSIONS.

1. The crisis in pneumonia is usually accompanied by (a) decrease in the serum antiferment; (b) the mobilization of a non-specific protease in the serum; (c) an increase in serum lipase; (d) a decrease in the non-coagulable nitrogen, and of the proteoses in the serum.

2. The crisis is associated with the beginning of an active autolysis, the latter depending on an altered relation between the ferment-antiferment balance.

3. The fibrin and leucocytic debris must be considered as one of the potential sources of toxic substances. With rapid autolysis proceeding, only non-toxic materials are absorbed.

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