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PERIARTERITIS NODOSA

by

Frank G. Johnson

Senior Thesis
1940

Presented to the
University of Nebraska
College of Medicine

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INTRODUCTION

In beginning this paper I should first like to give credit to Dr. J. P. Tollman and Dr. E. L. MacQuiddy for graciously allowing me to use case reports of patients coming to their attention who had died with Periarteritis Nodosa. Neither of the cases have been reported in the literature and I feel that they have a definite value in a work of this type. They serve to show how bizarre are the symptoms and the difficulty in reaching a clinical diagnosis of this little known and poorly understood disease.

It is the purpose of this thesis to review the literature as we now find it and present the salient facts as they appear to the author. No attempt is made to cover all the various aspects of the clinical diagnosis, etiology or pathology, but rather it is the aim to condense all the work done up to the present and present it in a simple, easily readable form. Naturally, after reading several reports you become aware that a few writers put forth their arguments more clearly and with better reasoning. You find yourself leaning toward their views and you see the answer to the problems in hand as they see it. If this paper leans toward the views of any one

particular writer I hope that it will be understood that it is more accidental than intentional. This paper is intended to be impartial and present fairly all sides of the question and it is not in my power to say who is right on any particular part of this interesting disease syndrome.

Periarteritis Nodosa is a rare infection of unknown etiology. The disease has seldom been recognized until post-mortem since characteristic pathology is usually limited to the internal organs especially the kidneys, heart, spleen, liver and lungs, however, there are occasionally subcutaneous nodules, skin manifestations of hemorrhages, urticaria and purpurea resembling Schonlein's disease. It is an acute to subacute infection which preponderantly terminates fatally within several weeks to months, rarely in several years, recognized by an inflammation of the walls of the medium-sized arteries. The outstanding features of the infection are localized areas of exudation, degeneration and proliferation in the adventitial and mesial coats of the arteries, with the formation of well-developed nodules.

The etiology will consist of the various theories which have been put forth as possibilities in determining the exact cause of this disease. I will attempt to

to give all the theories which have been offered throughout the literature. I will not attempt to state which is right but will present them for what they are worth.

The clinical aspects will be considered and those symptoms which have predominated in the largest number of cases will be emphasized. Needless to say the true clinical picture has not yet been worked out completely and the relation of the clinical symptoms to the pathology has been largely worked out at the autopsy table. In most cases a clinical diagnosis before death has been accidental or has been based on biopsy material. I cannot emphasize too strongly that in the present state of the literature no symptoms have been definitely related to this disease syndrome well enough to base a diagnosis when they are found present.

The case reports have been included in this thesis to give you an actual word picture of the disease and to show how few clinical symptoms are present upon which you might base a diagnosis. Then too, they show how only a few organs may be affected or it may be a general widespread involvement of the entire body.

In the summary I shall try to discuss these case histories and how they agree or disagree with other

cases which can be found in the literature. These cases compare very favorably with the findings of many investigators both here and abroad.

The conclusions will be those of a variety of writers according to their own findings and their own ideas as to the etiology, pathology and where possible any therapeutic suggestions they may have. It is my hope and desire that this paper may be of some little benefit to the reader in leading to a rational approach to the treatment of the disease known as Periarteritis Nodosa.

HISTORY

The history of this comparatively unknown disease has been quite well summed up in the literature. Periarteritis Nodosa was first completely described by Kussmaul and Maier in 1866. Because of their description the disease has borne the name of the former investigator, especially in the Continental literature. Prior to that in 1852 Rokitansky reported the finding of innumerable aneurysms in the wall of small arteries over the entire body, except the brain, in a man 23 years old, who had died with symptoms of dysentery. This was written up in his paper entitled "The Formation of Aneurysms of the Arteries in General Except the Aorta and Most of Its Important Branches, With the Further Exception of the Cerebral Arteries". This gave us our first complete description of the disease. In 1887, Eppinger examined a piece of mesentery from this patient and, with improved methods of examination, was able to find lesions identical with those described by Kussmaul and Maier. Along with this it is interesting to note that even earlier, three cases of multiple aneurysm had been reported, in 1775 Michaelis and

Matani each reported a case, whereas in 1810 Pellatan described a case in which 63 aneurysms were found. This portion of the history follows that of Rothstein and Welt (46).

From the time the disease was first described until the present there are less than 395 cases reported. German investigators are by far the most active in finding cases of this type because of the number of autopsies which are performed in that nation while in contrast might be mentioned Spain, since they have a dislike for postmortem examinations, have not reported any cases. In 1928, Strong (49) described the first case of periarteritis nodosa in Canada. American workers at the present time are among the most active in investigating this little known disease.

As the disease of Periarteritis Nodosa has been studied and as the cases have become increasingly frequent in the literature the idea that this is a rare disease has gradually been discarded. As we understand the disease at the present time it is generally thought that a great many cases are very mild attacks and are passed over with no lasting harmful attacks. It is only the extremely acute

forms that produce death and coupled with the fact that most cases of Periarteritis Nodosa are discovered at the autopsy table has led to the supposition of its high fatality. Then too many patients are only sick for a short time before death, having many bizarre symptoms which render a clinical diagnosis virtually impossible with present knowledge of the disease syndrome.

The name Periarteritis Nodosa has been somewhat of a stumbling block in that it indicates nodule formation which many investigators and clinicians have searched for without success. Many cases are now reported in the literature which displayed no nodular formation or the nodules were almost microscopic, others in which there are many aneurysms and those which have none. It may affect only a few organs of the body or it may be generalized. To more accurately characterize this disease syndrome other names have been suggested, some of which are; Multiple Aneurysm by Meyer, Arteritis Nodosa Proliferans by Fletcher, Polyarteritis Acuta Nodosa by Ferrari, Mesoperiarteritis by Hart, and Panarteritis, Arteritis Nodosa or Polyarteritis Nodosa by Beitzke.

In the American literature the reports of Lamb (35) in 1914 and Ophules (44) in 1923 stand out as the best description of cases in this nation. They, as well as others, tried to explain the cause of the disease with little success but both have noted the stages of destruction and attempted repair which are characteristic of the disease.

With all the investigation it was natural for bacteriologists to become interested and considerable experimentation with attempted transmission of this disease into laboratory animals with varying results can now be found in the literature. This will be discussed more fully under etiology and pathology.

At this time enough cases have gained entrance into the literature so that in the near future the next step in the history of this disease will be taken and the causative factor found. The disease has been discovered, described and the relation of the pathology to the symptoms recorded. Now the etiological agent must be recognized and a definite rational therapeutic approach made to combat this disease.

ETIOLOGY

It must be said in beginning this section of the treatise on Periarteritis Nodosa that the causative factor has as yet resisted all methods of detection. Most of the etiology as we now know it is presumptive and theoretical, and cannot be proven as yet. It has for its basis or background only the cases which the investigators themselves have in hand. Much thought and energy have been given to adequately determine the cause of Periarteritis Nodosa, and make a clinical recognition possible thus laying the background for a satisfactory method of treatment.

Early workers in several cases found that their patients had a positive serology, others noticed the close resemblance of the lesion of Periarteritis Nodosa and Syphilis and they proposed the theory that the spirochete was the etiological agent. The foremost authority to suggest this possibility was Virchow. This possibility was promulgated by the early investigators in Germany. Since then this theory has been disproven countless times. Many sections have been studied to find the organism without result and the proposal that Syphilis has any relation to Periarteritis Nodosa is now considered untenable.

Other theories have had a brief period of acceptance and then have been discarded. Some of these are mechanical, in which it was thought that undue stress and strain on the arterial walls both from within and without caused a weakening of the wall at that point with the resultant formation of aneurysms which ultimately fibrosed thus forming a nodule. This theory was advanced by Rokitansky. This has never been proven and at the present time with our knowledge of the dynamics of the arterial system together with our conception of the pathology rules out this possibility entirely.

Along with the other theories we also have the concept that heredity plays a part. Credit for this proposal must be given to Eppinger. In studies of families in which this disease was proven in a patient there was nothing to prove the theory and if our conception of this disease syndrome is correct there is no indication that heredity has any part as an etiological factor.

In reviewing the cases in the literature we are struck with the fact that the disease attacks males a great deal more often than females. The

ratio is set at 4 or 5 to 1. This would seem then that Periarteritis Nodosa has a definite relationship to the sex. There is at this time no explanation for the preponderance of males but the fact remains that in a study of the etiology we must deal with the sex of the individual. Age is a fairly important factor, the average being 31 years. We find instances where a child of 2 1-2 months and 9 months have had a proven case and records of a man 71 years old who died of Periarteritis Nodosa but the greatest percentage of cases are in the adolescent an early adult group. Occupation and past history have variously been offered as possibilities but with little grounds and no further substantiation so are of slight importance.

We come now to those theories which at the present time are in the best standing: namely, the allergic theory of sensitization proposed by Gruber (22) and the infectious or toxic theory offered by Spiro and Gruber (22). These two theories both have many adherents although the balance has swung in favor of the infectious or toxic form of etiology. It is not the purpose of this paper to take any one viewpoint but rather to compare their relative

virtues as they are seen in a review of the literature.

The Allergists point out many cases where the patient has a history of asthma or is proven to be sensitive by skin tests. This theory was first advanced by Gruber in 1925. Kline and Young (31) also called attention to the allergic basis in reviewing three of their cases all of which had a high sensitization. Ophules is also of the opinion that allergy may have a very important part in causing Periarteritis Nodosa. Berger and Weitz (5) explained the etiology thusly,"when cells in the allergic state are brought into contact with an antigen to which they are sensitive a characteristic reaction occurs. This reaction is vascular in nature and results in the outpouring of fluid into the reacting area followed by the extravasculation of leukocytes. Reactions vary greatly in severity, depending upon the degree of sensitization of the tissues and the doses of the antigen. Most of them disappear without tissue change. These are the reversible reactions, as we see when skin testing a patient. Some, however, are so severe that tissue death results with healing by scar tissue formation. This is known as the

Arthus phenomena and is entirely applicable in Periarteritis Nodosa. Allergists feel that the eosinophilia described in several cases is because of a sensitization base."

Those investigators who lean toward the infectious or toxic theory argue as follows: the patients follow the course typical of an acute infectious disease with increased temperature, pulse and respiration. They complain of pains in the joints and muscles. The histologic lesions are of a distinctly inflammatory character (Cook--13), and rheumatic heart disease has been found in many cases as proven by Aschoff Bodies found in the heart muscle. Then too, the arthritis and myositis may be considered typical of rheumatic fever because in not all cases is there a pronounced eosinophilia the authors agreeing on the inflammatory nature of the disturbance say, one of the most characteristic features of Periarteritis Nodosa in the early cases is a tremendous infiltration of the adventitia with partly neutrophilic, partly eosinophilic polymorphonuclear leukocytes mixed with a smaller or larger proportion of small lymphocytes and plasma cells. Then too, foreign body giant cells are often noted.

Still other writiers wish to think that the disease is a special infection "Sui generis" or the lesions are the result of the action on perhaps predisposed arteries of a variety of infectious or toxic agents the latter having been suggested on account of the general inability to demonstrate bacteria in the microscopic sections. It might be stated here that Allergists feel that tissue may be sensitized to streptococci and form an explanatory basis for Periarteritis nodosa.

The idea of a special infection derives its main support from these facts (1) a disease practically identical with it has been observed by Lupke (IV), as quoted by Ophules, in a herd of stags; (2) twice, vonHaun (VIII) and Harris and Friedrichs (26), the claim has been made that there has been a successful experimental transmission of the disease to laboratory animals. The results have been confusing and there are no uniform results. Both blood and tissue emulsions were injected into a variety of laboratory animals.

Ophules (44)in discussing the possible etiology of Periarteritis nodosa goes on to say, "much discussion

has arisen because of the resemblance of Periarteritis Nodosa to rheumatic fever. It is interesting to study this relationship of the two and the ill-defined group of subacute and chronic "septic" conditions with so-called "rheumatic" symptoms and frequently associated with endocarditis. The evidence connecting the two conditions are often ushered in with an acute tonsilitis. During the course of the illness almost all clinicians have been impressed with the resemblance of the syndrome to that of a slow, comparatively mild septic condition, and various skin eruptions have been observed which seem to favor this impression. They may be erythematous or resemble purpura rheumatica as seen in Zimmerman's case (IX). They may be urticarial in nature (Veszpremi and Jansco VII) and Klotz' case was a typical erythema nodosa. It has been known to follow injury of the hand "Fishberg" which during the course came to resemble an erysipelas. In Schrieber's case a patient was suffering from chronic non-Syphilitic ulcers of the skin of the legs when the disease developed. Kroetz' patient had a septic infection of the urinary tract. In Lamb's, diplostreptococci were found on the diseased heart valves and

other parts of the body. Douglas obtained a pure culture of streptococci from the subcapsular hemorrhage of the kidney. Jonas found streptococci in a culture from the kidney. It has also been recovered from the gall bladder, heart blood, bile, subcapsular lymph channels of the liver (Strep. Anginosus and Salivarius). Strep. Anginosus proved too virulent for laboratory animals but with less virulent cultures at times a subacute Periarteritis Nodosa with slight involvement of the media was obtained by Klotz. Harris and Friedrichs transmitted disease to laboratory animals after filtering through a Berkfeld filter proving that it approaches the virus if not".

These do not prove anything, save that streptococci may be a secondary invader. The affected arteries are usually more focal and associated with more cicitrization in media and adventitia than simple artero-sclerosis. This would lead to the inflammatory basis of the etiology of Periarteritis Nodosa.

CLINICAL ASPECTS WITH REVIEW OF THE LITERATURE

The true clinical picture, if there is one of this disease syndrome, is extremely difficult to ascertain. In general it must be stated that Periarteritis Nodosa simulates many diseases and symptoms are localized to the organs affected in any one particular case. Most cases which are recognized clinically before death are accidental or are the result of biopsy report. Even biopsy material may not be recognized at the time and when autopsy determines Periarteritis Nodosa a careful search of the biopsy material has revealed the presence of the disease. This may be due to the fact that Periarteritis Nodosa is not a specific disease but results as Friedberg and Gross (18) believe, from the activity of many toxic or infectious agents.

To find a true clinical picture it is necessary to determine which signs and symptoms are most commonly dealt with. First, febrile illness (90%) resembling chronic general infection (sepsis) but with negative blood culture. Next in importance are the renal symptoms of nephritis pointed out by Keegan (30) who believes that Periarteritis Nodosa is the cause of pathology known as chronic vascular nephritis. His reasoning may be interpreted in sequence as follows--

acute vascular infection and vascular infarction in the kidneys lead to little urinary changes; subsequent gradual fibrotic intimal obliteration of the arteries lead to tubular atrophy, with probable loss of reabsorptive power and consequent nocturia and low fixed specific gravity. The rapidity and severity of the arterial obliteration leads to cardiac decompensation with less blood flow through the arteries and the glomeruli with a resultant decreased urine output, a nitrogen and terminal retention. In his patient a kidney was removed two months before death because the disease simulated an acute condition in which Periarteritis Nodosa was proven conclusively and at autopsy the other kidney showed vascular nephritis of the chronic type. Therefore, as he sees Periarteritis Nodosa in its relation to renal symptoms it may be considered as an acute vascular nephritis leading in non-fatal cases to chronic renal arteriosclerosis and chronic vascular nephritis. He feels that the term "chronic vascular nephritis" is applied to a large group of contracted kidneys in which the primary pathologic condition is in the arteries and the secondary pathologic change is due to

gradual arterial obliteration.

Thirdly, acute abdominal symptoms simulating an acute intra-abdominal complication or those of entero-colitis. This is extremely common and is spoken of as abdominal rheumatism by several writers. Many cases have been explored surgically because of the symptoms as evidenced by the work of Allen (1). Poly-neuritis may be a symptom in many cases as are those of polyarthritis and polymyositis which simulate the pains of rheumatic fever. The difficulty of diagnosis of Periarteritis Nodosa is not because of the inade-quacy or indefiniteness of symptoms but to the variety of common diseases which it can simulate because of its extensive pathological process.

According to Weiner (55) the relative frequency of organs and structures affected are: kidneys 80%, heart 70%, liver 65%, gastro-intestinal 50%, muscles 32%, pancreas 36%, peripheral nerves 20%, spleen and adrenals 8%, gall bladder 13%, skin and subcutaneous tissues 14%, nervous system 8%. This in general shows how widely generalized the pathological process may extend and the multitude of symptoms which will result. Carr's (9) clinical description is quite representative of all the works, "Periarteritis Nodosa is a disease

which is characterized by symptoms of sepsis, with scattered local manifestation of vascular disease, which baffle explanation; and anatomically by nodular inflammatory foci in the smallest and middle sized arteries. He believes the symptoms which occur with greatest frequency are those commonly associated with infectious disease, fever, leukocytosis, prostration, increasing weakness, anemia, occasionally splenic tumor tachycardia with evidence of renal involvement with albuminuria, hematuria, edema and signs of renal insufficiency.

At this point I believe it is a good time to point out the differentiation of rheumatic fever and Periarteritis nodosa. A. thrombosis is common in Periarteritis nodosa and absent in the rheumatic lesions. B. Periarteritis Nodosa attacks arteries of medium calibre while rheumatic fever attacks small arteries, arterioles and sinusoidal capillaries. C. nodules form in Periarteritis nodosa which are macroscopic and microscopic while in rheumatic fever there is no nodular vascular development and lesions are invariably microscopic. D. There is absence of infarction, and hemorrhage from rupture in the rheumatic lesions. E. eosinophilic infiltration is

present in most cases of Periarteritis Nodosa while it is minimal in rheumatic lesions. This is in accordance with the view of Vining (53).

He goes on to state, however, that it is possible that a primary rheumatic infection in certain cases acts as a sensitizing factor and prepares the way for the destructive attack by the infective agent of Periarteritis Nodosa.

So far the incidence of this disease has not been truly worked out. According to the literature the postmortem incidence is: 1:10,000 (Haising and Kimball--24) 6:13,000 (Bernstein--6) 1:2,000 (Dunbar--17) 2:2,035 (Bennett and Levine--4) 2:3,000 (Klotz) 12:17,316 (Maresch) 2:1,613 (Jacobson--28).

In all ages the clinical course was variable and unpredictable. The age groupings compiled by Boyd are as follows: (7)

Age	M	F	Sex Unknown	Total
0-4	1	1	2	4
5-9	7	5	1	13
10-14	17	9	1	27
15-19	19	7	-	26
20-24	28	7	2	37
25-29	19	8	-	27
30-34	45	15	1	61
35-39	40	5	-	45
40-44	25	7	-	32
45-49	17	11	-	28
50-54	26	7	-	33

Age	M	F	Sex Unknown	Total
55-59	16	6	-	22
60-64	4	9	-	13
65-69	5	3	-	8
70-74	5	4	-	9
75-79	1	-	-	1
Unknown	5	2	-	7
Total	280	108	7	395

The study of previous diseases is interesting and I believe it should be included in this paper:

1. Rheumatic Fever--36
2. Sore Throat--36
3. Syphilis--35
4. Influenza--24
5. Gonorrhea--17
6. Scarlet Fever--15
7. Typhoid Fever--14
8. Pneumonia--12
9. Bronchial Asthma--11
10. Whooping Cough--10
11. Injury and Infecton--9
12. Sinusitis--9
13. Nephritis--9
14. Pulmonary TB--8
15. Mumps--8
16. Typhus--5
17. Furuncle--5
18. Exposure to Cold--4
19. Minor Infection--3
20. Appendicitis--3
21. Gastric Ulcer--3
22. Erysipelas--3
23. Enteritis--2
24. Alcoholism--2
25. Erythema Nodosum--2
26. Meningococcic Meningitis--1
27. Renal Calculus--1
28. Lupus Erythematosis--1
29. Gout--1

In summarizing this section of clinical symptoms Lamb seems to give the best picture of Periarteritis Nodosa. According to him the symptoms are as follows:

1. Pains in the muscles 50% and joints 40%.
2. Fever 94% show febrile course. The temperature follows an irregular curve.
3. Abdominal pain, very common and of the epigastric type.
4. Edema 61% of cases. Generally of the ankles and face.
5. Weakness.
6. Disturbance of sensation.
7. Diarrhea, sweating, purpuric eruption, sore throat.
8. Chilliness, headache, vomiting, anorexia, constipation, cough.
9. Dizziness, urticaria, hemoptysis, pain in chest, eruptions, cyanosis, dyspnea, icterus, swelling of testis and asthma.
10. Subcutaneous nodules. Not a constant sign and absence should not alter the diagnosis.
11. Superficial lymph nodes--found in very few cases.
12. Skin eruptions are hemorrhagic in character, petechial, purpuric or echymotic. May be diffuse erythema. May be found in all stages of disease.

13. Blood pressure. This is an inconstant sign.
14. Pulse. In 97% of the cases it is increased.
15. Blood. Anemia in 55% of the cases. Often an eosinophilia. White blood cells may be very high.
16. Respiratory symptoms. Asthma is occasionally found.
17. Gastro-intestinal--shows many symptoms.
18. Abdomen. 50% of cases have abdominal rheumatism.
19. Genito-urinary--albumin in 82% of cases. Kidney tests altered.
20. Nervous system. Quite frequently have headaches, disturbance of sensation, palsies, convulsions, visual disturbances and may have muscle atrophy.

There seems to be no agreement in the literature as to the general duration of the disease. It may last a few weeks to one year or so and the prognosis is bad insofar as we know the disease at the present time.

CASE REPORTS

Case 1.

Miss M. S. entered the University of Nebraska Hospital for the first time 4-5-33. She was a white, single female aged 24 whose occupation was housework. Her complaints were as follows:

1. Inability to hear for past two months.
2. Difficulty in breathing through nose.

Patient was well until two months before entry to the hospital. At that time she began to have pain in her left ear. About one month ago was unable to breathe through nose. Has had considerable discharge from left ear and nose since onset of present illness.

Past History: measles, whooping cough, scarlet fever. She had an operation on her neck at age 6, reason unknown. Not subject to colds, headaches or sore throats. No shortness of breath or swelling of feet or ankles. Appetite good but is constipated most of the time.

Catamenia--began age 13, regular ever since. No excessive amount.

No nocturia or burning. Has had pain in left in left hip at times the past month.

Physical Examination: The patient is a poorly developed anemic looking adult female, lying in bed

breathing through mouth with difficulty.

Head--not remarkable.

Eyes--unusually prominent. Pupils react to light and accommodation.

Ears--deaf in both ears.

Right--left reflex is absent. Drum is scarred

Left--pus discharging.

Nose--crusted, bleeds easily, complete obstruction. Copious discharge.

Throat--tonsils enlarges and infected.

Pharynx--covered with post-nasal discharge.

Neck--large, hard glands beneath angle of the mandible.

Lungs--resonance not impaired. No rales.

Heart--rapid (130) no murmurs. Blood Pressure 100 over 70.

Abdomen--no palpable masses, no tenderness.

Extremities--no deformities. Coarse tremor of hands. Reflexes hypoactive. Babinsky is negative.

Impression--Otitis media, sinusitis, infected tonsils, anemia and thyroid dyscrasia.

Laboratory--

Blood	4-20-33	4-24-33	4-27-33
Hemoglobin	47%	42%	45%
R.B.C.	3,200,000	2,820,000	2,920,000
W.B.C.	20,800	27,400	34,200
Differential			
Polys-Segs	45%		46%
Staff	34%		39%
Young	3%		
Lymphs	7%		10%
Monos	6%		5%
Eos	4%		
Myelocyte	1%		

Blood	Creatinine	4-21-33	6.0 mgms. per cent
"	N.P.N.	4-21-33	114.0 mgms. per cent
Serum	N.P.N.	4-22-33	106.0 mgms. per cent
"	Alb.	4-22-33	4.9%
"	Glob.	4-22-33	1.6%
"	Prot.Total	4-22-33	6,5%
"	Cholesterol	4-22-33	150.0 mgms. per cent

Urine	4-6-33	4-28-33
Color	Amber	Cloudy Amber
		100 c.c. in 24 hrs
Specific Gravity	1.018	1.015
Reaction	acid	acid
Albumin	1plus	3plus
W.B.C.	occ.	10-20 per hpf.
R.B.C.	none	20-30 per hpf.
Epith.cells	few	few
Crystals	few	few
Granular casts	none	loaded

Cultured for diphtheria--suspicion not confirmed.

Hospital Course:

4-6-33 Admitted. General diet. X-rays of mastoids and sinuses. Argyrol pack to nose for thirty minutes. Neosilvol 10% Ephedrine 3%, Gtts.iv into each nostril q.i.d. followed by gtts. ii of liquid abolene.

4-7-33 Consultation with Medicine. Basal to be done as soon as temperature normal.
4-14-33 Clinical diagnosis of nasal diphtheria made. 20,000 U. Diphtheria Antitoxin given with no reaction.
4-15-33 Temperature 101.6°. 10,000 U. Diphtheria Antitoxin given. No reaction. Membrane in nose separated and was removed. Can now breathe through nose.
4-18-33 Transfusion with 200 c.c. of whole blood.
4-21-33 Considerable ascites present.
4-22-33 Seen by Medical Department who recommended hot body packs b.i.d. Intravenous injection of 100 c.c. of 50% glucose.
4-26-33 N.P.N. 201 mgms. %. Creatinine 10 mgms. %.
4-27-33 Blood pressure 154 over 110. Patient seen by Dr. Bliss, who states "patient has developed skin lesions on both knees and elbows. Decrease in general edema, little edema of the kidney evident. Advised against decapsulation, force fluids, thyroid extract gr. x daily and high protein diet."

Seen by Dr. Kirk 4-27-33 who adds the following comment "this patient presents in general an infectious process involving all of the sinuses with an intermittent septic type of temperature and leukocytosis, and nephritis characterized by albuminuria,

nitrogen retention and slight edema formation. From the history obtained from the mother of scarlet fever at the age of 5 which was followed by evidence of edema, as swelling of the ankles together with the present picture of marked nitrogen retention and relatively negative findings of urinary sediment, in my opinion it is a case of chronic nephritis. There has been a rapid increase of the N.P.N. and Creatinine with elevation of blood pressure with a striking decrease of water output. The latter accompanied by marked low chlorides and total nitrogen output. This marked water retention might point to edema of the kidney of which I am doubtful." He advised forcing fluids, 2,000 c.c. or better, a low salt diet (NaCl output is .491 grams per day) and combat infection present.

4-29-33 Ophthalmoscopic examination by Dr. Judd.

Right eye--media clear, retinal vessels small. Arteries quite contracted as in hypertension. Diffuse edema of the retina especially along primary vessels above. No hemorrhage or exudate.

Left eye-- essentially the same as right eye.

4-30-33 Patient semicomatose. In convulsions at times. Dying of uremia. Died at 8:15 A.M.

Autopsy

External Examination--

The body is that of a well developed, well nourished young woman who looks to be about the stated age of 24. Hair is reddish in color and eyelids are edematous. The face looks puffy and the skin somewhat waxy. There is slight edema of the tissues of the body particularly over the back and the ankles. There are numerous points of discoloration particularly about the knees and hands. These discolored areas range from 1 to 5 cm. in diameter and are principally purplish-red in color, although a few are slightly brownish. A few of these spots are scattered over other parts of the body.

Primary Incision--

The primary incision is of the usual Y-shaped type beginning at the axillary folds, continuing to the midline of the chest and then to the symphosis pubis. The subcutaneous tissues are quite edematous, muscle appears to be in good condition.

Abdominal cavity. On opening the abdomen 500 to 600 c.c. of clear amber fluid was found. Mesenteric nodes are slightly enlarged so that they are very prominent through the mesentery and some of these appear on the

wall of the bowel. There is no abnormality of disposition of the abdominal viscera.

Thorax. The thorax is opened by removing the chest plate in the usual manner. No fluid is found in either pleural cavity. There are no adhesions about the lungs although these are fairly firm to palpation. Mediastinum is not enlarged and there is no evidence of remaining fatty tissue.

Pericardial cavity. Contains probably 50 c.c. of clear amber fluid. The heart is not enlarged by gross inspection.

Heart. Weighs 230 grams, no antemortem thrombi found in either auricle. The tricuspid ring admits two fingers easily. The tricuspid valve cusps are normal in appearance. The muscle of the right ventricle is rather pale and somewhat irregular in color varying from pinkish to almost yellow in color. The pulmonary valve cusps show no change. The mitral ring admits two fingers with some difficulty. On opening the ventricle the mitral cusps are found to be entirely normal in appearance. The aortic cusps are smooth. There was some atheromatous changes in the first portion of the aorta. The coronary vessels show slight atheromatous change in the wall. Several small aneurysms are found particularly

on the wall of the ventricle. One of these was about 3 mm. in diameter. Beside it is a rather firm mass of white granular tissue which is interpreted as a small abscess. Section through the heart muscle shows a number of very pale areas some being quite yellowish in color and the tissue is soft in the center of these areas.

Lung. The right lung weighs 820 grams and the left lung 500 grams.

Left lung. A mass of antemortem thrombus about 1.5 inches in length and about 6 mm. in diameter is found in the main branches of the pulmonary artery. Similar very small masses are found deep within the lung tissue and in association with these are wedge-shaped areas in which the lung is solid and very dark in color, these masses being very sharply delimited from the surrounding lung tissue. Several small abscesses were encountered ranging up to about 4 cm. in diameter. The remainder of the lung tissue is very edematous but no pneumonic consolidation can be made out. There is a great deal of frothy fluid in the bronchi.

Right lung. No large mass of antemortem thrombus was found in the artery although a few are found in the

smaller branches corresponding to the areas of infarction which are scattered particularly through the lower lobe. Several small abscesses are found ranging up to about 2 cm. in diameter. The lung tissue is very edematous and the lower lobe especially shows a rather widespread but somewhat irregular consolidation. Frothy fluid similar to that in the left lung is noted throughout the bronchi.

Gastro-intestinal tract. Is opened from the stomach to the rectum. There are a few areas of petecchial hemorrhage on the gastric mucosa but no areas of ulceration are found. The duodenal mucosa is normal in appearance. The wall of the small bowel shows several discolored areas up to about 1.5 cm. in diameter. In the center of these there is usually a small white area which evidently represents a small abscess. The lymphoid follicles are enlarged to about 2-3 mm., firm white nodules are noticed throughout the mesentery and bowel wall. Peyer's Patches are not appreciably enlarged.

Liver. Weighs 1360 grams. It is quite normal in size and shape. The surface is smooth with a few small reddish spots being evident. These are 4-5 mm. in diameter. Section through one of these shows a small abscess centered

about .5 cm. below the surface of the liver. A few similar abscesses are found on section through the liver. The liver surface in general is rather pale with the markings well retained. The bladder is quite edematous. No calculi are found within the lumen and the mucosa is quite normal in appearance.

Spleen. Is adherent to the diaphragm over its entire superior surface. There are numerous hollow white bodies throughout the spleen, some of which are broken down to form small abscesses ranging up to .5 cm. in diameter. The amount of pulp is very considerably decreased although the amount of fibrous tissue shows comparatively little change. The smaller white nodules appear to be quite firm and may represent the beginning abscesses. The spleen weighs 141 grams.

Kidney. Right--weight 300 grams. Left--weight 310 grams. Both kidneys are smooth in contour. They are quite normal in shape although very considerably enlarged. They are quite soft. On stripping back the capsule the surface is speckled with very numerous tiny red spots ranging up to approximately .5 mm. in diameter, although occasional larger areas of reddish discoloration are found which are approximately 7-10 mm.

The remainder of the kidney surface is yellowish gray in color. Section across the kidney shows the color combination to persist throughout the cortex. The larger masses are found to be small abscesses many of which appear to be small infarcts which are undergoing degeneration. The vessels are very prominent because of marked thickening of the walls with reduction in the size of the lumen. Many of these appear to have a zone of purulent material around the blood vessels. There is not much congestion of the kidneys. The markings are somewhat obscured by edema and a grayish discoloration of the kidney substance. There is some tendency to eversion over the cut edges of the capsule indicating some tension of the kidney substance. Pelves of the kidney show no striking change. Ureters are quite normal in appearance.

Adrenals. Adrenals are of normal size, shape and consistency.

Head. The head is opened by reflecting the scalp in the usual manner. There are numerous petecchial hemorrhages along the under side of the scalp. The calvarium is then removed and the dura is freed. The calvarium is entirely normal in appearance. The median and sagittal sinus contains no thrombi.

Brain. The leaves of the dura are then reflected.

There is a large area of reddish discoloration over the left temporal and occipital lobes. There appears to be marked edema of the arachnoid along with escape of much blood. There is no evidence of clotting of the blood, however. The right hemisphere is edematous and the vessels somewhat congested but there is no evidence of hemorrhage. The brain is then removed by severing the nerves and blood vessels and cutting the tentorium. This edema of the arachnoid is apparently generalized over the entire brain surface. A small incision is then made into the occipital lobe in the region of this discoloration previously noted but there was no evidence of pathology in the underlying brain tissue. The blood sinuses of the dura are then opened. No thrombi are found in amy of the vessels although in the left lateral sinus immediately adjacent to the mastoid a small mass of granular material is found firmly attached to the lateral wall of the sinus. Some of this material is rather friable and breaks off easily.

Pituitary Body is then removed. It is of twice normal size and considerably flattened.

Skull and sinuses. A careful inspection is then made of the base of the skull and there is no evidence of perforation of the sinuses through the bone tissue. The

core drill is then used to remove a section of the base of the skull so that the sinuses might be explored. Practically no left sphenoid sinus can be encountered and the right was very small. The posterior ethmoidal sinus is rather small. The epithelium is thin and there is no evidence of inflammatory reaction. The maxillary sinuses are then opened. The mucous membrane is thin and no purulent material is found within them.

Mastoids. The left mastoid is found to contain a large amount of purulent material which involves the middle ear as well. There is an osteomyelitis of the surrounding bone extending down along the lateral sinus for some distance. The right mastoid is very sclerotic so that the air cells are almost entirely obliterated although no appreciable amount of purulent material is found and the middle ear appears to be quite clear.

Microscopic Report:

Heart--there are two sections of heart muscle. Pericardium and endocardium are represented as well as the muscle itself. Pericardium shows a slight mononuclear infiltration but this is not particularly marked. The muscle itself is quite well preserved for the most part although in some places there is evidence of swelling in the muscle fibres and the nuclei especially are moderately enlarged. A number of arteries are present through the section, both small and medium sizes.

The larger vessels especially show a rather marked periarteritis which in some cases were marked enough to involve the whole thickness of the wall and has led to a partial thrombosis of the vessel in a few places. The inflammatory reaction is not very widespread through the surrounding tissue.

Lung--there are five sections of lung tissue. These are all quite similar in appearance. There are numerous abscesses scattered throughout the lung substance ranging from 1 mm. to 5-6 mm. in diameter. In these areas the lung tissue is entirely destroyed and the tissue is replaced by very numerous inflammatory cells. There is some evidence of organization in a few places. Bronchi contain a small amount of purulent material but did not appear to be very greatly involved. Other parts of the lung tissue show an extreme congestion with the alveoli almost entirely filled with red blood cells. There is comparatively little areated tissue through any of these sections.

Liver--There is one section of liver. The liver substance in general is well preserved although there is some swelling of the liver cells so the sinusoids are not particularly prominent. The central spaces are not dilated. Only one small area of inflammatory reaction is noted. This is quite small and probably not more than 1 mm. in diameter. This surrounds one of the portal areas which

contains blood vessels and bile ducts. The vessels themselves do not appear to be appreciably enlarged.

Spleen--There is one section of spleen. The substance of the spleen is almost entirely involved in abscesses which range from 1 mm. to several mm. in size. Occasionally a small bit of splenic pulp shows comparatively little involvement but this is a very small portion of the total area examined. In several places the relation to the blood vessels is quite marked but in most places no such relation can be made out.

Pancreas--The pancreas shows no abnormality. Glandular and island tissue is represented and is normal in appearance.

Bowel--there is one section of small bowel. This is through one of the small nodules on the surface. This nodule is produced by a perivascular inflammatory reaction involving the wall and surrounding tissue about a small artery. This has caused considerable proliferation of the intima so that the lumen is almost entirely closed in one section and entirely so in a small adjacent artery. Inflammatory reaction involves the muscularis only very slightly and does not involve the mucosa.

Kidney--there are ten sections of kidney. These sections show a variety of changes. Glomeruli show very extreme damage. Only an occasional glomerulus is approximately

normal in appearance. Next to these glomeruli the cells are usually swollen and the endothelium particularly of the blood capillaries shows a great deal of swelling. In others there is some escape of blood in the glomerular spaces and a few polymorphonuclear leukocytes are infiltrated into the glomerular tuft or lie free in the glomerular space. All stages of damage are encountered from glomeruli containing 1-2 capillary loops which show thrombosis and cellular infiltration to glomeruli which are entirely obliterated by fibrous tissue. Most of the change appears to be fairly recent. The fibrous tissue which is infiltrating the glomerular tuft or is forming crescents about the capsule and the fibrous tissue which is obliterating the glomeruli in many places is apparently somewhat active because the cells are large, nuclei are prominent and intracellular substance is not particularly marked. Polymorphonuclear infiltration is prominent everywhere and in some places make up the larger portion of the tissue occupying the glomerular space. Careful search for bacteria was made in Methylene Blue stain but no definite organism could be made out. The tubules show considerable atrophy. In some places they are almost entirely collapsed but generally are somewhat dilated. The epithelium is markedly thinned and the space is filled with precipitates of serous and occasionally bloody fluid. Casts are found in many

places. The interstitial tissue shows rather marked edema. Capillaries are congested through most of the tissues. The blood vessels show perhaps the most striking change. The medium sized vessels of the size of the arcuate arteries practically all show a marked arteritis with a heavy infiltration of inflammatory cells extending for a short distance into the surrounding tissue forming a rather firm cuff about the vessels and infiltrating the full thickness of the wall. In some places partial thrombi have formed within the lumen which partially occlude the space. An occasionally completely thrombosed artery is found. One of these is noted in association with an infarct measuring approximately 2 mm. in diameter. The center of this is necrotic although the shadows of the cell membrane still remain. About the border there is a marked cellular infiltration and a rather marked degree of congestion. Collecting tubules are in fairly good condition.

Adrenals--there are two sections of adrenals, one for each gland. The adrenal substance itself is fairly normal in appearance. The most striking change is in the blood vessels surrounding the adrenals which practically all show a periarteritis or arteritis. Intimal proliferation is very common and several vessels are entirely occluded.

Pituitary--there is one section which is entirely normal.

Final Diagnosis--

Mastoiditis .	Periarteritis of the kidney, heart and adrenals.
Abscesses of lung, liver, kidney and heart.	Bronchopneumonia
Acute Nephritis.	Acute glomerular nephritis.

Case 2.

Miss J.A.N. entered the Covenant Hospital for the second time on 1-13-36. She was a white, single female aged 28 whose occupation was that of store detective.

Her complaints were as follows:

1. Loss of 40-50 lbs. of weight in one year.
2. Severe pains in the chest and abdomen for 6 months.
3. Severe anginal pains over her heart.

Patient was well until one year ago when, because attacks of pain over her heart, she began consulting doctors. She was treated with KI and her symptoms were ameliorated. and she gained some weight. She enters the hospital at this time in coma.

Present Illness: The patient worked until July of 1935. Beginning about January 1935 noticed she had some cough and tired easily. In July the cough became much more severe and necessitated her going to bed. X-ray examination and sputum tests were negative for tuberculosis. Asthmatic symptoms developed in September 1935. She was referred to an eye, ear, nose and throat specialist and an operation was performed on both antra. No relief was experienced

and the asthma increased in severity. Administration of adrenalin became quite frequent and gave relief for only short periods of time.

Past History: Only childhood disease was measles. She had the influenza in 1918 and was quite sick for one week. During this year she was in contact with an active case of tuberculosis. Tonsils removed in 1922. She had the unilateral mumps in 193-. She was always slight of build but very active. Manteaux and wasserman negative.

Physical Examination: (November 1, 1935) Revealed an emaciated white female in bed. Pupils reacted to light. Examination of mouth showed tongue and pharynx normal. Examination of nose showed no marked pathology although there was some slight chronic inflammatory tissue present. Examination of the heart revealed rate very rapid, no murmurs or enlargement. Examination of lungs showed coarse resonant rales throughout both lung fields. Examination of the abdomen showed some tympany, no masses or tenderness. General musculature of the entire body was poor. Emaciation was marked. Due to the extreme weakness of the patient she was not weighed. Estimated weight sixty pounds.

Laboratory: Urinalysis done on four separate occasions showed only a trace of albumin. Blood counts done on numerous occasions ranged between 4,600,000 and

5,300,000 reds, the hemoglobin from 90% to 100%. The white count varied from 15,000 to 22,000 with marked eosinophilia from 15 to 60%. Repeated stool examinations were negative for parasites and ova. Wasserman was negative. Basal Metabolism tests made when the patient was able to have the tests run were plus 16 and plus 19. A barium meal was given and the roentgenologist reported the Gastro-intestinal tract negative. Examination of the fundi of the eye showed them to be normal. Sputum examination was made for fungi and the results will be reported in a separate section. N.P.N. was within normal limits.

Hospital Course: The patient was first seen by Dr. MacQuiddy on November 7, 1935. The asthma was of the status asthmaticus type with nonproductive cough. There was some temperature but not marked. Adrenalin had to be given every two hours and caffeine sodium benzoate was being given to stimulate the heart action. On November 8, Potassium Iodide by mouth was started. Within twenty-four hours the cough became productive and the use of adrenalin became much less frequent. Within four to five days the patient was breathing normally and the cough had materially decreased. The patient appeared improved. The change in the patient was rather startling and the gain in weight was marked. She was

able to leave the hospital on December 1, 1935. Her weight at that time was 89 lbs. The patient continued to improve at home for about a month, when she seemed to have reached a stationary point. There was some trouble in eating although this was not marked. On January 12 the patient had a headache severe enough to necessitate her going to bed. There was no paralysis at this time but some stiffness of both arms, more marked in the right than in the left. On the morning of January 13 the patient complained of the headache being very severe and about eight a.m. she began having convulsions. The convulsions were succeeded by a coma and the patient died at one-thirty p.m.

Autopsy:

General Nutrition: Poor

Appearance: Emaciated.

No scars or abnormalities on external surface.

Pupils and sclera normal.

Very little subcutaneous fat.

Pleura: Right lung--no adhesions. Left lung--some adhesions anteriorly.

Lungs: Areas resembling infarcts in lower lobes of both lungs. Pneumonic areas throughout both lungs with miliary nodules studding both lungs--also peculiar striated markings that resembled anthracosis.

Pericardium: Miliary nodules studding the pericardium.

Heart: Normal in size. Miliary nodules and vegatative growth in the walls. The valves show vegatative growth and are very friable. The anterior coronary was almost entirely obliterated with atheromatous changed.

Aorta: Miliary nodules.

Stomach: wall studded with miliary nodules.

Liver: studded with miliary nodules.

Gall bladder: normal.

Spleen: studding of spleen with miliary nodules.

Pancreas. suggestion of nodules present on wall.

Kidneys: suggestion of nodular studding.

Pelvic organs: normal.

Intestines: miliary nodules studding almost the entire length of the wall of the intestines.

Head: large orange-sized hemorrhage encapsulated with softening around it, in the left cerebral hemisphere. The hemorrhage extended into both lateral ventricles.

Anatomical Diagnosis: Generalized blastomycosis; cerebral embolism.

Microscopic Examination:

Heart--Pericardium shows extensive cellular infiltration. Eosinophils are present in large numbers in most areas. The most severe reaction is perivascular although only a few vessels are involved in this type of reaction. The myocardium shows scattered areas of degeneration usually

associated with inflammatory reaction which is also perivascular in position. The vessels involved in this process contain a thrombus of white cells and fibrin, the wall of the vessel is necrotic, being infiltrated by inflammatory cells. This reaction is continuous with the surrounding tissue. The endocardium shows several areas of severe inflammatory reaction some extending deeply into the underlying muscle. Large thrombi have attached themselves to these inflamed areas, eosinophils and red cells are the principal components of these thrombi.

Lung--There are several sections of lung showing no changes in the pleura. There are a moderate number of pigmented phagocytes in the alveoli but no areas of inflammatory reaction are present in these sections. Bronchi and blood vessels show no change.

Liver--several sections of liver show several areas of vascular and perivascular inflammatory reaction entirely similar to those described in the heart. The central portions of the lobules frequently show some atrophy of the liver cords and vacuolization of the liver cells is rather common.

Spleen--the single section of spleen available shows a number of areas of necrosis with surrounding inflammatory reaction. Eosinophils make up a large proportion of these inflammatory cells and the number of eosinophils in the

spleen, elsewhere is greatly increased. Only a few blood vessels seem to be involved in this inflammatory process. Kidney--sections of kidney show perivascular abscesses similar to those already described. Several small abscesses are present in the cortex where they spread to involve tubules and glomeruli but apparently involving the glomeruli last. The lining cells of the tubules are quite swollen and there is some sloughing of their free edges. Brain--there are several sections of brain, only the superficial parts being represented. None of these show inflammatory reaction similar to that found in other tissue.

Eosin-methylene blue stains have been studied carefully for the presence of bacteria or fungi. Neither could be identified.

Pathological Diagnosis: Periarteritis nodosa involving heart, liver, spleen and kidney.

Periarteritis nodosa complicated by a
Pulmonary Yeast Infection
as shown by the work of Dr. MacQuiddy

The case at hand was first diagnosed as a fungus infection due to the large numbers of yeasts found and cultured from the thick mucilaginous yellow sputum; and the final pronunciation of Periarteritis Nodosa not given until autopsy.

At the time the first sputum specimen was taken, on November 7, the patient was near death from an asthmatic asphyxiation. Examination of sputum in 20% NaOH showed spherical to ellipsoidal cells which were doubly contoured, granular, and averaged 7 microns in diameter, isolated or sprouting by buds or with septate extensions up to 50 microns; also some larger heavy-walled spherical cells of 10 microns in diameter. A second specimen taken two days later revealed the same condition. Cultures on wort agar yielded pure colonies within two days. The KI therapy effected instantaneous relief and within two weeks the asthmatic symptoms had entirely disappeared and the patient's general condition seemed much improved. A saline suspension of the organism, heat killed, was injected intradermally (0.05 cc.) and caused a slight skin reaction. However, since the vaccine was not used for a month or more after preparation, the result is not regarded as necessarily significant; because in other cases of our experience old vaccines have given slight or negative results whereas fresh ones have subsequently been strongly positive. Unfortunately later cultures from the patient were not attempted and the body had been injected before autopsy, making culture impossible then.

On wort agar there was an ivory pasty growth (which

became pale pink at times or deep brown in age) with small convolutions and deep penetrations into the media; and which gave moderately rapid growth at room temperature. Microscopically there were many capsulated cells (6.3 microns) and ordinary yeasts of 5.5-6 microns in diameter, often showing irregularity in outline, (both indicating unfavorable conditions); transitional yeasts (11x2.5 microns), racquet mycelia of cells about 5-12x4.5-7 microns and chlamydospores of 7 microns in diameter.

On glycerine agar there was a smooth white pasty growth, ridged in the center, and just barely penetrating the agar. It consisted of narrow elongated yeasts (4.5-1-.5x1-2 microns), irregularly shaped, and also of small round yeasts (3.5-4 microns).

On Sabouraud's dextrose agar there was a pasty growth, white and cerebriform, which slightly penetrated the media and whose center was covered by small tubercles. Microscopically there were mostly spherical cells of 5.5-6.5 microns in diameter, thin-walled, containing one large oil-droplet, with unipolar to multipolar budding and a few transitional elongated yeasts averaging 1-.5x3.5 microns.

On potato dextrose agar there was a smooth white pasty growth with no penetration of the media. Microscopically there were strictly small yeasts 2.8-3x2.5 microns in diameter, with mostly unipolar budding.

On Gorodkova's-Maneval agar the growth was ivory pasty with small convolutions and deep penetration into the media. Microscopically the surface growth consisted of small spherical cells of 3-5.5 microns, very granular and often showing multipolar budding; intramedially, pseudomycelia of cells 8.5x3 microns with granular chromophilous contents; some terminal chlamydosphores of 7 microns with thick capsules of 1.5 microns; similarly sized isolated cells containing three visible endospores were noted frequently; linear tetrads were also occasionally found and chlamydospores of 7 microns in diameter.

On nutrient broth there was no ring nor pellicle but a fuzzy basal growth and a yeasty deposit. Microscopically there was a relatively filamentous growth, with cells 35 x 7 microns and with walls of 1.2 microns pseudomycelial cells of 7.5x4 microns; large heavy-walled resting cells of 7 microns with capsules of 1.5 microns; large budding yeasts of 6 microns in diameter with buds of 3.5 microns; some capsulated cells containing four endospores of 2-3 microns in diameter. In hanging drops on broth the growth was mostly as budding yeasts with occasional short chains of pseudomycelial cells.

The organism grew well at either room temperature or at 37° C. It was a normal aerobe but capable of anaerobic growth in broth.

A culture grown on Sabouraud's agar was fixed in Hermann's fluid, put up in paraffin and cut at 7 microns and stained with Haidenhain's iron-alum haematoxylin. No definite nuclei were noted but there was much scattered chromatic material in the form of deep-staining granules of about 0.5 microns and open networks of fine threads apparently running around the periphery of the cells. The chromophilic material was especially conspicuous in the young avacuolate yeasts. All parts were surrounded with a fine mucous capsule. Only a few recognizable yeasts were found and they were in advanced stages. No change was noted in inter-agar growth, except that there was more pseudo-mycelial growth.

Biochemistry.

Gelatin showed no liquefaction in thirty days but a hollow basin growth with an inverted pine tree along the stab.

Litmus milk was acidified and coagulated within two weeks, without subsequent digestion of the curd. There was a slight ring, but mostly basal growth. The organism grew as a spherical yeast of 3.5 microns in diameter or with elongated cells averaging 12 x 3.5 microns.

Sugar reactions were as follows:

	Acid	Gas	
Dextrose	x	x	In 17 days becoming alkaline and with gas receding in all cases.
Levulose	x	x	
Maltose	x	x	
Sucrose	x	x	

	Acid	Gas
Galactose	x	o
Lactose	o	o
Mannitol	x	o
Inulin	x	o
Rhamnose	o	o
Arabinose	o	o

Animal experimentation.

Five white mice were injected: (a) with a 1:1 sputum-saline suspension, 1-2 cc. intraperitoneally (the sputum was two months old but had been kept on ice); (b) saline suspension of the organism on Sabouraud's agar, 1-2 cc. intraperitoneally; (c) 1-2 cc. intrapleurally; (d) 1-10 cc. intravenously; (e) several feedings on food. Mouse (a) was killed a month after injection and showed no obvious pathology. Cultures were negative for the yeast. There was a fine filamentous fungus obtained from the kidney and B. megatherium from the liver.

Mouse (d) died 24 days after inoculation. The anal region was swollen, there was blood in the peritoneum; the liver was brownish and slightly spotted; the lungs were small, shrivelled and white spotted; the abdomen was enlarged and the intestines swollen with gas. Yeasts were seen in smears from the kidneys but cultures were negative as were they also from the brain, liver and spleen.

Mouse (c) died in 45 days. There was a swollen red spot to the left of the anus with a large quantity of thick yellow pus which yielded a growth of Streptococcus. The stomach was much congested with food and contained many

yeasts which were found to differ biochemically from the test organism. The lung cavity was shrunken and pushed back by the swollen abdomen. The lungs and heart were adherent to the pleura. The lungs contained blood clots and were friable. The liver was normal and the kidneys slightly inflamed. Brain was normal; no peritoneal fluid. Apparently the immediate cause of death was stomach congestion. Cultures were negative.

The other two mice were killed in 45 days. Mouse (b) showed a large pus bag in the anal region. The kidneys and lungs were inflamed and the spleen noticeably enlarged; the brain was normal. Cultures negative. Mouse (e) showed no pathology.

A guinea pig was inoculated intraperitoneally with 2 cc. of a saline suspension and a week later intradermally with 0.05 cc. A positive skin sensitivity was demonstrated especially in 24 hours. Moreover, the site of the second inoculation developed a definite deep nodular infection with pus similar to that in the anal region of the mouse. This displayed no foreign organisms in the smear and was not cultured. A large subcutaneous nodule developed at the site of the intraperitoneal inoculation likewise. Autopsy 36 days after the initial injection revealed much necrotic tissue in the dermis and a rather large area of adhesion of the intestine to the peritoneal wall; no other

macroscopic nodules were visible. Cultures of the skin nodule yielded a positive yeast culture which agreed with the test organism. The various organs were negative for cultures and showed no histopathology.

The second guinea pig received 2 cc. of a saline suspension intramuscularly in the high thigh and a month and half later the same dose intraperitoneally. Nodules developed at both sites. The animal was killed 2 1-2 months after initial injection. Lesion in the thigh had healed but on the abdomen there was a swollen red area of about 2 cm. in diameter which extended from the peritoneal wall to the surface. It was composed of necrotic growth and a white pus. Smears showed many yeasts in the lymphocytes. The cultures were positive.

Serology.

Blood taken from guinea pig (1) just before death was centrifuged and the serum used to check the agglutinating power of the test organism and that of Monilia albicans, M. spp., and Saccharomyces cerevesiae; titers from 1-10 to 1-1280. There was no lysis and although there was some agglutination it was of a low titer and not very specific for the injected organism not could relationships to Monilia or Saccharomyces be determined. Repetition of this experiment gave identical results. The same procedure was also carried out with guinea pig (2) using the test

organism and a Monilia very pathogenic to rabbits. There was specific agglutination in the low titers only.

Serological Tables:

Guinea Pig (1)

Culture	1-10	1-20	1-40	1-80	1-160	1-320	1-640	1-1280
Sacch. monilioforma	4	3	3	4	3	3	3	2
Sacch. cerevesiae	1	1	1	2	1	1	1	1
Monilia albicans 1-6	3	1	3	2	2	2	1	1
Monilia spp. 143	1	1	2	1	1	2	0	0

Guinea Pig (2)

Culture	1-10	1-20	1-40	1-80	1-160	1-320
Sacch. monilioforma	3	2	1	1	1	0
Monilia spp. 148	1	1	0	0	0	0

Identification of the organism:

This organism is classified in Saccharomyces because of the production of ascospores parthenogenetically in isolated cells. However, it does have the ability to penetrate solid media with a "monilioid" type of growth not

usual for true yeasts. In old cultures heavy-capsulated chlamydospores are formed which burst from the mucilaginous covering upon germination. These latter two factors would remove the organism to the genus "Monilia" if it were not for the endospores. Comparison with several species of "Monilia" and with Saccharomyces cerevesiae revealed this organism to be a separate identity.

Because of the great confusion and lack of consistency in yeast nomenclature, as well as the lack of agreement of this organism with the commoner pathogens, it was thought best to designate this by a new name - hence, Saccharomyces monilioforma.

Discussion:

Although we are not able to offer definite proof that the fungus concerned had any direct connection with this case of Periarteritis Nodosa, we have felt it worthy of attention. The association of yeasts with asthma in a great percentage of cases is becoming noteworthy. Autogenous vaccine therapy and the use of the more or less specific fungicide, KI, have given marked relief. The types of lesions, progress and pathology associated with certain other mycotic infections such as Blastomycosis, Coccidiodal granuloma and Torulosis show many similarities to Periarteritis Nodosa (Jacobson). They become systemic and metastases through the blood vessels

are fairly common resulting in nodules in the skin, lungs, kidneys, heart, spleen etc. Robertson (Ophuls 1923) said that it is probably true that veritably every granulomatous infection in the body gives rise to a Periarteritis Nodosa to a certain extent.

Yeasts have been isolated from other diseases of unknown etiology i.e. sarcoma, Hodgkin's disease etc. with no proof of association. The interesting Rose monograph on Hodgkin's disease tackles the yeast problem vigorously and pauses long over the "Barber" yeast with definite evidences of pathogenicity but not of the disease, and then passes on to a likely virus etiology. Fitchett and Weidman have made observations on generalized torulosis associated with Hodgkin's disease. The present report is, to our knowledge, the first of a yeast associated with Periarteritis Nodosa and is offered primarily as an observation.

Most investigators believe that this disease is definitely of an infectious nature, but whether primary and specific there is no general agreement yet. The occurrence of epidemic forms in wild deer strengthens the view (Nieberle). The old idea of Syphilitic origin has been abandoned. The relationship to streptococcus infections, arthritis, etc. is still a plausibility even

though cultural proof is yet lacking. Virus (the intangible) is the goat. However, the positive animal infections by use of pathological tissue extracts is rather substantial evidence (Lamb). Ophuls mentioned crystals in cultures and pathology which might be virus. Robertson (Ophuls) further suggests the disease as a form of rheumatism with a tissue specificity.

In reviewing the case histories in the literature we were struck with the frequency of pulmonary involvement both early and especially in the final stages. It is suggested that in the future sputum be examined for yeasts in addition to TB organisms.

The fact that the main pathology is localized in the media of the blood vessels or occasionally in the lymphatics is unique, and the presence of a specific enzyme, toxin or virus seems likely.

Eosinophilia where noticed came late in the disease associated with the asthmatic condition and was confined to infiltration in the lesions and not in the circulating peripheral blood (Motley). Its significance is not understood, but it indicates simply the absorption of necrotic tissue and so is to be expected in granulomatous infections. Lothrup has recorded 60% plus eosinophilia in mycotic infections of the Blastomycotic type and in some Streptococcus

infections, such as scarlet fever, there may be 25% eosinophiles (Cecil).

We have concluded that the yeast isolated from the sputum in this several-months advanced case of periarteritis Nodosa is pathogenic and was no doubt influential in the Patient's condition. Regarding its initial connection with the disease we are unprepared to state.

THE HISTO-PATHOLOGY OF PERIARTERITIS NODOSA

In reading over many cases of this interesting disease syndrome we find that the pathology may be divided into four histological groupings:

1. Early acute stage.
2. Advanced acute stage.
3. Granulating stage.
4. Healed stage.

This concurs with the belief of Weir (56) Arkin (2) and others.

In examining sections there is found a great difference in the acute stage and old chronic or healed periarteritis Nodosa. The early acute stage consists on one hand of an alterative degenerative process in the media, sometimes including the intima, sometimes all three coats eventually leading to a characteristic ring-like band of necrobiotic tissue including degenerative muscle cells and fragmented elastica. The beginning stage is first characterized by edema of the media and the appearance of thready fibrinous exudate about the elastica interna.

The acute inflammatory or advanced stage is of the exudative type. It is characterized by infiltration of media and externa by eosinophils, lymphocytes, polymorphonuclear leukocytes and plasma cells. There is

destruction of the media and fragmentation. It is generally thought that at this stage we have the first signs and symptoms, such as chills, fever, abdominal pains, myositis, etc.

Following this we enter the granulating stage in which we see nature's attempt at repair of the injured blood vessels. Fibroblasts move in. Occasionally we see foreign body giant cells present and the scar tissue is laid down. If the wall is severely weakened we find aneurysms forming which thrombose and granulate. In others the healing stage is limited to the media and externa and we find nodular masses of connective tissue laid down having the appearance of tubercles. These masses of scar tissue vary a great deal depending upon the size of the lesion. A rather curious feature of this repairative stage is that the intima at the site of the lesion often thickens until the lumen may be occluded. This causes areas of infarction and extensive tissue death. This is found rather commonly in examination of sections of the kidney.

The final stage is reached when the repair is complete and possibly there is some attempt at new elastic fibrile formation in the media. When this stage is reached it is generally concluded that the patient has

his fall in temperature and period of general well-being. After a varying time it is typical for the process to be repeated and it is definitely known that this disease is characterized by exacerbations and remissions.

In examining any autopsy material with this disease we find all four stages going on at nearly the same rate. This is supposed to be the cause of death. The acute changes overcome the repairative stages and the body can no longer cope with the infection.

To study the involved histo-pathology of the organs of the body and indicate what may be expected when they are affected by the disease known as Periarteritis Nodosa I propose to give a typical description of each organ so involved. In the following description it must be remembered that the lesions may be microscopic or macroscopic in size but histologically all are alike.

First let us consider the lesions in the arteries. It is common for this disease to attack only the medium-sized arteries and the lesions consist in a heavy infiltration of the peripheral layers of the adventitia with leukocytes, mostly with eosinophiles but there may be also lymphocytes and plasma cells. In the central parts of the adventitia we see the greatest number of these cellular elements. As we go inward we find that the

leukocytes are much less numerous. Here they are mostly fusiform or irregularly shaped cells which contain large clear nuclei. The general appearance of these cells is that of fibroblasts. The muscular layer is generally fairly well preserved but you often see areas in which the muscle cells are more or less vacuolated and the media invaded both by the eosinophiles and the large proliferating cells of the adventitia. The changes in the adventitia often are not localized in the shape of nodules but may be quite diffuse and adjacent to this you may find stretches of the arteries which are quite normal in appearance. It is characteristic of the intima to show a marked cellular thickening apparently corresponding more or less closely to the damaged parts of the media. The cells in the intima may present a fibroblastic appearance. When the process is recent some of these cells may be derived from the endothelium. In the thickened intima we also find scattered eosinophiles. In many vessels evidence of recent thrombosis can usually be found. It is also common to find aneurysmic dilatation at the site of the lesions.

The lung usually shows an involvement of the arteries of the pleura, the interlobular septum, of the bronchial tubes and of the pulmonary tissue proper. The pleura and

interlobular septum as a rule are heavily infiltrated with eosinophilic leukocytes and the blood vessels will be very much congested. The endothelial cells of the pleura are often distinctly swollen. There may or may not be nodular deposits on the surface of the pleura.

The wall of the bronchi is usually diffusely and heavily infiltrated with eosinophiles and plasma cells and in addition you may see some fibroblasts. The pulmonary tissue proper is usually loaded with eosinophiles. This in places may lead to small areas of bronchopneumonic consolidation in which the aerating spaces are completely occluded with eosinophiles, lymphocytes, red blood corpuscles and considerable fibrin. Hilar lymph glands often show a marked infiltration of eosinophiles but there is usually no nodule formation.

Spleen. The pulp of the spleen is usually found to be diffusely infiltrated with eosinophilic leukocytes. The arterial lesions are not marked but the media and intima of the arteries are often thickened and fibrous with a few eosinophiles in the new fibrous tissue.

Heart. The heart is often affected by the disease syndrome of Periarteritis Nodosa. We may see the nodular formation macroscopically as a diffuse studding along the coronary vessels. Quite often there are considerable

collections of eosinophiles and lymphocytes between the myocardium and endocardium. In the diseased muscle there are usually some fairly large cellular scars. The most remarkable lesions may be found in the pericardium where, in addition to the characteristic changes in many arteries and some veins, there may be a diffuse infiltration of the fat with leukocytes and a nodular proliferation of the top layers. These nodules arise from the connective tissue of the surface layer of the pericardium with a broad base and project onto the surface. They are about the size of tubercles and present much the same appearance. They are often found to consist of vascular young connective tissue full of eosinophiles and plasma cells.

In studying the effects of Periarteritis Nodosa on the kidney we see all of the forgoing changes in the vessels with damage to the kidney tissue proper with a resultant decreased urinary output and with developing symptoms of retention. The effect has been quite well summarized by Keegan (30). From the perivascular connective tissue granulation tissue heavily infiltrated with eosinophiles and plasma cells extend out into the kidney tissue proper, filling the spaces between the tubules and causing their collapse. The connective tissue overgrowth may extend out from the glomerular tufts completely obliterating the capsule. In the tubules

areas are often found which appear as accumulations of more or less degenerated eosinophiles and hyaline casts. The epithelial cells of the convoluted tubules are usually found to be swollen and desquammated. Throughout the blood vessels there is a marked congestion while in the obliterated vessels we see all stages of infarction. This infarction may range from less than 1 mm. in diameter to several mm.

The lesions in the liver are much like those of the kidney. Often the destruction of the arterial walls is even more complete and the tendency of the granulation tissue to arrange itself in circular nodules is even more marked. There may be a pronounced tendency to proliferation of the vascular endothelium in these nodules. In the center of some of the obliterated arteries attempts at canalization are found apparently developing from dilated capillaries. Again there is the usual leukocytic infiltration. The liver cells are often quite normal in appearance except that the central capillaries are greatly dilated and the liver cells surrounding them may be distinctly atrophied.

There is few characteristic changes in the pancreas. It is entirely dependent upon the amount of arterial involvement and in the worst cases we find a moderate infiltration of connective tissue and

leukocytes which is usually concentrated about the ducts. Even between the acini and in the islands of Langerhan's eosinophiles may be found singly or in groups.

In a study of the stomach we often find moderate to diffuse infiltration of the mucous membrane with leukocytes. Usually the glands are normal. In the submucosa there may be many eosinophiles in the immediate vicinity of the arteries. The connective tissue between the bundles of the muscularis are in various degrees of infiltration. Similarly the peritoneum may contain leukocytes and show a miliary studding of nodules over the mesentery. In general, the effect of Periarteritis Nodosa on the stomach is characteristic of the entire intestinal tract.

In studying the the skeletal muscles we usually find some evidence of waxy (hyaline) degeneration; the endomysium and the parimysium showing moderate infiltration with eosinophiles. Many of the small arteries will show their walls entirely replaced by cellular fibrous tissue and their lumina in all stages of obliteration.

The brain tissue characteristically shows areas of infarction with abscess formation or aneurysmic dilatation of the vessels and connective tissue

infiltration into the nervous tissue. It is a matter of record that nervous tissue is less often affected than the other organs of the body. We may have lesions affecting the arteries supplying peripheral nerves with resultant atrophy or symptoms of polyneuritis depending upon the degree of affection.

SUMMARY AND CONCLUSION

In case (1) of this series the predominate symptoms were those of a nasal diphtheria with considerable upper respiratory difficulty. The patient had had the usual childhood diseases and scarlet fever. She had been well up until two months before her entry into the hospital. She had no symptoms of Periarteritis Nodosa at any time until her hospitalization. The predominating symptom then became one of nephritis with gradually increasing uremia.

Case (2) was proven to have blastomycosis and responded to KI treatment. Her symptoms were severe anginal pains over her heart as well as pains in the chest and abdomen for six months as well as a weight loss of 40-50 pounds. Neither of these cases had any dominating myositis or abdominal rheumatism . In the second case there was a pronounced eosinophilia while in the first there was no definite increase.

In the first case the final diagnosis was Periarteritis Nodosa of the kidneys, heart and adrenals, complicated by acute nephritis, mastoiditis and abscesses of the lung, liver and kidney. With this great variation of pathology it is needless to say that it is difficult to determine what part of the pathology gave the

symptoms. In the second case the final diagnosis was Periarteritis Nodosa involving the heart, liver and spleen which was complicated by pulmonary yeast infection. In neither case was there any intimation before death that Periarteritis Nodosa was a factor. Case (2) is of interest because of the fact that the patient developed a large brain abscess from the Periarteritis Nodosa of the cerebral vessels. This is a rather unusual finding because of the fact that the nervous system is attacked in only about 8% of the cases. Usually when the brain is attacked there is atrophy or connective tissue proliferation rather than tissue break down and abscess formation.

Periarteritis Nodosa may be said to be either an inflammatory or an allergic disease of the smaller arteries, usually focal in character which may involve any and all vascular territories. The disease probably starts in the adventitia but soon involves all the coats of the arterial wall and leads to the development of microscopic and macroscopic granulomatous nodules, later to coarser fibrous nodules in the wall of the affected arteries usually with the formation of multiple aneurysms. Thrombosis is evidently quite common in the diseased arteries and may lead to necrosis in the tissues, (Infarcts

hemorrhagic necrosis and ulcerations. The inflammation may extend from the arteries into the adjoining tissue. The serous and mucous membranes are likely to become involved in this process. The etiology of this disease remains obscure. Many observers point to the relation to subacute "septic" rheumatic infection. The clinical picture seems to be in the main one of a subacute infection with localized symptoms resulting from the more or less marked involvement of various organs.

Friedberg and Gross (18) report that in four cases that came to autopsy widespread Periarteritis Nodosa was associated with rheumatic fever and rheumatic heart disease; the latter confirmed by Aschoff Bodies in the myocardium. These cases were all discovered in a series of eight cases of Periarteritis Nodosa which came to autopsy in the course of two years. Friedberg and Gross seem to believe that the simultaneous occurance of the symptoms of each make it probable that rheumatic fever is the common cause of the vascular lesions termed Periarteritis Nodosa. One of their cases had an attack of scarlet fever eight weeks before the symptoms of Periarteritis Nodosa became manifest and suggest it as a possible clue in that streptococcus veridans may be a causative agent. Neither of the two cases here presented show any relation-

ship to an allergic condition although they were not skin-tested. It is well to be remembered that the body tissues may become sensitized to the streptococcus thus giving a basis of foundation for the theory that the syndrome of Periarteritis Nodosa may be due to allergy.

In closing it might be well to suggest that when acute abdominal symptoms are present in a patient suffering from rheumatic fever, complicating Periarteritis Nodosa should be considered.

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