Dr. Fred Klenner reviews the etiology and history of the medical treatment of trichinosis. He reports that massive doses of intravenous vitamin C in conjunction with orally administered para-aminobenzoic acid (PABA) were used to successfully treat trichinosis. He recommends that all patients, whether medical or surgical, who are not responding to treatment be given four to twelve grams of vitamin C by needle each day. The rationale for massive doses of vitamin C given by needle, he says, is its value in "antibody formation and as a detoxifier in all pathological states."—*R.D.M.*

The Treatment of Trichinosis with Massive Doses of Vitamin C and Para-Aminobenzoic Acid

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Trichinosis in man is a disease that results from the eating of raw or improperly cooked pork. It has incapacitated and killed many thousands of people over the past centuries; even changed the habits and customs of many of our people. Although the muscle pathology was first described by Tiedemann in 1822, it was not until 1835 that the worms were demonstrated under the microscope by James Paget. This observation was made from a study of a section of striated muscle taken from a human at autopsy. The name Trichina spiralis was given to this disease by Sir Richard Owen shortly thereafter. In 1846 Joseph Leidy discovered the trichinae in the extensor muscles of the thigh of a hog. He noted that there was no difference between these trichinae and those seen in several human subjects in the dissecting room. Herbst, in 1850, established that an animal that eats trichinous meat may develop trichinae in its muscles. Leuchast in 1856 and 1857 and Virchow, also in 1857, conducted feeding experiments in which they showed that the muscle trichinae are freed from their cysts upon ingestion by the 'new host' and grow in size within the intestine of the latter. It was Leuchast who demonstrated that the female intestinal trichinae are viviparous. In 1860 Zenker demonstrated that the parasite could cause a fatal illness in man in the course of a few weeks. Zenker suggested that the larva were disseminated by way of the chyle ducts and the blood stream. In 1866 Zenker gave the disease the name Trichiniasis; later he adopted the name TRICHINOSIS. The first case diagnosed during the phase of acute illness was reported in 1862 by Frederick of Heidelberg. It is of interest to note that as early as 1863 the microscopic examination of pork for trichinae was practiced in some parts of Germany as a public health measure. By 1866 Virchow was successful in instituting governmental inspection of pork in this same country, and in 1879 a law was passed in Prussia for this practice. In 1896 Railliet changed the name Trichina

spiralis, proposed by Owens in 1835, to that of Trichinella spiralis. Chazal from the Medical College of South Carolina was the first to observe trichina cysts in the United States. The same year, 1842, Bowditch reported the first case in America in a human. Although Fielder as early as 1864 reported trichinae in blood clots in the right auricle and ventricle of experimental rabbits, it remained for Slaubli in 1905 to demonstrate larva in the heart's blood of living infected guinea pigs 7 to 18 days after infection. In 1909 Herrick and Janeway showed that young Trichinella spiralis were present in the circulating venous blood of a patient 10 to 12 days after onset of symptoms, and in 1941 in the arterial blood of a man by Dammin. In 1914 Van Colt and Lintz recovered young trichinae from the cerebrospinal fluid of a female patient 28 days after onset of the disease. Heller in 1933 reported that after 'escape' from their capsules in ingested meat, muscle trichinae lost no time in boring into the mucosa of the small intestine so that the necessary nutrition for their development could be obtained.

The life cycle as set down by Gould in 1945 follows: (1) infective pork is eaten by host, (2) meat fibers and cysts walls are digested, (3) muscle trichinae are liberated, (4) trichinae larva develop in small intestine into sexually mature adults which capsulate, (5) gravid females deposit young trichinae in mucosa of intestine, (6) from lymphatics young trichinae reach blood circulation, (7) finally, the trichinae encyst in the muscle of the host. Routine autopsy findings reveal that the incidence of infection in America is roughly 16 percent. This makes trichinosis a major health problem and warrants the discovery of a specific drug for its control. This paper is to present this specific antibiotic.

The diagnosis of trichinosis is generally not an easy one to make. This is especially true when the disease occurs sporadically rather than in epidemic form. Hall in 1937 enumerated fifty different disease conditions which have been mistakenly diagnosed in persons ill with Trichinosis. Our own case might have been interpreted as being: (1) influenza, (2) angio-neurotic edema, (3) conjuctivitis, (4) erysipelas, (5) nephritis, (6) encephalitis, (7) atypical pneumonia, (8) typhoid (our case gave a titer of 1:80 for typhoid. When first seen the impression entertained was virus pneumonia with a complicating Bright's disease. A urine analysis, however, was negative, ruling out the nephritis. Since there were definite pulmonary findings by auscultation (not confirmed by fluoroscopy), the patient was admitted to the local hospital for study and treatment. Osler in 1899 regarded the following symptoms as characteristic of the disease: (1) edema of the eyelids (transverse facial edema of Magath 1937), (2) leukocytosis with eosinophilia, (3) pain and swelling of the muscles. To this must be added fever and profuse sweating. The term 'English Sweat' as given by Glazier in 1881 was not too far afield. Profuse sweating WITHOUT correlation to the fever curve was demonstrated by our case. This 'sweating syndrome' was found to exist only in the morning, usually around eight o'clock. (Interesting enough to report was the observation that the same pathology was found to exist with an identical pattern in a case of tick bite fever, which it was our privilege to treat several years before and which now was to play an important role in the treatment of the patient with trichinosis). An absolute diagnosis depends on a careful history that will reveal the ingestion of raw or improperly prepared pork, a complete physical examination, repeated white blood counts with the differential. The latter to indicate

the degree of eosinophilia and, what is more important, the degree of lymphocytosis. Positive skin and precipitin test are confirmatory evidence. Cardinal points to remember: (1) transverse edema of eyelids, (2) orbital headache, (3) photophobia, (4) chills, (5) morning sweats, (6) fever, (7) aching in muscles, (8) anorexia, (9) conjunctivitis, (10) hacking cough, (11) profound weakness.

The important discovery. of 'eosinophilia' as a diagnostic sign in trichinosis was made by Thomas Brown in 1897. Magath in 1937 stated that eosinophilia of more than 10 percent and "especially an eosinophilia that rises rapidly over a number of days" should suggest trichinosis. On the other hand, eosinophilia does not persist in the chronic phase of the disease when the trichinae are encysted in the muscles of the host. Wintrobe in 1952 indicated that this observation was not correct and that eosinophilia has been known to persist for years. One must question this report by Wintrobe and suspect that eosinophilia in such instances was due to other factors. Angio-neurotic edema can produce an eosinophilia count from 20% to 85%. This is true of many other allergic disorders. To accept the opinion of Wintrobe in this instance would be to deny the fact that the blood picture is due to the reaction of foreign proteins produced when the larva invades the muscle tissue. Confirmation of the absence of eosinophilia once the disease is relatively chronic with the larva 'hibernating' in their calcium shells within the striated muscle was made by Naught and Anderson, who examined 200 human diaphragms for trichinae at autopsy and found organisms in 48 instances (roughly 25 percent). However, in 58 percent of the positive cases differential white blood counts had been done during life and the highest eosinophilia cell count recorded in this group was 4 percent. In one instance in which 3,800 larva were recovered by the digestion of 50 grams of diaphragm muscle, no eosinophilia were found in the blood during life. In 1905 Staublin theorized that the eosinophilia was a reaction of the host to chemotactic substances given off by the larva during travel through the blood and during their growth in the muscle. This deduction is not correct. As pointed out by Thompson in 1910, if eosinophilia was due to specific toxin elaborated by the parasite, one would expect the count to be highest just before the larva become encysted and quiescent. Such is not the case. It is generally accepted that the eosinophilia is due to the stimulation of the bone marrow by foreign proteins arising from the invasion of the tissues by the larva and their development in the striated muscles, and by split products of the degenerated muscle tissue. A repeat wave of eosinophilia is sometimes seen, but this is always due to a 'new crop of larva.' Many investigators have found that even high counts will suddenly drop to zero or to an insignificant low in fatal cases. The same picture is seen in tuberculosis when with the closing days of a fulminating case the tuberculin test becomes negative. Likewise, people not infected with the tubercle bacilli but debilitated by any severe constitutional disease, marked malnutrition or even old age may react negatively to the tuberculin. Certainly, a morbid state does exist in patient's terminating their earthly sojourn with trichinosis. This break in allergy means nothing more than that the "powder is wet."

Another diagnostic test was fostered by Strobel in 1911. This was an antigen prepared from the animal muscle which demonstrated complement-fixing antibodies in the sera of infected experimental animals. In 1906 the idea was again sponsored by Fulleborn and in 1928 Bachman crystallized the idea by preparing a much

improved antigen. In 1932 Augustine and Theiler working with Bachman's new antigen concluded that it was of real value in the diagnosis of human trichinosis. In 1933 McCoy, Miller and Friedland found that the antigen test (skin reaction) of Bachman could be elicited as long as seven years after infection. For this reason the SKIN TEST, by itself, cannot be accepted as conclusive evidence in an acutely ill patient yet un-diagnosed.

If one examines the blood picture more carefully a most significant point becomes apparent. The following chart shows the white blood differential as found on twelve consecutive counts in our case.

	Eosinophiles	**Neutrophiles**	**Lymphocytes**
(Admission)	15%	73%	12%
10/ 8/51	20%	61%	19%
10/ 9/51	34%	51%	15%
10/10/51	35%	48%	17%
10/11/51	38%	34%	28%
10/12/51	37%	41%	22%
10/13/51	34%	46%	20%
10/15/51	30%	42%	28%
10/18!51	38%	38%	24%
10/20/51	41%	33%	22%
10/23/51	32%	45%	23%
10/24/51	32%	37%	31%

Here, on admission, the eosinophilia existed actually at the expense of the lymphocytes, indicating a toxic patient without antibody resistance. At this point the patient is in desperate circumstances. If time becomes a factor in favor of the 'host' the eosinophilia changes to increase at the expense of neutrophiles. This has no pathological inference except to connote rapid invasion of the muscle or muscles of the host. To be sure, the progressive increase of the eosinophiles does make the diagnosis more conclusive. The neutropenia which develops is not the important factor; it is the relative increase of the lymphocytes. The increase of the lymphocytes represents the degree of resistance of the individual and demonstrates the effort of response that the 'host' has against the toxins which are liberated by the parasite. We observed that as the lymphopenia 'cleared' the condition of the patient improved. This return to normal of the lymphocytes was in the final phase at the expense of the neutrophiles. (Interesting, too, was the fact that this same blood picture pattern was demonstrated in the case of tick bite fever to which we previously referred. In the tick fever case the initial differential count was 86% polymorphs and 14% lymphocytes. Twelve days later the count was 76% polymorphs and 24% lymphocytes. Here, too, the patient had reached a point of convalescence. The behavior of the lymphocytes is the real story of the changing blood picture and actually determines the prognosis. Rich, Lewis and Wintrobe observed that one of the functions

of the lymphocyte is concerned with the body's reaction to foreign protein. This is an allergic response and is characterized in trichinosis by the simultaneous stimulation of the bone marrow by 'foreign proteins' and the stimulation of antibody formation. Since the lymphocytic response runs parallel with the recovery of the patient, it emphasizes the fact that lymphoid tissue is responsible for this antibody build-up. McMaster found agglutinin formation in local lymph nodes draining the area of intradermal injection of antigen in mice before antibodies could be demonstrated in the blood. This finding would seem to refute the contention of others that antibody formation is a function of the reticulo-endothelial system or of 'plasma cells.'

CASE HISTORY: R. G., White male, age 31. Family history, habits and past history of no essential merit. Present illness began 9/26/51 with severe headache which was described as generalized but more intense through the eyes. He had dyspnea and chest pain, the latter not aggravated by deep breathing. There was generalized muscle pain particularly of the shoulder girdle. He had periodic phases when he felt like he was 'burning up' but this syndrome was not associated with the profuse morning sweats which he experienced the two days prior to admission to the hospital. He complained of extreme weakness and confessed complete anorexia. Swelling about the face began to develop the day of admission as did a very annoying hacking cough. It was the swelling about his eyes that prompted him to see his physician. Physical examination revealed a large white male who gave appearance of being 'over-grown' for the size of his integument. This was not a swelling compatible with myxodema or Bright's disease. There was a constant hacking bronchial cough which was non-productive. Fever was 104° F. There was a grade IV transverse facial edema limited to the orbits which failed to pit on moderate pressure. (The edema of trichinosis is firmer and pits less readily than does the edema of renal or cardiac origin). Photophobia was marked as was the conjunctivitis. These conditions 'framed' by the severe edema presented a ghastly picture. What appeared at first glance to be generalized swelling proved to be nothing more than solid muscle 'a bit out of proportion.' The throat was injected as was the nasal mucous membrane. Diminished breath sounds prevailed over the right lower and middle lobes and a few moist bronchial rales persisted over the main tree. The heart was essentially normal to auscultation although an ECG taken later in the course of the disease showed inverted T waves. This was not interpreted as cardiac pathology 'per se' but as a peculiarity of trichinosis. Repeat cardiograms made several months later gave normal tracings. The abdomen was negative except for low grade tenderness elicited on deep palpation. Genito-urinary system was that of a normal male. There was suggestive hyperalgesia of all striated muscle. The skin was warm and moist. Reflexes within normal limits. Laboratory test showed admission white blood count of 14,200 with a differential showing 15% eosinophiles, 72% neutrophiles and 12% lymphocytes. Hemoglobin 84.5%. Slight anisocytosis and polychromatophilia. Red blood count 5.2. Urea nitrogen was 12.4 grams. Urine was completely negative except for calcium oxalate crystals and an occasional white blood corpuscle. Blood agglutinations were negative for all the 'fevers' except for S. Typhi O which was reported by the State Laboratory as 1: 80. Trichinosis skin test was positive at 24 hours, manifested by a 14 mm. circle of

redness. This was on the 24th day of the illness and it was performed primarily for the records. Precipitin test also was positive for Trichinosis. Differential studies showed a climbing lymphocyte and eosinophile count. NOTE—After the patient recovered he remembered eating raw sausage.

His course in the hospital was stormy. Fluids were forced, especially citrus fruit juices. Massive doses of Vitamin C were given by needle. The rationale of this therapy was for its known value in antibody formation and as a detoxifier in all pathological states. Calcium-gluconate was given intravenously, 10c.c., for several days. The reason was purely empirical. Penicillin, aureomycin, terramycin and streptomycin were all employed in therapeutic amounts as were the triple sulfa drugs. These medications were given from 9-28-51 to 10-8-51. There was no evidence observed as to their value as the patient's condition gradually became critical. At eleven p.m. on October 8th the fever curve rose to 106° F and a state of semi-coma prevailed. At this time, following a careful review of his hospital course with special emphases on the fever curve, it became apparent to me that the syndrome was identical to that of another patient whom I treated in August of 1947 for tick bite fever. In this latter case PABA was used with dramatic results. The thought occurred to me that the possibility existed that, although the two diseases were remote as to gross relationship, the underlying toxin responsible for the pathology might be the same. Working on this premise, the patient, with great difficulty, was made to swallow 4 grams of PABA. Three grams were then given every two hours. Eight hours later he ate a full breakfast, the first food taken by mouth in several days. Strangely enough, the profuse sweating always present about this time in the morning was noticably absent. His temperature was normal. Over the next 48 hours the fever curve made a stepladder descent to absolute normal. At this time the PABA was discontinued in order to study the clinical picture. The recovery might possibly have been due to normal circumstances instead of the 'NEW DRUG.' This proved not to be true as the fever returned by the next recording and then generally went back to 101° F within 36 hours. The morning sweating returned and he began to revert to his previously described morbid state. After 48 hours the drug (PABA) was again administered and as before the clinical pattern changed to one of absolute normal. On this second trial the drug (PABA) was given 3 grams every two hours during the day and every 3 hours at night. Nausea was a complicating factor with the use of PABA but this was definitely controlled by crushing the tablets and giving it mixed with applesauce. This time the PABA was continued for nine days after which there was no reversal of symptoms, and the patient has remained in good health to the present time. It is debatable whether the nine days treatment was necessary. This can only be ascertained by its use on other cases or by the use of the drug on experimental animals which are not at my disposal. The allergic response was attacked with Kutapressin 1 c.c. given I.M. each day. Whether or not this influenced the eosinophile count is a matter of conjecture. From an academic view it would be interesting to administer this to subsequent cases of trichinosis under rigidly controlled conditions.

Para-aminobenzoic acid is a factor of the vitamin B complex occurring in yeasts and elsewhere. It is a peculiar drug in that it is essential for the growth and multiplication of certain bacteria and of a few higher organisms while, on the other hand, it inhibits

the bacteriostatic activities of the chemically similar sulfinamides. An observation made with the tick fever case indicated that the B complex should not be given as a tonic while administering sulfa drugs since the active factor is highly sensitive. In this instance of the tick case at least a 60% cure was effected by merely giving by needle Parabexin-S 1 c.c. B.I.D. and Brenonex Stronger 1 c.c. T.I.D. The addition of the PABA brought a complete cure within 36 hours.

Since there was some vague similarity of trichinosis to that of Rocky Mountain spotted fever, it was felt that a review of a large number of cases might give some light as to the correctness of the hypothesis. Permission was granted by the Committee on Records at Duke Hospital for this survey. No acute cases of trichinosis were on record at the Duke Hospital and the cases of Rocky Mountain spotted fever did not present all the detailed information desired simply because treatment was so diversified. It was very evident that the choice of drugs was based, not on results but on the trend of the time. Had some resident in medicine taken the time he would have found that of all the cases of Rocky Mountain spotted fever seen at Duke Hospital the medication that produced the most rapid cure was PABA. The records showed that the temperature was normal at least two days sooner when PABA was used than with the use of the newer mold derived drugs. Only one case with this disease died when treated with PABA and in this instance only half as much PABA was given as with all the other cases. This child also received ⅙ molar lactate solution. It was the only time this type of solution was employed in the Duke series and one wonders whether or not this played a part in the death. Case after case showed that the heavier the dose schedule for PABA the faster the cure regardless of the degree of illness of the patient. One patient admitted with 103.8° F was fully recovered in 48 hours receiving 24 grams of PABA per day. In another instance a child of eight years received 2 grams of PABA every 2 hours and here too the recovery was rapid. This suggested that the amount in 24 hours rather than the dose per hour was the significant finding. On the other hand, a case similar to the above required 6 days for recovery when only 1 gram of PABA was given every two hours. With drugs such as dramamine at our disposal one no longer need worry about nausea. It should be a maxim of medicine not to use a mold-derived drug in therapy when another type of drug is available. Medicine is in a peculiar era—a time when the choice of drug more often is dictated by the current pressure of an alert drug house than by the wisdom of the prescribing physician.

We believe that massive doses of vitamin C is an essential factor in treatment so as to assist the body in building antibodies. In 1934 Yavorsky, Almoden and King reported the Vitamin C fraction of the adrenal glands to be absent or greatly reduced in humans having died of various infectious agents. With patients refusing their diet and living at times for many days on dextrose by needle, subclinical scurvy will certainly develop. All are agreed that the store of vitamin C must be replenished each day. How can a patient obtain his required vitamin C if he is not eating and his doctor fails to meet his needs with injectable vitamin C. All must remember that the amount recommended by the National Research Council is a requirement necessary to prevent gross disease and is not a measure of the amount needed to maintain good health. This insignificant amount suggested by the Council fails to appreciate the individual renal threshold for vitamin C. Many people have a minimum requirement 20 times the recommended dose, and if

this is not ascertained by chemical analysis or allowed for by massive therapy, grave pathological consequences ensue. The individual who is not responding to treatment, whether it be medical or surgical, will respond if physicians will add four, eight or twelve grams of vitamin C each day, by needle, to their treatment schedule.

This paper has only one case to offer in the use of Para-Aminobenzoic Acid in the treatment of trichinosis. Thomas Brown had only the case when he presented his paper on the eosinophile count to the staff at Johns Hopkins. In discussing the paper Osler remarked that all realized that the evidence was on one case, but, he continued, if all of us will try the same procedure on all of our cases it will not take long to evaluate the facts. I trust the spirit of Osler still lives.

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