MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
February 19, 1970

Coccidioidomycosis, Leprosy and Biological Role of Lymphocytes

James W. Smith, M.D.

Coccidioidomycosis

[redacted] a five month old [redacted] male developed low grade fever, malaise, and irritability in [redacted] 1967. He was treated with sulfa for three weeks for urinary tract infection although the culture was negative. One month later the mother brought him to the physician because he had developed a slight cough and was not eating very well. Chest x-ray at this time revealed a nodular infiltrate covering the left upper lobe. A presumptive diagnosis of media stinal mass or tumor was made. There was over expansion of the left lower lobe; otherwise, physical examination was entirely negative. The patient looked good for a 6 month old. He had no fever in the hospital. An aspiration broncho gram was done which showed no filling in the left upper lobe. An angiogram was done which revealed narrowing of the arteries compatible with pulmonary parenchymal disease. Because of the possibility of tuberculosis, skin tests were applied. The tuberculin skin tests was negative but the coccidioidal test was greater than 20 mm of induration. Complement fixation titer showed a titer of 1:32. Gastric washings were obtained and spherules were demonstrated in the smear and a positive culture for Coccidioides immitis was demonstrated.

The patient had never been traveled outside of Dallas County. His grandfather worked at the local zoo but he had never been to the zoo. Finally, a history was obtained that in December a package of paintings from an estate in Southern California was opened in the living room of the home. The paintings had been wrapped in excelsior and the baby had been in the vicinity. Further studies could not be done since the excelsior had been removed. Skin tests of the parents and sibling were negative and complement fixation test of one parent was negative. After consultation with authorities in California and Arizona it was decided that no therapy would be given and the patient would be followed. He did very well and six months later nearly complete resolution of the infiltrate was present.

This case demonstrates the possibility of infection by fomites at sights distant from the endemic area of Southern California, Arizona and Western Texas. Previous studies have demonstrated that the organism

can be shipped many miles away from the endemic site. Although the infection in the lungs was far advanced in this individual, there was no evidence of dissemination. Consequently, the patient was followed without specific therapy. This demonstrates that even in a very early age group most individuals do very well with even far advanced primary pulmonary coccidioidomycosis.

[redacted], a 32 year old [redacted] male from [redacted], Texas, became ill in [redacted], 1968, with a productive cough, left chest pain, night sweats, malaise and weight loss. An x-ray showed left upper lobe pneumonitis and a small cavity in the left lower lobe. After antibiotic treatment, the infiltrate resolved to some extent but a coin lesion remained. He was referred to a thoracic surgeon in Dallas who removed the superior segment of the left upper lobe which contained the residua of a lung abscess. A complement fixation test was negative at this time but sputum and specimens from the abscess cavity grew Coccidoides immitis. Pathological examination revealed numerous inflammatory cells and fibrous tissue but no granuloma. No fungi were seen on microscopic examination. He was given two and a half grams of Amphotericin B intravenously following surgery. A thick-walled cavity developed and increased to 2 1/2 cm diameter and in thickness during observation; however, by June, 1968, the cavity became smaller. The patient continued to have malaise, heavy cough with occasional hemoptysis, night sweats and weight loss. He was transferred to the [redacted] in [redacted], 1968. He had a rapidly enlarging cavity in the left upper lobe. A chest tube was inserted into the cavity for drainage. Sputum, cavity material and urine cultures all grew Coccidiodes immitis. Laboratory findings at this time included a Hct. of 43, white blood cell count 8,000 with normal differential, BUN 21, creatinine, 0.8, and an SGOT 45. Serum electrophoresis was within normal limits. A coccidioidal complement fixation was 1:4, histoplasma 1:16. The patient was treated with 800 mg of Amphoteracin B in two months. Toward the end of the two months, he developed elevated BUN's and urinary changes with very small quantities. In the meantime, his cavity decreased in size and the sputum became negative. Consequently he was discharged and followed. He did well throughout the summer and his weight stabilized. He attempted to work but he would be tired after three to four days on the job. Dust bothered him considerably by aggravating his cough. Six weeks prior to admission in [redacted], 1969, he developed a head and chest cold with increasing sputum, which became purulent and foul smelling. He was re-admitted to the [redacted] in [redacted], 1969. At this time, he had decreased expansion of the left chest and moderate quantity of expiratory wheezes throughout the chest.

Chest films showed enlargement of the cavity with some pulmonic infiltrates surrounding the cavity. Sputum culture was negative. CF tests on admission was negative but was 1:16 one month later. His x-ray improved prior to institution of Amphoteracin B and patient remained afebrile and free of symptoms on hospital ambulation. He did develop hemoptysis during December, at which time infiltrates increased in the vicinity of the cavity and the size of the cavity increased. However, in three weeks, both the cavity and the infiltrate had improved. During this time he did receive Amphoteracin B but only 110 mg of it prior to the time of improvement.

This patient course demonstrates some previously observed features of coccidioidomycosis. First of all, surgery during the time of active infection often leads to worsening of residual pulmonary finding and may even result in dissemination. His most recent admission appears to be the result of a secondary bacterial infection in a persistent coccidioidal cavity. There is little evidence of dissemination or even activation of the coccidioidal infection at this time, consequently treatment is probably not necessary at the present time.

Coccidioidomycosis is an infectious disease produced by the inhalation of the fungus Coccidioides immitis. The disease is endemic in the Southwestern United States, including a large area of West Texas. The primary infection is asymptomatic in many, and symptomatic infections (Valley fever, San Joaquim fever, Valley rheumatism) are short lived in most. Less than 1% of those with an infection develop disseminated infection. It is important to recognize this stage of the infection since treatment does reduce the mortality rate.

Epidemiology

Coccidioidomycosis is endemic in the semi-arid Southwestern United States in an area corresponding to the limits of the lower Sonoran Life Zone. The area of endemicity extends into Mexico, including the states of Sonora and Baja, California. Other endemic areas include the Comayagua Valley of Honduras, certain Venezuelan states and the Gran Chaco-Pampa region of South America (Paraguay and Argentina).

The organism exists in soil in a mycelial form, from which are produced great numbers of chlamydospores which are infectious. In a series of studies, Smith and co-workers made significant observations which demonstrated that dust is the mechanism by which the fungus is transported (1-3). Studies under controlled conditions show that the fungus is hardy and resists very high and low temperatures, is even resistant to NaCl at 4 C, and that spores remain viable for many months in water (4).

A larger percentage of soil samples collected at the end of the rainy season are positive for fungus. They are positive at the surface at this time whereas samples are positive 4 to 12 inches below the surface following the dry season (5) In the San Joaquim Valley, it is a disease which occurs from June to December. It has been shown that maximal infection rate of coccidioidomycosis occurs in the dry summer and autumn following unusually heavy precipitation during the wet winter season (1, 3). Presumably, a wet winter season aids in the multiplication of the fungus in nature, although an immediate beneficial effect of the rain is to keep the chlamydospores from blowing about in the air Annual infection rates of up to 25% have been demonstrated. Dust control at military bases does reduce infection rates (3, 6). The control measures includes paving roads and runways at airfields, grassing in recreation areas, the encouraging of swimming as a sport rather than baseball, and the use of highly refined oil on athletic areas.

Coccidioidomycosis which occurs out of the endemic area from fomites transported from the endemic area has been clearly demonstrated, as illustrated by the present case report and others (7). The individual infected in Georgia had been unloading "short-fiber cotton" from freight cars which had been loaded in Tulane California (in the San Joaquim Valley). Man-to-man infection has not been a major problem in hospitals in the endemic area. However, six human infections developed following exposure to the dressings from a patient with coccidioidal osteonyelitis (8). Laboratory acquired infection is a problem since infectious particles are produced in great numbers within the first week of growth (9). Slants only (not petri dishes) should be used in direct mixture Delayed hypersensitivity to coccidioidin skin-testing antigen appears from 2 to 21 days after the onset of symptoms (incubation period is 7 to 28 days). In patients with erythema nodosum the testing antigen must be diluted sometimes to 1:1,000 or local or systemic reactions can occur (9). This sensitivity is generally of long duration, although it may wane slowly. Loss of previous skin testing sensitivity may be a bad prognostic sign. In patients with disseminated disease, 70% fails to react to a 1:10 dilution (10).

Precipitin antibody test is positive early in the infection, with positive tests occurring during the second to fourth week of illness (11, 12). The precipitins are transient and are no longer demonstrable in a majority of cases by the seventh week Complement fixation antibody (CF) to coccidioidin develops from three to eight weeks after infection, and tends to persist for longer periods. It has been demonstrated that the precipitin antibody is of IgM class and CF is in IgG class (13). Although the CF test is of limited value in the diagrams of many mild to moderately severe primary cases, it is invaluable in the evaluation of the progress of disease. In general, low levels of CF (less than 1:16) are seen in many patients with

pulmonary disease that does not progress (11, 12, 14). However, a CF level of 1:32 or above is generally regarded as indication of dissemination (11, 12, 14). Persistence of high CF levels (greater than 1:16) are indicative of progressive disease, while diminishing CF levels are generally associated with clinical improvement. The CF level in cases with dissemination is too late to be of much value. The titer may not rise until 8 to 12 weeks of the infection, whereas evidence of dissemination may be present by 4 weeks of illness (14). Residual CF titers of 1:2 to 1.8 may persist in some patients following recovery from a disseminated infection. One form of disseminated infection with which low CF levels are found is central nervous system disease, usually meningitis (12). In 76% of the patients with meningitis, the cerebrospinal fluid CF is elevated (11). In some instances the CSF titer may be positive and the serum CF negative. This antibody is very likely locally produced antibody. The CF titer is not affected by the prior administration of the skin testing antigen, such as occurs in histoplasmisis (15). Thus, the serology in coccidioidomycosis is of significant value, not only in the diagnosis of actively infected cases, but also as a guide to prognosis. The CF test is of decidely more benefit than in disseminated histoplasmosis and blastomycosis (12). Cross reactions are common place, since both CF levels with blastomyces and histoplasma antigens may be as high as 1:64 in coccidioidin CF negative sera from patients with primary coccidioidomycosis (12). Studies in animals have indicated that immunity to re-infection is present, especially with spherule-endospore vaccines (16). The antigen is a cell wall antigen and not in the soluble fraction (17). Protections against reinfection in humans has been suggested from the fact that reinfection is highly uncommon in inhabitants of the San Joaquim valley (1).

Clinical Features

As with many other infections of fungal origin, infection with Coccidioides immitis was assumed to be uncommon for many years, and the disseminated form (called coccidioidal granuloma) was the only recognized form. Dickson was the first to be alert to the association of infection with the fungus and the common phenomenon of Valley fever (18). He collected 350 cases of "San Joaquim Fever" in 5 months in 1937 and demonstrated skin test sensitivity to coccidioidin in all. Smith then inaugurated the studies which unfolded the clinical manifestations of this common infection (1, 2).

Smith observed that approximately 60% of newly infected individuals had no symptoms. Of the remaining infectious 16% were such mild infections that individuals did not seek medical assistance whereas 24% of all

cases were seen by a physician. The clinical picture is that of an "influenza-like" syndrome, with malaise, easy fatiguibility, fever, weight loss, and a non-productive cough in a majority of those with symptoms (2, 9, 19). Occasional patients will have mild hemoptysis with a productive cough. A majority of the symptomatic cases have pleural pain, sometimes sudden in onset and severe enough to interfere with breathing. A macular, erythematous, rash is present in about 10%. Erythema nodosum is present in 4 to % of all cases, occurring usually as red nodules over the anterial tibial area. A higher prevalence rate of erythema nodosum (24%) is present in females, whereas it is very uncommon in Negroes. Erythema nodosum occurs from 2 to 14 days after the onset of symptoms, usually between 1-2 weeks, and skin test hypersensitivity is present at this time. No relapses of reinfections have been noted in those with erythema nodosum (1). Many symptomatic cases have arthralgias, but arthritis occurs in about 8% of symptomatic cases, termed "desert rheumatism". The ankles and knees are commonly involved, although it may affect any joint. The symptoms usually last no more than two weeks and clear without sequelae. Joint effusion is uncommon.

The radiological picture in acute primary disease is varied. Peribronchial infiltrates are frequent; parenchysial lesions can vary from mottling to homogenous consolidations. Although lesions may be anywhere, they are more commonly in the lower lobes or the base of the upper lobes. Resolution of the x-ray findings is usually rapid, but dense consolidations may require several months to clear. Acute complications which are usually benign include pleurisy with effusion, pericarditis, and acute cavitation; most of the latter close spontaneously.

The dread feature of this infection is dissemination of the infection to involve distant sites. Dissemination of the organism without clinically apparent evidence and without progression is likely as common in this disorder as it is in histoplasmosis (21). Clinically recognizable dissemination occurs in less than 0.5% of Caucasians (2). The risk for non-Caucasians is considerably greater however, and Smith has calculated such risk as 23 times greater for Negroes and 190 times greater for Filipinos. Another group at great risk from disseminated disease is pregnant females, whereas females normally have a low risk of dissemination. Most have dissemination during the initial part of the illness, a majority within 1 month of onset and all in Smiths' experience within 4 months (2). In none of Smith's group was there a long latent period, but all continued to have symptoms until dissemination was recognized.

The best description and delineation of the course of individuals who have disseminated coccidioidomycosis is that by Colwell and Tillman (14). They studied 42 patients with primary pulmonary coccidioidomycosis and 8 with disseminated infection. Similar complaints on admission to hospital were present in both groups (Table 1). However, malaise and weight loss were more prominent in those who later had evidence of dissemination.

Table 1

Major Differences in Two Groups with Coccidioidomycosis upon Admission

Findings	Primary (42)	Disseminated (8)
History		
Negro	12%	62%
Chest pain	84%	25%
Malaise	4%	65%
Weight Loss	5%	88%
Physical		
Temperature	100	102
Extrapulmonary	0	25%
Laboratory		
Paratracheal Adenopathy	2%	75%

Table II

Major Differences in Two Groups after Four Week Observation:

Findings	Coccidioidomycosis Primary (42)	Disseminated (8)
Temperature	2%	100%
Extra pulmonary findings	0	71%
X-ray		
Stable	78%	0
Unstable	8%	100%
New Infiltrate	5%	71%
Transbronchial spread	2%	29%
Paratracheal Adenopathy	2%	71%

Physical findings were similar in both groups although two already had evidence of dissemination on admission. One early clue that separated the groups was the radiological findings of right hilar and paratracheal adenopathy in six in the disseminated group, whereas only one with primary disease had this.

The course in the first 4 weeks was different in that fever persisted, weight loss was still prominent and physical evidence of dissemination (supraclavicular adenopathy, septicemia, skin lesions) was often present. In addition, changing chest x-rays with mediastinal adenopathy and transbronchial spread were common. They were able to prove dissemination by obtaining cultures from lymph nodes, skin or blood. Unfortunately, serological titers, although ultimately helpful, did not change until at least 11 weeks after spread. Liver biopsy was not used in this series, but it has been helpful in establishing the diagnosis (22). Since a majority of those dying have pathological changes in the liver including microscopic evidence of the fungus, this should be as a helpful test as it is in disseminated histoplasmosis (23, 24).

Meningitis as a manifestation of dissemination may appear in the course of the primary disease. More often it appears with an insiduous onset 1 to 2 months later with headache, nuchal rigidity, and frontal lobe signs such as confusion or drowsiness. At this stage, laboratory findings

are often limited to the spinal fluid, and are those characteristic of a granulomatous meningitis (elevated protein, low CSF sugar, and pleocytosis with mononuclear predominance). Occasionally, a significant number of eosinophiles may be present. The organism is rarely culturable, but the CSF CF titer is often positive (11).

Other manifestations of disseminated disease include cutaneous lesions such as subcutaneous nodules which often lead to an abscess or draining sinuses, bone involvement, and eye involvement. Primary cutaneous involvement with an ulcerative nodule arising at site of inoculation has been demonstrated (25).

Primary infection often leaves residual findings on chest x-ray (50% of cases) (26). This includes fibrotic scarring, calcified lymph nodes, and cavities. These lesions rarely are evidence of dissemination except under the situations as outlined above. In particular, the continued persistence of a cavity is rarely associated with evidence of dissemination. In most, surgical intervention is not necessary, since most recede slowly. Later, they often can only be demonstrated with planograms. Increase in cavity size may occur when secondary bacterial infection occurs (due to partial bronchial obstruction leading to ballooning of cavity) (27). This is not a result of spread of infection as was thought in the case described above and is very rarely associated with dissemination of the infection. Positive cultures can be obtained from residual cavities, much as individuals with cavitary tuberculosis may have positive cultures with bacterial pneumonia even when disease is inactive.

Therapy

Most individuals do well with no specific therapy. The major concern is to recognize those who disseminate, and this should be observed far early in the course. If evidence of a dissemination occurs, treatment with Amphotericin B should be instituted. Although the organism is moderately resistant to Amphotericin B (unlike cryptococci and histoplasma) early treatment is very effective (14, 26, 28). In cases treated early, 1-2 grams have been effective. Individuals with skin lesions and coccidiodal meningitis require intrathecal treatment as well as intravenous therapy (29). The intratheral treatment is best accomplished with injections into the lateral ventricle via an Onmaya pump (30, 31). The meningitis frequently relapses and often weekly treatment is necessary on a continuous basis.

Treatment with Amphotericin B is fraught with hazard due to the local and systemic reactions as well as the renal complications of therapy (32).

The best evidence indicates that mild abnormalities do persist in individuals treated with the drug, that this is dose related (> 4 gm), and that re-treatment is often difficult. Consequently, one must be certain dissemination is present before therapy is instituted; guidelines for such are rather well established (14).

1. Smith, C.E.: Epidemiology of acute coccidioidomycosis with erythema nodosum. Am. J. Pub. Health. 30:600, 1940.

2. Smith, C.E., Beard, R.R., Whiting, E.G., and Rosenberger, H.G.: Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases. Am. J. Pub. Health 36:1394, 1946.

3. Smith, C.E., Beard, R.R., Rosenberger, H.G. and Waiting, E.G.: Effect of season and dust control on coccidioidomycosis. J.A.M.A. 132: 833, 1946.

4. Freidman, L., Smith, C.E., Pappagians, D., and Berman, R.J.: Survival of Coccidioides immitis under controlled conditions of temperature and humidity. Am. J Pub. Health 46:1317, 1956.

5. Egeberg, R.O., and Ely, A.F.: Coccidioides immitis in the soil of the southern San Joaquin Valley. Am. J. Med. Sciences 231:151, 1956.

6. Drips, W., and Smith, C.E.: Epidemiology of coccidioidomycosis. J.A.M.A. 190:136, 1964.

7. Albert, B.L. and Sellers, T.F.: Coccidioidomycosis from fomites. Arch. Int. Med. 112: 151, 1963.

8. Eckmann, B.H., Schaefer, G.L., and Huppert, M.: Bedside interhuman transmission of coccidioidomycosis via growth on fomites: epidemic involving six persons. Am. Rev. Resp. Dis. 89:125, 1964.

9. Emmons, C.W., Binford, C.H. and Utz, J.P.: Coccidioidomycosis in Medical Mycology. Lea and Febiger, Philadelphia, pp. 164-184.

10. Winn, W.A.: Coccidioidomycosis. J. Chron. Dis. 5:430, 1957.

11. Smith, C.E., Saito, M.T., and Simons, S.A.: Pattern of 39,500 serologic tests in coccidioidomycosis. J.A.M.A. 160:546, 1956.

12. Campbell, C.C.: The accuracy of serologic methods in diagnosis. Ann. N.Y. Acad. Sci. 89:163, 1960.

13. Sawaki, Y., Huppert, M., Bailey, J.W., and Yagi, Y.: Patterns of human antibody reactions in coccidioidomycosis. J. Bact. 91:422, 1966.

14. Colwell, J.A., and Tillman, S.P.: Early recognition and therapy of disseminated coccidioidmycosis. Am. J. Med. 31:676, 1961.

15. Campbell, C.C. and Hill, G.B.: Further studies on the development of complement fixing antibody following a single histoplasmin skin test. Am. Rev. Res. Dis. 90:927, 1964.

16. Levine, H.B., Cobb, J.M., and Smith, C.E.: Immunogenicity of spherule-endospore bacteria vaccines of Coccidioides immitis for mice. J. Immunol. 85: 218, 1961.

17. Levine, H.B., Kong, Y.M., and Smith, C.E.: Immunization of mice to Coccidioides immitis: dose, regimen and spherulation stage of killed spherule vaccines. J. Immunol. 94:132, 1965.

18. Dickson, E.C. and Gifford, M.A.: Coccidioides infection. Arch. Int. Med. 62:853, 1938.

19. Baum, G.L. and Schwarz, J.: Coccidioidomycosis: a review. Am. J. Med. Sci. 230:82, 1955.

20. Denenholz, E.J., and Cheney, G.: Diagnosis and treatment of chronic coccidioidmycosis. Arch. Int. Med. 74:311, 1944.

21. Straub, M. and Schwarz, J.: General pathology of human and canine histoplasmosis. Am. Rev. Res. Dis. 82:528, 1960.

22. Coodley, E.L.: Disseminated coccidioidomycosis: diagnosis by liver biopsy. Gastroent. 53: 947, 1967.

23. Forbus, W.D.: A study of 95 cases of disseminated coccidioidomycosis with special reference to the pathogenesis of the disease. Milit. Surg. 99: 633, 1946.

24. Smith, J.W. and Utz, J.P.: Disseminated histoplasmosis. (unpublished observations).

25. Goodman, D.H., and Schabarum, B.: Primary cutaneous coccidioidomycosis. Visible classic demonstration of delayed hypersensitivity. Ann. Int. Med. 59: 84, 1963.

26. Winn, W.A.: The use of amphotericin B in the treatment of coccidioidal disease. Am. J. Med. 27:617, 1959.

27. Winn, W.A.: Coccidioidomycosis. Arch. Int. Med. 106:463, 1960.

28. Utz, J.P., and Andriole, V.T.: Analysis of amphotericin treatment failures in systemic fungal disease. Am. N.Y. Acad. Sci. 89:277, 1960.

29. Wilson, J.W.: Therapy of systemic fungus infections in 1961. Arch. Int. Med. 108:292, 1961.

30. Witorsch, P., Williams, T.W., Ommaya, A.K., and Utz, J.P.: Intraventricular administration of amphotericin B. Use of subcutaneous reservoir in four patients with mycotic meningitis. J.A.M.A. 194:699 1965.

31. William, T.W.: Treatment of mycotic meningitis. Modern Treatment 4: 951, 1967.

32. Butler, W.T., Bennett, J.E., Alling, D.W., Wertlake, P.T., Utz, J.P. and Hill, G.J.: Nephrotoxicity of amphotericin B. Early and late effects in 81 patients. Ann. Int. Med. 61:175, 1964.

Leprosy

[redacted], a 41 year old [redacted] from [redacted], Texas noted an erythematous nodular eruption over left leg 20 years ago. She also noted intermittent swelling of ears and nasal obstruction. A serological test for syphilis was positive, but penicillin and later bismuth/arsenical treatment failed to affect the course of lesions. The skin lesions left thickened areas but she did not note sensory changes. Ten years ago the eruption was intermittently present over her face, forehead and arms. Three years ago she noted an increase in the eruptions over extremities and face. The eruption would be painful and red, would swell and form a scale followed by ulceration. The nasal discharge became purulent, the nose eventually flattened and she lost eyebrows and eyelashes. She also noted cloudiness of vision and deepening of voice.

While staying with daughter in Dallas, she came to the Dermatology clinic, where a presumptive diagnosis of leprosy was made and a biopsy obtained. This showed histiocytic infiltrate in skin with large numbers of acid fast bacilli. Physical examination showed a slightly obese female with erythematous papules, some scaling and hyperpigmented areas over upper and lower extremities. She had multiple superficial large and small ulcers over lower extremities. She had a flattened nose with perforated septum, leonine facies, loss of eyebrows and eyelashes. Her cornea had punctate corneal opacities bilaterally, which were subepithelial and stromal.

Corneal sensation was diminished. The nerves were only moderately thickened. The spleen was enlarged. She had multiple areas of diminished touch sensation, especially over mid forehead and anterior wrist.

Laboratory examination revealed Hct=35, wbc=7,300, platelets 310,000, urinalysis=1.028 S.G and negative sediment. Latex was negative, BUN=11, creatinine 0.8 mg%, TP=7.2 gm% with albumin 3.5, globulin=3.7 (gamma globulin=2.2 gm%). Liver function studies showed Br=0.3 mg%, SGOT 54, albaline phosphatase=27, cephalin flocullation=3+, thymol turbidity 9.9. VDRL was negative one time and reactive another; FTA was reactive. PPD=10 mm induration; Mitsuda, not done.

Leprosy is a chronic infectious disease caused by Mycobacterium leprae. One of the major endemic areas for leprosy in the United States is Texas, especially for cases in persons born in the U.S. (Table3). Since the patient above illustrates that far-advanced disease may be permitted to develop in individuals in our area and since the disease is associated with more mythology than virtually any other disease in the so-called modern times, the following review is presented to edify and demythologize. The outstanding review of leprosy is the revision of Duoll's Medical Bulletin by Guinto and Binford (33).

Table 3

Leprosy - 1950 - 1968 - U.S.

(States with greatest number)

	50-54	55-59	60-64	65-68	Total
California	64	60	100	107	
Hawaii	119	77	71	66	
Louisiana	21	18	11	11	
New York	40	26	53	23	
Texas	98	84	91	80	374 (21%)
Puerto Rico	88	41	46	47	
Total (All States)	480	357	456	429	1820

History

Myth #1 Biblical leprosy was not leprosy

In spite of the frequent mention of the "lepra" and the disease, such description as is presented does not suggest leprosy (33, 34). The word "lepra" (vaguely applied to scaly skin eruptions) was chosen to avoid confusion with any well-recognized entity. In particular, depigmentation is not a feature of leprosy and no leprous lesion was "white as snow" as was Naaman's. The disease was present before the Christian era, in Egypt, Africa, China, and India. It spread through Europe by military movements, crusaders and to America very likely by the discoverers of America (a swap for syphilis (34)).

Myth #2 Leprosy not always tropical

The history of leprosy indicates that leprosy was endemic in Europe in Medieval times. One study indicates that 76% of skulls from graveyards (12th to 16th century) show characteristic atrophy of lepromatous leprosy. In the 16th century, the disease declined in Europe but not in Scandinavia. It was especially prevalent in Norway, and the peak year of infections there was the mid-19th century. In fact, immigrants to the Upper Mississippi Valley brought leprosy with them, and few second generation persons acquired the disease. Leprosy is not only present in the Tropics today, but in Korea and Northern Japan.

Epidemiology

The total number of cases worldwide approaches 10,000,000 (3/1,000). The highest prevalence rates are in tropical African countries, followed by India and Southeast Asia. Cases continue to be reported in the United States with a small number of states providing the great majority of cases (not the least of which is Texas) (Table 3). The area of Texas endemicity is from Bexar County southward to the border. In addition to the areas mentioned, sporadic cases have occurred in veterans who acquire the disease in military service. The incubation period varies, and is up to 16 years in some, so that patients may present with clinical illness long after their return from such endemic areas (35).

Myth #3 Feeble contagiousness

Many individuals in contact with active cases rarely acquire the clinical disease. Human and most animal transmission studies have produced no clinical disease, however, certain features suggest that leprosy is a highly contagious disease. 1) Contagiousness has a different connotation when applied to leprosy. Up to one-half of all new cases of leprosy have not been associated in any way with anyone known to have the disease. In these instances, ancestors or relatives who had the disease were not

available for study when disease was first noted. In some of the best epidemiological studies from Dr. Duoll's group working in the Philippines, the peak attack rate occurs in the age group 10-14 (36). Furthermore, the reactivity to lepromin increases rapidly from 2 to 10 years so that less than 10% are lepromin negative by age 20 (cross-reactivity with tuberculin confuses the data to some degree). These data would support the contention that infection is common and the positive lepromin test is secondary to previously acquired infection.
2) Susceptible populations often have a very high prevalence rate in a short period of time. The best example of this is of the epidemic on Naur following the introduction of leprosy in 1912. By 1920, 3 individuals who were contacts of the first case had leprosy. By 1925, one quarter of the population was affected (50 cases/1,000/year) Examples to the contrary, such as the failure of any physician to acquire the disease, are simplistic justifications of the feebly contagiousness concept applied to an exceedingly complex disease. Of the multiple factors at work in spread of leprosy, the most important would appear to be that a prolonged exposure is necessary, that inapparent infection rates are high among family contacts, and that certain poorly understood factors enhance resistance to clinical manifestations of the disease.

The mode of transmission is not known, and the long incubation period hampers the gathering of important information. The only known source of infection is human contact. No connection exists between human leprosy and murine (rat) leprosy or with other natural mycobacterial infections of man or animal. It is not proven whether inhalation of organisms, direct infection with inoculation through breaks in skin or through mucous membranes of the nose and throat, or indirect contact with ingestion of organisms occurs. The most appealing hypothesis (to me) is that organisms are taken up from contaminated material through breaks in skin or mucous membranes and a mycobacteremia ensues. Because of features of the organism (to be described below), the bacilli establish themselves most often in skin and peripheral nerves. Most of the bacilli are removed and killed. The long incubation period and the failure to grow bacilli except in immunologically deficient mice suggest that it is a "slow mycobacteria" infection comparable to recently described slow virus infections (37). Since such mycobacteremia would involve very few organisms, it is unlikely that bacilli would be detectable on blood smears from patients in endemic areas, and cultures can not be done as yet. The small number also would favor the ability of many to kill and remove the bacilli. An epidemiological point favoring the hypothesis is that attack rates are highest in contacts of those with lepromatous leprosy (6/1,000/year), the individuals with largest number

of organisms in skin and other external secretions (36). Attack rates in contacts of tuberculoid cases, who shed few bacilli, are 1/1,000/year. A careful study of available data thus supports the thesis that leprosy is indeed quite contagious. The myth that is hardest for us as well as patients, family and friends to shake (Myth #4 A person with leprosy is unclean) is sociological support for this difficult to establish epidemiological fact.

Bacteriology

Mycobacterium leprae is an acid-fast, pleomorphic bacillus. It is an obligate intracytoplasmic infective agent not found in the nucleus of the host cell. The bacilli may form membrane-bound globi which are characterized by opague droplets and a foamy structure (lepromatous leprosy). Under other conditions (borderline cases), bacilli occur singly or in small groups without forming a limiting membrane.

The bacilli do not multiply on or in ordinary bacteriological media, but it has been cultivated in typical fashion in the mouse foot pad and systemically in thymectomized-irradiated mice (38, 39). A significant feature of the organism is its predilection for certain tissue, each having in common a lower temperature than internal body temperature. These would include peripheral nerves in subcutaneous tissue, nasal mucosa, the anterior portion of the eye, the testes, lymph nodes draining the skin and skin itself. Pathologic studies of peripheral nerves indicate that the following nerves: ulnar nerve at medial condyle and wrist, median nerve at carpal tunnel area, radial nerve at wrist and above elbow, posterior tibial nerve at flexor reticularis, common peroneal nerve at flexor reticularis and at neck of fibrila, facial nerve at zygomatic process, great auricular nerve at sternoclavicularmastoid muscle, and supra-orbital nerve at forehead all are involved with an inflammatory process just as the nerve leaves muscle bundle or bony process (40).

Pathology

Early lesions, such as those present in so-called indeterminate cases, show a mild degree of round cell infiltration around small vessels of skin appendages and around small nerves. Bacilli are found in nerves which appear normal otherwise. In tuberculoid leprosy, lesions in the skin resemble other granulomatous diseases. Epithelioid cells are arranged in a cluster which may or may not contain giant cells. A lymphocytic infiltrate will extend into the epidermis, small nerves will be absent, but bacilli are rarely present. Granulomas may replace the intraneural structure in peripheral nerves. The pathological feature of lepromatous cases is the proliferation of histiocytes around blood vessels, nerves and dermal glands. The macrophages are infiltrated with bacilli and "globi"

(bacilli in compact globular masses) replace intracellular structures of the cells Bacilli are present in large numbers in small nerves, in macrophages in blood vessel walls, and even in cells of the buffy coat. The peripheral nerves show both round cells and macrophages with edema and infiltration of the neural cells. The thickened part of nerves show early a marked increase in numbers of bacilli and later destruction of axis cylinders with replacement with fibrous tissue (40). Since M. leprae is the only bacillus known to invade nerves primarily, the demonstration of acid fast bacilli in nerves is conclusive evidence of leprosy.

The pathological changes of the lepra reaction are similar to erythema nodosum although leprologists consider erythema nodosum leprosum (ENL) as unique to leprosy. Pathologically, the major difference is that acid fast bacilli are found (since the phenomenon primarily occurs in lepromatous cases). A rare but distinctive pattern found particularly in leprosy patients from Mexico (and demonstrated by our patient) is the "Lucio" phenomenon (erythema necrotisans). In this reaction, acute vasculitis of the capillaries occurs which leads to ischaemic necrosis and ulceration.

Immunology

The skin test utilized in leprosy is heated tissue from lepromatous cases. This material containing organisms and standardized to 600 million organisms per ml is injected intradermally. An early reaction (positive Fernandez) with induration occurs in some individuals at 48 to 72 hours. The Mitsuda response is the formation of a nodule in approximately 7 to 10 days which reaches its peak in 3 to 4 weeks. The Mitsuda test is said to be negative invaribly in lepromatous leprosy and positive in tuberculoid cases.

Fluorescent antibody techniques reveal antigenic relationships between M. leprae and M. calmetti-guerin. Thus, it is possible some lepronin positive patients have had tuberculosis rather than leprosy, thus decreasing the usefulness of the test in epidemiological surveys. This cross-reactivity has been cancelled out in some studies in which fewer organisms are used in the test (41). The test is most useful in classification.

Specific antibodies M. leprae antigens have been demonstrated by FA and precipitating antibody techniques. Hypergammaglobulinia has been known as a feature of lepromatous leprosy for some time Recent studies reveal that this is due to an increase in immunoglobulins G and A (42). Other positive antibody tests in leprosy include false positive tests for syphilis (BFPS) and positive LE cell phenomenon.

Recent studies have demonstrated impairment of DNA synthesis in stimulated leucocytes from patients with leprosy (42, 43). Impairment of lymphocyte transformation of leucocytes from lepromatous patients is present when streptolysin O is used as antigen, although conflicting data exists when PHA is used. In one study, DNA synthesis is impaired when patients' serum is used in the test but not with normal serum. This finding of depressed DNA synthesis in lepromatous cases correlates with the depression of delayed hypersensitivity reactions to lepromin as well as to dinitrochlorobenzene (44, 45).

Clinical Features

The first manifestations of leprosy are usually slight and are often ignored by the patient. In one prospective study of children of parents with leprosy, neurological signs such as thickening of nerve trunks and small areas of hyperesthesia or anesthesia preceeded skin lesions which were evanscent reddened areas of skin (46). In indeterminate leprosy (which may well be the early stage of leprosy) hypopigmented macules which are anesthetic are present. Few bacilli are seen in skin scrapings. The classification of the clinical types is given in Table 4 and a detailed comparison of lepromatous and tuberculoid leprosy is given in Table 5.

Table 4

Fundamental Distinctions Among the Two Types and Two Groups of Leprosy Cases

Clinical Features	Lepromatous Type	Borderline Group	Indeterminate Group	Tuberculoid Type
Character & prognosis	Stable, malign and progressive	Unstable, either progressive or regressive	Unstable, often regressive; may progress to either "polar" type	Stable, benign, usually regressive
Skin lesions	Lepromas, papular or nodular	Plaques, often annular	Pale or pink macules	Pale macules or raised plaques, often annular
Nerve damage	Slow and symmetrical	Generally more rapid than in lepromatous; symmetrical	Usually only slight and symmetrical	Sudden, severe, asymmetrical
Bacterioscopy	Abundant bacilli	Many bacilli	Few bacilli, if any	Usually no bacill except during reactions, and in nerves
Histology	Xanthoma-like	Sarcoid-like but with some lipid-filled cells: "dimorphous"	Banal round-cell infiltration	Sarcoid-like
L omin reaction	Negative	Negative or weakly positive	Negative or weakly positive	Positive, often strongly so

Table 5

Detailed Comparison of the Two "Polar" Types of Leprosy

CLINICAL FEATURES	Lepromatous	Tuberculoid
Site of election	Skin (and nerves)	Nerves (and skin)
Distribution	Generalized usually	Localized often
Type of lesion	Leproma or nodule	Macule and plaque
Visceral involvement	Widespread subclinical	Perhaps lymph nodes
Mucous membrane lesions	Regularly and early	Nose only; infrequently
Eye involvement	Often; late	Very rarely
Hypopigmented macules	Occasionally; early; many	Frequently; few
Annular plaques	Sometimes	Frequently
Erythema multiforme or nodosum	In reactions often	Not seen
Fever	In reactions usually	Rarely
Eyebrow alopecia	Often	Not seen
Gynecomastia	Sometimes; late	Not seen
Symmetry of involvement	Usual	Exceptional
Nerve enlargement	Slow and symmetrical	Rapid and asymmetrical
Nerve damage	Late; often partial	Early, often complete
Skin anesthesia	Late but inevitable; often on extremities	Early and coextensive with skin lesions
Visceral damage	Testicle only	Not seen
HISTOLOGIC FEATURES		
General pattern	Xanthoma-like; macrophages and histiocytes	Sarcoid-like: epithelioid cell tubercles and lymphocytes
Vacuolated lepra cells	Always	Rarely; in reacting cases only
Giant cells	Occasional; foreign body or Touton type	Often; Langhans' type
Lymphocytes	Few	Abundant
Lipoid	Abundant	Minimal
Necrosis	Rarely	Caseation: rare in skin, common in nerves
Nerve changes	Fibrosis: structure well preserved	Obliteration of normal architecture
Visceral amyloidosis	Common; late	Not seen
BACTERIOSCOPY		
Acid-fast bacilli (*M. leprae*)	Abundant except in long-treated or burned-out cases	Rare or lacking except during reactions; never abundant

Table 5 (continued)

	Lepromatous	Tuberculoid
SPECIAL TESTS		
Lepromin (Mitsuda) reaction	Negative	Positive
Serologic tests for syphilis	Biologic false positive in half of cases	No false positives
Hyperglobulinemia	Usual	Exceptional
Erythrocyte sedimentation rate	Elevated, especially during reactions	Usually normal

In lepromatous leprosy, a nasal discharge is often the first symptom. the first cutaneous manifestations are macules, less commonly papules. The macules may be hypopigmented or erythematous and this lesion may or may not be hypopigmented, but it will be bacteriologically positive. Later in the course, diffuse infiltration of the skin progresses to thickening of the skin of the extremities and face and exaggeration of the natural lines. With infiltration around hair follicles, hair becomes sparse and eyebrows and eyelashes are lost The nasal discharge (which is bacteriologically positive) becomes thick and purulent, nasal obstruction develops and destruction of cartilage ensues. With fibrosis, the nose becomes flattened and deformed and perforated nasal septum is common. The uvula and larynx may be involved and voice changes are common. Eye involvement is common; the eyelid, sclera, cornea. iris and ciliary body become infiltrated and nodules form. All stages of keratitis may be seen. Nodules of the skin and subcutaneous tissue may be present but seem to vary from country to country. If touch or temperature sensation is tested for, areas not accounted for by peripheral nerve will be anesthetic. These areas occur in cooler areas of the skin, whereas palms and antecubital fossae which are warmer are spared.

The lepra reaction, most commonly erythema nodosum lepronim (ENL), is a poorly understood but very troublesome phenomenon in lepromatous leprosy. The lesions occur as crops of erythematous nodules over extremities and face. last few days to a week, and are associated with fever and severe constitutional symptoms and signs. Painful neuritis, peripheral nerve enlargement, bony involvement (anterior tibia) and arthritis may be features The attacks may recur and be quite prolonged. The "Lucio" phenomenon is a special variant of reactive leprosy in which red painful spots appear, progress to form ulcers and heal with scarring. These recur just as ENL does. It is a form of leprosy seen in Mexico and Costa Rica and has been seen in cases from the U S (47).

Tuberculoid leprosy is heralded by a small anesthetic patch or macule The onset may be sudden with erythematous papules and with accompanying painful neuritis. However, the typical lesion is a well defined, distinct erythematous or hypopigmented anesthetic patch. The lesion is negative bacteriologically. The lesions may be solitary or multiple;

temperature and pain sensation may be disturbed prior to touch. The area will be dry (sweat glands are destroyed) and hair will be missing. These lesions will be asymmetric in contrast to the symmetrical distribution of the lesions in lepromatous cases. Enlargement of peripheral nerves (enumerated in pathology section) is more frequent in tuberculoid leprosy than in lepromatous patients. The infiltrative and fibrotic changes are particularly prominent in the ulnar and common peroneal nerves so that thenar, hypothenar and hand muscle atrophy may develop. "Claw hand" and foot drop are common. Trophic ulcers are a secondary manifestation of nerve damage. Since bony prominences are the site of ulcers, gradual absorption of fingers and toes may ensue.

Laboratory abnormalities are more common in lepromatous disease. These include mild hypochromic anemia, elevated sedimentation rate, decreased albumin and increased globulin (IgG primarily), BFBS, and mild BSP retention with otherwise normal liver function studies. Proteinuria is present during reactions. It persists in those with secondary amyloidosis.

The course in untreated lepromatory leprosy is slowly progressive with death in 10 to 20 years. In the U.S., the most common cause of death is renal failure secondary to amyloidosis (48). In other parts of the world, tuberculosis or secondary bacterial infections are the greatest problem.

Diagnosis can be made presumptively on clinical grounds. Conclusive proof is best established with the demonstration of acid-fast organisms from smears of skin or upon histological examination of biopsy material. Since bacilli may not be demonstrated in tuberculoid or indeterminate cases, the clinical findings of an anesthetic macule and biopsy evidence of granulomatous involvement of the skin or terminal nerves will confirm diagnosis. Acid-fast organisms in nasal secretions should not be relied upon for diagnosis since nonpathogenic acid-fast organisms may be recovered. Bacteremia has been demonstrated in buffy coat smears in a majority of patients with lepromatous leprosy (49). Bacteremia was persistent in untreated cases and more than 60% of the bacilli were intracellular. These patients also demonstrated large numbers of bacilli in Kupffer cells and liver parenchyma, and one half had intracellular bacilli in bone marrow aspirates. Despite this finding these patients were afebrile and asymptomatic.

Treatment

Good control studies have demonstrated that the sulfones, particularly p, p^1 sulfonyldiaminine (DDS), are effective in the treatment of lepromatous leprosy. DDS is the most commonly used sulfone since it is the least expensive. Recent studies in experimental mouse infection

has shown that most strains are sensitive to 0.01 ug/ml of DDS (50). Such levels can be achieved within daily dose of 1 mg. The usual dosage schedule is to begin with 25 mg once weekly and slowly shorten interval of treatment and increase dosage (51). With such treatment, the greatest improvement is observed in those with ulcerated lesion. Nasal obstruction and hoarseness usually improve in 3-6 months. Bacteriologic negativity is slowly attained, and even after 5 years of treatment, 50% of lepromatous cases have positive smears.

One of the features of sulfone therapy that has been striking is the apparent increase in reactions (particularly ENL) which occurs upon institution of therapy. Some recommend reducing the dosage or stopping the drug altogether while administering steroids (51). A notable advance in the therapy of such reactions has been made recently with the observation that thalidomide treatment is successful in suppressing such reactions in 91% of the attacks (52).

A promising drug (B663) has been studied recently and has demonstrated clinical efficacy in lepromatous cases, especially in those with ENL (53, 54). Marked improvement in ENL and neuritis is seen in 10 weeks, and steroids can be discontinued. This drug is of particular usefulness in the uncommonly encountered lepromatous case in which M. leprae is resistant to sulfones. Toxicity is minimal, although ruddiness and hyperpigmentation of the skin does occur. The drug has not been evaluated long enough to know if disease is reactivated after discontinuing therapy such as occurs in sulfone therapy.

Ethambutol and rifamycin have been tried recently with fair results. Ethambutol in particular seems to have a rapid bacteriocidal effect, but rapid resistance appears also. Although combination therapy has not been tried often in leprosy, the future use of one of these relatively non-toxic agents in combination with a sulfone or B663 may be the approach. The limiting factor will be the cost since at present leprosy is primarily a disease of the non-affluent countries of the world.

Prophylaxis with BCG has been recommended by some since it induces lepromin reactivity. This may mean no more than that M. leprae cross reacts with other mycobacterial antigens, and it may bear no relationship to protection against infection. Extensive field trials have been performed and results at best are controversial. I personally would favor (as done in some countries) sulfone treatment of contacts of lepromatous cases, since it has been postulated that 80% of acquired cases are derived from lepromatous patients (36).

33. Duoll, J.A., revised by Guinto, R.S. and Binford, C.H.: Leprosy. Medical Bulletin, MB-10, V.A., 1965.

34. Arnold, H.C.: Paradoxes and misconceptions on leprosy. J.A.M.A. 196:139, 1966.

35. Leprosy, United States and Puerto Rico, 1949-1968. Morbidity and Mortality Report 19:17, 1970.

36. Duoll, J.A.: The epidemiology of leprosy: present status and problems. Int. J. Leprosy 30:48, 1962.

37. Gajdusek, C.: Slow virus infections of the central nervous system. New Eng. J. Med. 276:392, 1967.

38. Shepard, C.C.: Acid-fast bacilli in nasal excretions in leprosy and results of inoculation of mice. Am. J. Hyg. 71:147, 1960.

39. Rees, R.J.W.: Recent advances in the transmission of human leprosy to mice. Int. J. Leprosy. 36:584, 1968 (abstract).

40. Job, C.K., and Desikan, J.: Pathologic changes and their distribution in peripheral nerves in lepromatous leprosy. Int. J. Leprosy 36:257, 1968.

41. Bechelli, L.M., Nakamura, S., Quagliato, R., and Lima Filho, E.C.: Lepromin test in non-contacts. Int. J. Leprosy 36:611, 1968 (abstract).

42. Sheagren, J.N., Block, J.B., Trautman, J.R., and Wolff, S.M.: Immunologic reactivity in patients with leprosy. Ann. Int. Med. 70:295, 1969.

43. Bullock, W.E. and Fasal, P.: Impairment of PHA and antigen-induced DNA synthesis in leucocytes cultured from patients with leprosy. Int. J. Leprosy. 36:608, 1968 (abstract).

44. Waldorf, D.S., Sheagren, J.N., Trautman, J.R., and Block, J.B.: Impaired delayed hypersensitivity in lepromatous leprosy. Lancet 2:773, 1966.

45. Bullock, W.E.: Studies of immune mechanisms in leprosy. I. Depression of delayed allergic response to skin test antigens. New Eng. J. Med. 278: 298, 1968.

46. Wayson, N.E.: The early diagnosis of leprosy. Int. J. Leprosy. 4:177, 1936.

47. Donner, R.S. and Shively, J.A.: The "Lucio phenomenon" in diffuse leprosy. Ann. Int. Med. 67:831, 1967.

48. Shuttleworth, J.S. and Ross, S.H.: Secondary amyloidosis in leprosy. Ann. Int. Med. 45:23, 1956.

49. Drutz, D.J., Lu, W.H., and Chen, T.S.: The continuous bacteremia of lepromatous leprosy. Clin. Res. 17:365, 1969. (Abstract)

50. Waters, M.F.R., Rees, R.J.W., and Ellard, G.A.: Experimental and clinical studies on the MIC of DDS in leprosy. Int. J. Leprosy 36:651, 1968 (abstract).

51. Trautman, J.R.: The management of leprosy and its complications. New Eng. J. Med. 273:756, 1965.

52. Sheskin, J. and Sagher, F.: The present status of thalidomide treatment in lepra reaction and leprosy. Int. J. Leprosy 36: 637, 1968 (abstract).

53. Williams, T.W., Mott, P.D., Wertlake, P.T., Rubio, J B., Adler, R.C., Hill, G.J., Suarez, G.P. and Knight, V.: Leprosy research at N.I.H. Experience with B663 in the treatment of leprosy. Int. J. Leprosy 33: 767, 1965.

54. Broune, J.G.: B663 in the treatment of leprosy. Int. J. Leprosy 36:654, 1968 (abstract).

Biological Function of Lymphocytes

The immunological response of the host has been divided into humoral (antibody) and delayed hypersensitivity mechanisms. Recent progress in the study of lymphocytes and macophages has broadened not only our knowledge of their function but also has opened up a whole series of inter-relationships. First of all, it is becoming apparent that the humoral factors (or antibody) which circulate indicate merely that lymphocytes have responded to antigenic stimulation at some site at the host. Recent studies have indicated that locally produced antibody (either secretory IgA or IgG) may correlate more with protection than circulating antibody (55-57). Furthermore, certain experimental evidence indicates that serum antibody may under certain circumstances be derived from antibody produced locally at the site of infection rather than from lymph nodes and spleen (58). There are some conditions in which circulating antibody is associated with an unfavorable clinical setting. Two such situations include severe bronchiolitis due to respiratory synticial virus in infants with maternal antibody and local reactions to rubeola or the attenuated vaccine strain in individuals previously immunized with a killed vaccine strain (59, 60).

Evidence of delayed hypersensitivity by denoting induration in the skin 48 to 72 hours after injection of antigen also represents the end result of a complex series of events. It does require the movement of sensitized cells into the area (hence cellular immunity) However, a number of clinical observations indicate that this test is only a marker of previous sensitization. "Anergy" is a feature of sarcoidosis, disseminated fungus infections such as coccidioidomycosis, disseminated tuberculosis and in lepromatous leprosy (14, 33). It has been demonstrated that this is not due to the inability to develop the local reaction since the transfer of buffy coat containing sensitized cells can lead to a positive reaction in such patients (61). On the other hand, the pathological feature of sarcoidosis, the granuloma, is in fact evidence of delayed hypersensitivity. Substantial evidence can be given (best worked out by Warren in Shistosomiasis) that granuloma formation is a manifestation of delayed hypersensitivity:

1) a granuloma represents sensitization;
2) this sensitization is specific and;
3) it can be transferred with cells and not serum (62)

In disseminated coccidioidomycosis and lepromatous leprosy, granuloma formation as well as the lymphocytic and histiocytic infiltration indicate cellular activity of the immunological system. The problem in disseminated coccidioidomycosis and lepromatous leprosy is not necessarily failure of host response as it is that antigen (or the infecting agent) is present in such excessive quantity that host response is overwhelmed. The failure of circulating lymphocytes to respond to PHA or SLO in lepromatous leprosy could mean that the cells are exhausted (from stimulation with M. leprae antigens) (42, 43).

There are numerous ways to analyze immune cells morphologically, functionally, biologically, and by stem cell derivation (63). The two immunological cell types are the macrophage and the lymphocyte. Macrophages are wandering phagocytic cells which are motile, stick to glass, stain with silver, and possess lysosomal enzymes. Most of these are derived from bone marrow. They have a rapid turnover of 1-2 days. Lymphocytes, in general, can be described as immunologic cells having none of the attributes of the macrophage. In particular, the failure of lymphocytes to stick to glass has enabled many investigators to separate lymphocytes on glass wool or bead columns and study them separate from other inhabitants of the buffy coat.

Biological observations, particularly studies using ablative techniques, have indicated that lymphocytes are heterogenous even though they may look alike (Table 6). Bone marrow cells are probably the original stem cell and it is not thymus or spleen dependent. Thymus cells are not immuno competent, although in certain animals they can participate in immune response.

Table 6

Derivation of Lymphocytes	Role in Antibody Production	Respond to PHA	Respond to anti-GG	Produce Lymphotoxin
Fixed				
Bone marrow	Antibody producing	+	+	+
Thymus	Antigen sensitive	+	-	-
Circulating				
Bone marrow derived				
Thymus derived				
Bursal derived				

Interactions between groups of lymphocytes and with other cells occur in response to stimulation. It is presently hypothesized that the macrophage processes antigen and presents it to the lymphocyte which produces antibody (64). Interactions between lymphocytes have been shown by Claman, later by Mitchell and Miller and by Talmadge (65-67). Reconstitution of irradiated syngeneic mice with either thymus or bone marrow cells does not stimulate antibody production (65). However, reconstitution with both cell types does lead to antibody activity. Studies using cells with markers have indicated that the thymus cell react specifically to antigen (antigen-sensitive) whereas bone marrow cells are the antibody producing cells(66). It has been shown also that incubating immune lymphocytes from mice in combination with spleen cells can lead to synthesis of antibody, whereas immune lumphocytes alone can not (67). In contrast, reconstitution of irradiated rats with immune lymphocytes from the thoratic duct can lead to production of antibody (68).

Further evidence that lymphocytes are not homogenous include the following: differences in life span of the cells, the central or peripheral origin of different cells, the differential migratory pathways of cells from the various lymphoid organs, physical fractionation of cells on a gradient, and the differing responses of cells from various organs to PHA and anti-gamma globulin anti serum (AGG) (69). Daguillard and Richter have shown that bone marrow cells and cells of other lymphoid organs respond to PHA, AGG, and allogeneic stimuli, whereas thymus cells fail to respond to AGG. They had previously shown that circulating lymphocytes from patients with agammaglobulinemia would respond to

PHA but not to AGG (70). They postulate that cells responding to PHA and allogenic cells have the capacity to mediate cellular immunity whereas those responding to AGG have the capacity to mediate humoral immunity. Although they postulate that the same cell would not be both, they have no evidence for this. Evidence that the antibody producing cell and cell mediating delayed hypersensitivity are from the same or different cell lines has been presented but neither possibility can be proved with any certainty (71).

It has been clearly established that lymphocytes in lymph nodes and other areas can synthesize immunoglobulin and antibody (57, 72-74). Attempts to demonstrate the mediator of delayed-type hypersensitivity have been unsuccessful until recently. Immune lymphocytes have been shown to produce a substance which inhibits the migration of normal peritoneal macrophages (74). A most significant advance in our knowledge of such mediators by lymphocytes is the demonstration by Granger that stimulated lymphocytes release a soluble toxic factor (lymphotoxin) which leads to destruction of target cells (75-77) Lymphotoxin has been identified in both human and mouse lymphocytes, can be produced by non-specific lymphocytes which are stimulated by a number of agents (PHA, trypsin, etc) and by immune lymphocytes from individuals given PPD, tetanus, BSA, or other agents: it has a molecular weight of 80-90,000 and acts at the membrane of the sensitive cell leading to lysis of cell. Circulating lymphocytes release the lymphotoxin, but thymus lymphocytes do not. The material obviously is not an immunoglobulin, but it is conceivable that it is one or more lysosomal enzymes. The role of lymphotoxin in disease is, of course, not established It is quite interesting that stimulated lymphocytes are capable of producing non-specific substances which would attack other cells than just bacterial cells. It is conceivable that such substances would play a role in the tissue damage which accompanies certain disease states, such as chronic pyelonephritis. It has been postulated that auto-antibody plays a role in the persistent inflammatory reaction, but recent studies demonstrate that antibody to kidney tissue is not a feature of the immunological response in pyelonephritis (78). One could hypothesize that lymphotoxins are elaborated from stimulated lymphocytes and contribute to tissue damage.

It is thus apparent that the small lymphocyte has come a long way since 1956 when it was stated that the "fact that no such function (for lymphocyte) has been demonstrated is, in itself, significant" (79). The pathological lesion termed inflammatory, or lymphocytic infiltrate contains cells which are 1) heterogenous in derivation, 2) capable of synthesizing antibody, and 3) capable of elaborating toxins with non-specific effects.

55. Tomasi, T. B.: Human Immunoglobulin A. New Eng. J. Med. 279:1327, 1968.

56. Smith, C.B., Bellanti, J.A., and Chanock, R.M.: Immunoglobulins in serum and nasal secretions following infection with type 1 parainfluenza virus and injection of inactivated vaccines. J. Immunol. 99:133, 1967.

57. Lehmann, J.D., Smith, J.W., Miller, T.E., Barnett, J.A and Sanford, J.P.: Local immune response in experimental pyelonephritis. J. Clin. Invest. 47:2541, 1968.

58. Hand, W.L., Smith, J.W., Miller, T.E., Barnett, J.A., and Sanford, J.P.: Immunoglobulin synthesis in lower urinary tract infection. J. Lab. Clin. Med. 75:19, 1970.

59. Chanock, R.M., Parrott, R.H., Kapikian, A.Z., Kim, H.W., and Brandt, C.D.: Possible role of immunologic factors pathogenesis of RS virus lower respiratory tract disease in Perspectives in Virology VI, New York, New York, Academic Press, pp 125-139.

60. Fulginiti, V.A., Arthur, J., Pearlman, D.S., and Kempe, C.H.: Serious local reactions following live measles virus immunization in previous killed vaccine recipients. J. Pediat. 69:891, 1962.

61. Paradisi, E.R., de Bonaparte, Y.P. and Morgenfold, M.C.: Response of anergic patients to transfer of leucocytes, New England J. Med. 280:859, 1969.

62. Warren, K.S., Domingo, E.O. and Cowan, R B.T.: Granuloma formation around schistosome eggs as a manifestation of delayed hypersensitivity. Am. J. Path. 51:735, 1967.

63. Waksman, B.H.: The cells of the immune response. Presented at Eighth Midwinter Conference of Immunologists. Jan. 26, 1969.

64. Feldman, M. and Gallily, R.: Cell interaction in the induction of antibody formation in Symposia on Quantitative Biology (Cold Spring Harbor Laboratory of Quantitative Biology) 32:415, 1967.

65. Claman, H.N., Chaperon, E.A. and Triplett, R F.: Thymus-marrow cell combinations. Synergism in antibody production. Proc. Soc. Exp. Biol. Med., 122: 1167, 1966.

66. Mitchell, G.F., and Miller, J.F.A.P.: Immunological activity of thymus and thoracic duct lymphocytes. Proc. Nat. Acad. Sci. 59.296, 1968.

67. Talmadge, D.W.: Cell interaction. Presented at Eighth Midwinter Conference of Immunologists, Jan. 26, 1968.

68. Ellis, S T., Gowans, J.L., and Howard, J.C.: Cellular events during the formation of antibody. Symposia on Quantitative Biology (Cold Spring Harbor Laboratory of Quantitative Biology) 32:395, 1967.

69. Daguillard, F., and Richter, M.: Cells involved in the immune response XII. The differing responses of normal rabbit lymphoid cells to phytohemagglutinin, . goat anti-rabbit immunoglobulin antiserum and allogeneic and xenogeneic lymphocytes. J. Exp. Med. 130:1187, 1969.

70. Daguillard, F., Heiner, D., Richter, M., and Rose, B.: The response of agammaglobulinemia subjects to phytohemagglutunin and antiimmunoglobulin antiserum. Clin. Exp. Immunol. 4:203, 1969.

71. Humphrey, J.H. : Cell-mediated immunity. General perspectives. Brit. M. Bull. 23:93, 1967.

72. Helmreich, E., Kern, M., and Eisen, H.N : Observations on the mechanism of secretion of gamma-globulins by isolated lymph node cells. J. Biol. Chem. 237: 1925, 1962.

73. Smiley, J.D., Sachs, C. and Ziff, M.: In vitro synthesis of immunoglobulin by rheumatoid synoiral membrane. J. Clin. Invest. 47:624, 1968.

74. Bennett, B. and Bloom, B.R.: Reactions in vivo and in vitro produced by a soluble substance associated with delayed-type hypersensitivity. Proc. Nat. Acad. Sci. 59:756, 1968.

75. Granger, G.A. and Kalb, W.P.: Ylmphocyte in vitro cytotoxicity: mechanism of immune and non-immune small lymphocyte mediated target L cell destruction. J. Immunol. 101:111, 1968.

76. Kolb, W.P., and Granger, G.A.: Lymphocyte in vitro cytotoxicity: Characterization of human lymphotoxin. Proc. Nat. Acad. Sci. 61:1250, 1968.

77. Granger, G.A., Shacks, S.J., Williams, T.W., and Kolb, W.P.: Lymphocyte in vitro cytotoxicity. Specific release of lymphotoxin-like materials from tuberculin-sensitive lymphoid cells. Nature 221:1155, 1969.

78. Miller, T.E., Smith, J.W., Lehmann, J.D. and Sanford, J.P.: Autoimmunity in chronic experimental pyelonephritis. (unpublished observations).

79. Schwarz, M.R.: Introduction to Symposium on the life history of lymphocytes. Anat. Rec. 165:105, 1969.