Survey of Recent Leprosy Research

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THE OBJECT of this review is to promote better understanding of the biology of *Mycobacterium leprae* and its interaction with its host. Experimental chemotherapy, clinical, or epidemiologic aspects of leprosy are not discussed. The review includes only contributions which I believe will illustrate best to workers in fields other than leprosy the present status of leprosy research. Within these limitations, information is presented on what is being done in the United States and in other countries, the reasons why it is being done, and what still remains to be accomplished. The time is propitious for reviewing this particular subject because of the scientific interest sustained by the Eighth International Congress of Leprology in Rio de Janeiro in September 1963. At this congress, some recent advances were confirmed which are bound to become milestones in the history of leprosy.

Some Characteristics of Mycobacteria

A brief discussion of some mycobacterial characteristics seems well justified, because much of the experimental work in leprosy is carried out with mycobacteria other than *M. leprae*. In fact, most of our current assumptions about the behavior of the leprosy bacillus are derived in this way. In addition, such procedure tends to make us aware that among the mycobacteria occurring in nature there exist several kinds of acid-fast organisms which display, in one form or other, the same traits that distinguish Hansen's bacillus. Some of these are (*a*) failure to grow independently, (*b*) a narrow host range, and (*c*) a relatively low optimum temperature for growth. For example, *Mycobacterium lepraemurium* causes rat leprosy in several species of wild rats. Only a few species of small rodents used as laboratory animals can be infected with this organism. While *M. lepraemurium* possesses a wider host range than the leprosy bacillus, it resembles the latter in its staunch refusal to grow in vitro. Lepra bubalorum, a skin disease of the water buffalo (*Bubalus bubalis*), similar to human leprosy, is regularly associated with acid-fast rods which, like the leprosy bacillus, fail to grow on culture media. The disease has not been transmitted experimentally. Skin tuberculosis of cattle is also associated with acid-fast bacteria which fail to grow on artificial culture media and experimentally infect cattle with great reluctance. A leprosy-like mycobacterial disease of a species of frog associated with a nongrowable mycobacterium has been described in Bolivia. The infecting organism seems to be species specific. Examples of acid-fast bacteria pathogenic for warmblooded animals, with optimum growth at temperatures from 30° C. (86° F.) to 33° C. (91.4° F.), are *Mycobacterium ulcerans* and *Mycobacterium balnei*. Both organisms can cause skin lesions in human beings. It is of interest that intravenous injection of *M. ulcerans* into mice results in bacterial multiplication in the cooler parts of the body, such as the tip of the tail (*1*). The low incidence of some of these mycobacterial diseases in man and animals suggests that infection occurs accidentally and that the ordinary habitat of these bacteria can be found somewhere else in nature, possibly in the soil.

Search for Growth Factors

The significance of obtaining *M. leprae* in large amounts by growth on artificial media or in cell culture need hardly be emphasized. Many recent attempts to induce *M. leprae* to

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grow independently on artificial culture media follow successful earlier attempts to achieve independent growth of *Mycobacterium paratuberculosis*. This mycobacterium causes Johne's disease, a chronic enteritis in cattle, sheep, and goats, and was considered noncultivatable until Twort and Ingram (*2*) succeeded in 1912 in growing the pathogen on a medium incorporating heat-killed *Mycobacterium phlei*. In 1953, Francis and associates (*3*) isolated a growth factor for *M. paratuberculosis* from *M. phlei*. The factor was named mycobactin. The search for growth factors for *M. leprae* is being continued and is not restricted to mycobacterial products. G. L. Fite, at Carville, in personal communication told of an investigation of the effect on mycobacterial growth of a carotenoid pigment extracted from the yeast Rhodotorula. As yet, none of these efforts have resulted in growth of *M. leprae* or *M. lepraemurium* in artificial culture. Of interest is the recent observation by Darzins (*4*) and Darzins and Pukite (*5*) that extremely small amounts of nucleic acids of diverse origin are capable of reducing the lag phase of aged mycobacteria. It might be advisable to extend this work to include *M. leprae* and *M. lepraemurium*.

Successful attempts at circumventing the seemingly highly specialized growth requirements of factor-requiring mycobacteria are also being made. Morrison (*6*), at the Johns Hopkins-Leonard Wood Memorial Laboratory, has reported that under special circumstances mycobactin-dependent cells of *M. paratuberculosis* are able to grow in the absence of this substance. Experiments on Scandinavian wood pigeons with factor-dependent strains of mycobacteria obtained from cattle revealed some simple chemical factors and conditions capable of substituting for mycobactin. Hanks (*7*) expressed the opinion that Morrison's findings indicate that these bacteria do not depend upon host enzymes or even complex or labile compounds within host cytoplasm. He surmises that *M. lepraemurium* and *M. leprae* are not truly intracellular parasites and that they obtain their requirements from host cell membranes which have folded inward to form phagocytic vacuoles. In view of this, Hanks tends to be optimistic about the prospect of culturing these microorganisms in vitro. Previously, Suter (*8*) had expressed doubts that the obligatory intracellular parasitism of the leprosy bacillus reflects complete host cell dependence, a condition mainly restricted to the true viruses. As an alternative, he suggested that intracellular parasitism might result from high susceptibility to extracellular factors. That such factors might exist for *M. lepraemurium* has been shown by Hanks and Gray (*9*).

The reasons for the recalcitrant behavior of *M. leprae* and *M. lepraemurium* continue to arouse much interest and speculation. In the opinion of some workers, lipoidal barriers impede the exchange of metabolites. Recently, it has been shown that the mycobacterial cell wall consists of a basal layer resembling the cell wall of gram-positive bacteria. In addition, there is an outer layer resembling the lipo-protein layer of gram-negative bacteria. This layer in mycobacteria is much richer in complex lipids. Localization of the mycobacterial lipids at the outer surface of the cell strongly supports the hypothesis that the lipid coat acts as an impediment to the transport of nutrients, substrates, stains, and so forth, into the cell. Tepper (*10*) has found that the rate with which glucose is taken up by resting mycobacterial cells correlates with the total amount of cell lipid. Impediment to exchange of metabolites may, however, not be the sole reason why some mycobacterial species so far have not been cultured independently. There is evidence of decreased aerobic metabolism in the pathogenic mycobacteria, compared with the saprophytes (*11*). In addition, Segal and Bloch (*12*) found metabolic differences between tubercle bacilli grown in vitro and in vivo. The latter are metabolically less competent.

Cell culture of *M. leprae* has not been accomplished with certainty. On the other hand, limited multiplication of *M. lepraemurium* has been reported for several years by Chang (*13*) in mouse peritoneal macrophages and by Wallace and associates (*14*) in fibroblasts of rats and mice. The most spectacular recent accomplishment, however, was that of Rees and Garbutt (*15*) of the National Institute of Medical Research in London, who grew the bacillus of rat leprosy in rat fibroblasts. At the congress in Rio de Janeiro, Fildes and associates (*16*) reported that they have succeeded in maintain-

ing the bacilli through many subcultures for more than 3 years. The total increase of bacilli during a period of 1,015 days was approximately 10^{20}, giving a mean generation time of 14 days. The rate of multiplication of the cell-grown bacteria, their pathogenicity for mice, and inability to multiply in bacteriological media have remained unchanged. Since the expected generation time of *M. leprae* might be as long as 30 days, it seems imperative to use tissue cells which multiply at a slow rate to avoid "diluting out" of the inoculated bacteria. This requirement becomes understandable if one considers a situation where successive doublings of a population occur at a constant rate. The number of individuals after time t is given by the following equation:

$N_t = N_o \times 2^g$ where N_t = number of individuals after time t
N_o = number of individuals present at beginning of multiplication at a steady rate
g = number of generations during time t

An additional requirement might be cells that are amenable to culture at relatively low temperatures. It is also suggested that cell strains derived from amphibians, reptiles, and fish be included in attempts to grow *M. leprae* in cell culture.

At the Eighth International Congress of Leprology, Chatterjee and Rees (*17*) reported that they have obtained multiplication of *M. leprae* in cultures of rat fibroblasts. Whether or not the cultured acid-fast organism is indeed the leprosy bacillus cannot be decided at present.

Experimental Transmission to Animals

The study of leprosy in the laboratory requires one or several species of animals which respond regularly and in a predictable fashion to challenge with *M. leprae*. Innumerable attempts at experimental transmission of leprosy have been made and a wide variety of techniques used in inoculating individuals of many species, ranging from fish to man.

Recognition that most individuals of nearly all species of animals tested seem naturally resistant to infection with *M. leprae* has led to a variety of experiments which depress the natural defenses of the prospective host. Binford (*18*), of the Armed Forces Institute of Pathology, produced hormonal imbalance in animals by treatment with steroids such as cortisone. Cortisone had previously been shown by Lurie and associates (*19*) at the Henry Phipps Institute in Philadelphia to depress the capability of macrophages to interfere with the intracellular multiplication of tubercle bacilli. Binford, however, concluded that neither cortisone therapy nor total body irradiation had any effect on the growth of *M. leprae* under the conditions of his experiments. Other workers have used whole body irradiation, antimetabolites, or nutritional deficiency states, such as the one produced by Bergel's "pro-oxidant" diet (*20*), to precondition animals before inoculation. Chatterjee in Calcutta has attempted to produce particularly susceptible mice by selective breeding (*21*).

Realization that *M. leprae* may require growth temperatures below those of internal organs of mammals has resulted in inoculation of such sites as testicles, ear lobes, skin, and foot pads. Recently, Shepard (*22–24*), of the Communicable Disease Center, reported multiplication of *M. leprae* in the foot pads of mice, including successful transfer of the bacteria from mouse to mouse. Multiplication was obtained regularly and in a great proportion of primary and sequentially inoculated mice. This differs from previously reported accomplishments where successes were sporadic and unpredictable. Furthermore, the phenomenon of bacterial fragmentation cannot account for the reported 1 to 10 thousandfold increase of acid-fast bacilli in the foot pads. Janssens and Pattyn (*25*) corroborated Shepard's findings. These workers also observed spread of the bacteria from the hind to the front feet. In addition, they made comparative studies with foot pad inoculation of *M. leprae*, *M. lepraemurium*, *M. balnei*, *M. ulcerans*, and *M. fortuitum*. The results of these experiments showed that *M. leprae* behaved differently in the mouse foot pad, quantitatively, clinically, and histologically. Shepard's findings have been duplicated in the laboratory of Rees in London (*26*) and by Kirchheimer in Carville.

Perhaps a few words should be said about the expected effect of mouse foot pad growth

of the leprosy bacillus on our knowledge of the biology of this bacterium and the host parasite relationship. Since, at most, 10 million bacteria can be harvested from a mouse foot pad, from 25,000 to 50,000 mice would be required to obtain 1 gram of moist bacterial mass, or something like 100 mg. of protein. This method is not likely to contribute the quantity of cells needed for extensive metabolic studies.

One outstanding feature of leprosy in man is the invasion of peripheral nerves by the leprosy bacillus. Since this invasion does not ordinarily occur in other mycobacterial infections, it has become the foremost criterion for judging successful experimental transmission. At the congress in Rio de Janeiro, Binford and Madison (*27*) reported nerve involvement in the ear lobes of the Syrian hamster, *Cricetus auratus*, following injection of suspensions of *M. leprae*, obtained from lepromatous skin lesions. Microscopic lesions consisting of histiocytes containing mycobacteria were also seen in the foot pads of hamsters following inoculation at this site. Neither the inoculated nor the harvested bacilli grew in artificial culture media. Bacillary multiplication with nerve involvement in ear lobes of golden hamsters was also reported at the congress by Niven and Waters (*28*). Intracellular mycobacteria were most readily found in cells of the perichondrium of the ear cartilage.

Of great interest is the work of Chatterjee and Rees (*17*), who succeeded in infecting a hybrid strain of mouse with bacilli from cases of untreated leprosy. The infections in these mice became generalized, involving liver, spleen, lymph nodes, skin, and nerves. The organism infecting the mice had a much shorter generation time than Shepard found in the foot pads of his mice. In addition, the bacterial mass obtained in mouse foot pads was much larger than Shepard had experienced. Furthermore, Nishimura (*29*) and Kawaguchi and associates (*30*) have reported latent infection with *M. lepraemurium* in a considerable proportion of their mice.

Cytological Studies

Some cytological studies of the leprosy bacillus and other mycobacteria are significantly related to all previously discussed experimentations. They aim at the microscopic distinction between viable, damaged, and nonviable mycobacteria. If microscopic distinction between living and dead leprosy bacilli were possible, we might have a quality control test for our inoculum. Recently, Rees and Valentine (*31*) reported that mycobacteria which appear irregularly stained under the light microscope are shown to be degenerate by the electron microscope and are assumed to be dead. There is no denying that the leprosy bacilli in many an inoculum were suffering from a high "granularity index."

Resistance and Immunity

It is a common observation that individuals exposed to leprosy bacilli may fail to develop readily detectable signs of infection. Others display partial resistance to the Hansen bacillus by supporting its growth in their tissue only with reluctance or for a limited time. The tissues of some individuals, however, seem quite incapable of any effective resistance to the multiplication of the invaders and their progeny. At present it is not possible to know whether an individual exposed to *M. leprae* and not exhibiting signs of disease actually has escaped infection. Because of the lack of a protein antigen for skin testing, it is not possible to measure the contagiousness of leprosy. Attempts to produce *M. leprae* antigens suitable for skin testing are being made. Also under investigation is the development of an infectious type of allergy in individuals with leprosy against various types of mycobacterial products. Morris and associates (*32*) have recently used the fluorescent antibody technique to reveal the presence of antibodies against *M. leprae* in the serum of individuals with the lepromatous and tuberculoid type of the disease. They discovered antibodies in 11 of 14 individuals with the lepromatous type of the disease and in 5 of 17 individuals with the tuberculoid type. This is a rather limited population for drawing general conclusions. However, these findings support the opinion that in leprosy, as in other mycobacterial diseases, resistance is not mediated through circulating antibodies. Previous findings of Hanks (*33*, *34*) with explanted fibroblasts of lepro-

matous and tuberculoid leprosy support the assumption that resistance to the Hansen bacillus might depend on biochemical characteristics of the invaded cells, expressed by superior capability for destruction of the bacteria.

It is indeed questionable that either the Mitsuda reaction or native resistance to the leprosy bacillus involves immunologic mechanisms. As far as the Mitsuda reaction is concerned, Tuma and associates (*35*) have presented evidence that the early infiltrate at the injection site of lepromin is always nonspecific. It consists of lymphocytes, histiocytes, fibroblasts, and polymorphonuclear leukocytes. These authors surmise that the later formation of a tuberculoid granuloma constituting a positive reaction depends on the presence of lipoidal material in the inoculum and of lipolytic enzymes in the macrophages of the individual subjected to the test. Absence of enzyme activity from cells of individuals highly susceptible to leprosy might account for their failure to respond with epithelioid cell formation to either lepromin injection or infection with the Hansen bacillus. Essentially the same view is expressed by Hadler (*36*) who stated that the difference between individuals with lepromatous and tuberculoid leprosy is one of biosynthesis of enzymes, some of which are directed against mycobacterial components.

At the Eighth International Congress of Leprology there was an increasing readiness of workers in leprology to regard the various clinical and histological types of leprosy as an expression of the amount of host resistance (*37*). The two polar types of leprosy, tuberculoid and lepromatous, respectively represent high and low degrees of resistance and stand at the ends of a spectrum encompassing all of the variations in resistance. That this exists certainly does not come as a surprise to the biologist.

Summary and Conclusions

Recent research into the biology of *Mycobacterium leprae* and its interaction with its host reveals that failure to grow independently, a narrow host range, and a relatively low optimum temperature for growth—known and assumed characteristics of the Hansen bacillus—are shared by some other acid-fast bacteria. In vitro growth of *M. leprae* and *Mycobacterium lepraemurium* has not yet been accomplished. It is encouraging, however, that some factor-requiring mycobacteria are adaptable to growth without specialized requirements. As has been shown recently, *M. lepraemurium* can grow in cultures of tissue cells. This bodes well for the ultimate success of similar attempts with *M. leprae.*

That the Hansen bacillus can multiply in the tissues of mouse foot pads has been confirmed by several independent laboratories. It is not likely, however, that this method can contribute the quantity of cells needed for extensive metabolic studies. It is generally appreciated that such studies depend on availability of great quantities of intact bacteria, subcellular fractions like mitochondria, or bacterial extracts. The growth of leprosy bacilli in the mouse foot pad is being exploited at present for purposes of experimental chemotherapy, immunizing efficacy of vaccines such as BCG, and may lend itself to studies of the emergence of drug resistance.

The possibility of distinguishing microscopically between viable and nonviable leprosy bacilli provides the experimenter with some kind of quality control test for his inoculums. In addition, it can guide the clinician in the treatment of the disease and the management of the patient. The different clinical and histological types of leprosy are now generally considered to reflect different degrees of host resistance. There is at this time no evidence that resistance to the leprosy bacillus depends on circulating antibodies. It is possible, however, that resistance to the Hansen bacillus is dependent on genetically determined characteristics of host cells. Research into the mechanism of native resistance might provide the answer.

REFERENCES

(*1*) Feldman, W. H., and Karlson, G. A.: *Mycobacterium ulcerans* infections: response to chemotherapy in mice. Amer Rev Tuberc 75: 266–279 (1957).

(*2*) Twort, F. W., and Ingram, G. L. Y.: A method for isolating and cultivating the mycobacterium enteritidis chronicae pseudotuberculosis bovis Johne, and some experiments on the prepara-

tion of a diagnostic vaccine for pseudotuberculosis enteritidis of bovines. Proc Roy Soc Bact 84: 517-542 (1912).

(3) Francis, J., Macturk, H. M., Madinavertia, J., and Snow, G. A.: Mycobactin, a growth factor for *Mycobacterium johnei*. I. Isolation from *Mycobacterium phlei*. Biochem J 55: 596–607 (1953).

(4) Darzins, E.: Desoxyribonucleic acid as growth stimulant of tubercle bacilli. Amer Rev Resp Dis 80: 866–870 (1959).

(5) Darzins, E., and Pukite, A.: Action of nucleic acids and plant-growth hormones on the growth and viability of mycobacteria. Amer Rev Resp Dis 84: 549–554 (1961).

(6) Morrison, N. E.: Circumvention of the mycobactin requirement of *M. johnei*. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(7) Hanks, J. H.: Origin and character of noncultivated states in mycobacteria. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(8) Suter, E.: Interaction between phagocytes and pathogenic microorganisms. Bact Rev 20: 94–132 (1956).

(9) Hanks, J. H., and Gray, C. T.: Extracellular inhibitors in leprotic infections and their role as barriers to experimental transmission. Int J Leprosy 22: 461–468 (1954).

(10) Tepper, B. S.: Surface properties as impediments to transport in mycobacteria. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(11) Geronimus, L. H., and Birkeland, J. M.: The relationship between the virulence of tubercle bacilli and the vigor of their oxidative attack upon certain substrates. Amer Rev Tuberc 64: 520–533 (1951).

(12) Segal, W., and Bloch, H.: Biochemical differentiation of *Mycobacterium tuberculosis* grown in vivo and in vitro. J Bact 72: 132–141 (1956).

(13) Chang, Y. T.: Growth of *M. lepraemurium* in cell culture. Fed Proc 18: 17 (1959).

(14) Wallace, J. H., Ellek, S. D., and Hanks, J. H.: Limited multiplication of *Mycobacterium lepraemurium* in cell culture. Proc Soc Exp Biol Med 97: 101–104 (1958).

(15) Rees, R. J. W., and Garbutt, E. W.: Studies on *Mycobacterium lepraemurium* in tissue culture. I. Multiplication and growth characteristics in culture of rat fibroblasts. Brit J Exp Path 43: 222–235 (1962).

(16) Fildes, C., Rees, R. J. W., and Garbutt, E. W.: Multiplication of *Mycobacterium lepraemurium* in cell cultures. [Abstract]. Int J Leprosy 31 (4): October–December 1963.

(17) Chatterjee, K. R., and Rees, R. J. W.: Experimental transmission of human leprosy to a hybrid strain of black mouse. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(18) Binford, C. H.: Histiocytic granulomatous mycobacterial lesions produced in the golden hamster (*Cricetus auratus*) inoculated with human leprosy: Negative results in experiments using other animals. Lab Invest 8: 901–924 (1959).

(19) Lurie, M. B., and Zappasodi, P.: On the mode of action of cortisone on the pathogenesis of tuberculosis and its implications for the nature of genetic resistance to the disease. Ciba Foundation Symposium of Experiments in Tuberculosis, 1955, pp. 246–258.

(20) Bergel, M.: Influence of various pro-oxidant nutritional conditions on the growth in vivo of *M. leprae*. Leprosy Review, July 1959, pp. 153–158.

(21) Chatterjee, K. R.: Experimental transmission of human leprosy infection to a selected laboratory-bred, hybrid black mouse. Int J Leprosy 26: 195–204 (1958).

(22) Shepard, C. C.: Acid-fast bacilli in nasal excretions of leprosy, and results of inoculation of mice. Amer J Hyg 71: 147–157 (1960).

(23) Shepard, C. C.: The experimental disease that follows the injection of human leprosy bacilli into foot-pads of mice. J Exp Med 112: 445–454 (1960).

(24) Shepard, C. C.: The inoculation of leprosy bacilli into mice by the foot-pad route. Transactions of the Leonard Wood Memorial-Johns Hopkins University Symposium on Research in Leprosy, 1961, pp. 247–255.

(25) Janssens, P. G., and Pattyn, S. R.: Experience with mouse inoculation of leprosy bacilli originating from the Congo. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(26) Rees, R. J. W.: The pathogenesis of leprosy. Ciba Foundation Study Group No. 15. London, J. & A. Churchill, 1963, p. 88.

(27) Binford, C. H., and Madison, R. M.: The transmission of *M. leprae* to animals: nerve lesions in the golden hamster. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(28) Niven, J. S. F., and Waters, M. F. R.: Inoculation of the golden hamster with human leprosy bacilli. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(29) Nishimura, S.: Experimental transmission of the leprosy bacilli to the black mouse. [Abstract]. Int J Leprosy 31(4): October–December 1963.

(30) Kawaguchi, Y., Nishimura, S., and Kosaka, K.: Studies on the acid-fast bacillus isolated from healthy mice. [Abstract]. Int J Leprosy 31 (4): October–December 1963.

(31) Rees, R. J. W., and Valentine, R. C.: The appearance of dead leprosy bacilli by light and electron microscopy. Int J Leprosy 30: 1–9 (1962).

(32) Morris, J. A., Aulisio, C. G., Boseman, F. M., and Guinto, R. S.: Fluorescent antibody study of the human leprosy bacillus. [Abstract M83]. Bacteriological Proceedings, 1961, p. 123.

(33) Hanks, J. H.: The fate of leprosy bacilli in fibroblasts cultivated from macular and tuberculoid lesions. Int J Leprosy 15: 31–47 (1947).

(34) Hanks, J. H.: The fate of leprosy bacilli in fi-

broblasts cultivated from lepromatous lesions. Int J Leprosy 15: 48–64 (1947).
(35) Tuma, M., et al.: A study of the mechanisms of the lepromin reaction. [Abstract]. Int J Leprosy 31(4): October–December 1963.
(36) Hadler, W. A.: Studies on the pathology and experimental transmission of leprosy. [Abstract]. Int J Leprosy 31(4): October–December 1963.
(37) Members of the Round Table on Borderline and Indeterminate Leprosy: Report. Int J Leprosy 31(4): October–December 1963.

Study on Rehabilitation of Drug Addicts

On the premise that rehabilitation of discharged narcotic addicts could be furthered through increased use of community facilities, the Community Services Branch of the National Institute of Mental Health, Public Health Service, supported a 5-year demonstration program in New York City. The methods developed during the project for speeding recovery of addicts through selected casework techniques are described in a 48-page monograph, "Rehabilitation in Drug Addiction" (PHS Publication No. 1013), recently published by the Institute. Leon Brill, aided by a case supervisor and five caseworkers, served as project director.

The New York Demonstration Center mobilized support of public and private agencies to help the type of patient many had considered hopeless. The New York City Departments of Health, of Hospitals, and of Welfare and various State employment and welfare agencies, as well as family agencies, mental hygiene clinics, and private hospitals, agreed to participate. Thereupon staff of the center began a careful program of referring addicts to the agencies, meanwhile working intensively with some addicts in its own offices. To overcome agency reluctance to work with addicts and increase the likelihood of success, only the best-motivated patients were referred initially. In time, however, some agencies agreed to accept irregularly relapsed patients.

However, the addict had great difficulty in making use of these community resources. The staff of the demonstration center recognized that work with the addict, who is emotionally at the level of the 3-year-old, is extremely precarious. Traditional casework approaches and techniques had to be modified, and a variety of techniques for reaching hard-core groups were used. All the workers arrived at certain common methods—using crisis situations to establish relationships, being permissive about appointments and openly manipulative demands, frequently providing the concrete services that the addict requested. Through intervention in crises and provision of concrete help a number of addicts were thus enabled to use casework aid in a limited way, to follow through on employment referrals with support from the caseworker, to remain on jobs longer, and to work out better ways of dealing with stresses in their familial and social relationships.

Perhaps the major implications of the study are that it is necessary to reach out to these unmotivated patients and their families and also to supply this "acting out" group with a "rational authority" as a means of sustaining treatment long enough to achieve rehabilitation. Among other clues are the need for easily accessible services or help, for a family-centered approach, and for avoidance, at the beginning, of intensive counseling or of attempts to elicit feelings and develop insight. The project also emphasized the need for limited goals and for study of the sociocultural factors of narcotic addition.

From its inception in 1957 to April 1961, the center served a total of 912 patients (mostly dischargees from the Public Health Service hospital at Lexington, Ky.). With certain considerations taken into account, staff of the demonstration center felt that many of the 912 could be considered to have responded to treatment efforts. Addiction has to be viewed as a chronic illness for which treatment must be long and continuing. Also, it is necessary to work with the addict's family so that its "endless destructive interaction with the addict" will cease.