MALARIA AND FILARIASIS IN THE RETURNING SERVICEMAN

The Ninth Charles Franklin Craig Lecture[1]

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The general problem of malaria as it exists in the returning serviceman is a familiar one to those interested in tropical diseases, at least in its broader aspects. More specifically, it is a disease present in large numbers of men and we are concerned with the task of reducing their latent infections and preventing malaria from gaining a foothold in receptive areas of this country. The basis of this report will be a discussion of the problem as seen in a group in excess of 3000 men assembled for care and observation at one place.

Since the station referred to is somewhat unorthodox as compared to other medical military installations, a word of explanation is in order. A little over a year ago it was the opinion of the Bureau of Medicine and Surgery, U. S. Navy, that a special installation for the care of malaria patients was justified. There were many reasons for this decision; first, because of the large volume of men involved; second, because the majority of these individuals were having repeated clinical breakdowns; third, they were only acutely ill for three to seven days during each episode, thus occupying valuable hospital beds urgently needed for other purposes; and finally, it was considered an ideal opportunity to assemble these malarial patients in one place for observation and study. Never in the history of this country has such a large group of men suffering from a single infection been returned to a clean area, without the opportunity for reinfection, where they can be retained as a body throughout their convalescent period. As these men are returned from overseas, they are immediately sent to Marine Barracks, Klamath Falls, Oregon, where they are carefully questioned as to their itinerary and malaria history, examined, and if physically able to travel, are given a month's furlough. The malariologist will probably question the wisdom of this last procedure, since it enhances the possibilities whereby malaria may establish itself in this country. This policy, in our opinion, is justified from the fact that already thousands of recurring cases have been dispersed by all military services through assignment, furlough or discharge to all states of the Union. There probably is not a community which has not received one of these servicemen suffering from this malady. Also there are relatively few areas in this country where the possibility of transmission can be excluded. Even if there were malaria-safe places it would mean the retention of these men until the last recrudescence has occurred—something no one can predict and many are now going into their third year of infection. Since the majority of cases seen in this country contracted their infection in Guadalcanal and adjacent islands late in 1942, one can easily visualize the difficulty of restricting a man who has served overseas two years, and especially in those who have hit the beaches on Guadalcanal, Tarawa, Eniwetok and Saipan with periodic malaria as a constant companion.

After their return from furlough, they were again examined and assigned to companies of 200 men each, where they can be closely followed and observed. An analysis of their malaria histories overseas reveals several interesting points. First, occasionally one encounters among the patients men from the South who have had previous malaria histories in this country and not in the too distant past. Of course these are few in number and it furnishes only inferential evidence on the possibility of the lack of cross immunity between American and South Pacific strains. Especially so since we do not see those men who have had malaria in this country and were exposed but did not acquire it overseas. The information is presented only as an observation for what it is worth.

An examination of the health records does not furnish an accurate picture of the species of plasmodia responsible for the initial infection, since many men were diagnosed and treated without the aid of blood smears, probably many blood

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smears were misdiagnosed and many unrecorded. However, from the hundreds of records examined little doubt remains that in the field a high percentage were accurately diagnosed as falciparum malaria. Also, from other records and statements of competent medical officers, it is known that falciparum malaria was extremely prevalent in the South Pacific area in general and in some areas it predominated over the vivax variety. However, the exact ratios of the two are not known. Likewise, the percentage of men suffering clinical reactivations following the initial attack is not known because unit strength information is not available, replacements were frequent, there were high casualty rates and men were constantly being reinfected. However, some careful studies were made on small units where it was possible to obtain non-controversial information and although the data has been placed on the restricted list, it is possible to state that the percentage of recrudescences is greater than that commonly observed with vivax malaria in this country.

Most of the men on the station, among 1424 cases analyzed, 1335 or 95%, took suppressive medication before their initial attack. From the histories only one positive statement can be made in regard to suppressive therapy, either quinine or atabrine, and that is; a sufficient number regularly took either drug in the recommended dosage or in excess and it did not prevent malaria. The individuals were subjected to so many combinations of suppressive drugs and dosage regimes a critical analysis of their malarial histories is not possible, especially as to number of clinical breaks through while under suppressive therapy.

From the records on the toxicity of atabrine given as a suppressive drug, it can be stated that in some instances dosages of 0.3 gm. daily were tolerated for long periods without difficulty. The toxicity of this drug has been studied in man and animal under the auspices of the Army, Navy and National Research Council, and it is the consensus of opinion that the toxic properties of atabrine in the recommended dosage is of little consequence. As to acute toxicity, there is a record at Oak Knoll Naval Hospital (1) of a man who was known to have taken at least 7.5 grams of atabrine and probably considerably more (18.0 grams) in a three hour period with a suicidal intent. He went into shock, was stuporous in about four hours, then went into coma. Within 48 hours he was conscious and went on to complete recovery. There was no evidence of liver or other visceral damage. On the second day, his atabrine blood level was 475 gamma, which is only 25 gamma below the saturation level. It it unfortunate in one respect that the man did not have chronic malaria because a golden opportunity was lost to determine the effectiveness of atabrine as a cure when present at an excessive level. Brigadier N. H. Fairley (2), Australia, has seen a similar episode which resulted fatally. This gives a mortality figure of 50% in a series of two cases. Although these are extreme cases, the dosages with survival does indicate that a slight increase in recommended dosage would not be attended by serious results.

TABLE I

Number of previous attacks related to results of blood smear examinations taken upon admission

NUMBER OF PREVIOUS ATTACKS	BLOOD SMEAR NUMBER		
	Total	Positive smear	Negative smear
All cases	1,419	116	1,303
1 attack elsewhere	33	1	32
1 attack here	3	0	3
2–4 attacks	130	15	115
5–9 attacks	437	28	409
10–14 attacks	418	40	378
15–19 attacks	241	18	223
20–24 attacks	95	7	88
25–29 attacks	44	7	37
30–34 attacks	10	0	10
35 and over	5	0	5

When the men are transferred to the station, all those with a malarial history have a stained thick smear of their blood examined. A summary of the results of these examinations is shown in Table I. In 1419 individuals, 116, or 8.2% were found to be positive. This does not include those men who arrive with an acute attack. When the degree of parasitemia is compared to the number of attacks that occurred previous to arrival, it can be seen that no correlation exists. For example, 418, or 29% of all cases aboard have experienced 10–14 attacks and in this group we find 34% of the positive smears. Although the positive smears are somewhat greater in this group, the difference is not a significant one. Separate from this group and not shown on the table are the results of the men who have had clinical malaria on the

station, who are treated and then followed by twice weekly blood smears. In 1427 such examinations, 132, or 9.7%, are found to have circulating parasites. As expected, this figure is slightly higher than the 8.2% showing a parasitemia upon arrival on the station.

TABLE II

Number of previous attacks related to spleen and liver examinations

NUMBER OF PREVIOUS ATTACKS	SPLEEN AND LIVER EXAMINATIONS NUMBER			
	Total	Palp. spleen	Palp. liver	Non-palp. spl. and liver
All cases	1,419	55	14	1,349
1 attack elsewhere	33	0	0	33
1 attack here	3	0	0	3
2–4 attacks	130	1	3	126
5–9 attacks	437	15	4	417
10–14 attacks	418	18	2	398
15–19 attacks	241	11	3	227
20–24 attacks	95	3	1	91
25–29 attacks	44	4	1	39
30–34 attacks	10	2	0	8
35 and over	5	0	0	5
Inf. miss	3	1	0	2

TABLE III

Spleen and liver examinations related to original blood smear results

SPLEEN AND LIVER EXAMINATION	RESULTS OF SMEAR NUMBER		
	Total	Positive	Negative
All cases	1,419	116	1,303
Pal. spleen	55	5	50
Pal. liver	14	2	12
Both	1	0	1
Neither	1,349	109	1,240

1 Less than 0.5 of one per cent.

In spite of the high incidence of falciparum malaria reported in the previously referred to initial infections, not a single infection of this variety has been seen on our station. Nor have any falciparum gametocytes been recognized. The men have come directly to the station from overseas without selection. Undoubtedly, many of them have acquired mixed infections, but as the biological characteristic of falciparum malaria is not to relapse, they are not seen here. With stricter suppressive atabrine discipline, falciparum malaria is failing to make its appearance where there is every reason to expect it. Probably atabrine neither prevents nor cures this type of malaria but merely suppresses until it is finally eradicated by the defense mechanism of the body.

Also in the same table the number of previous attacks are shown. Since the information is gained by testimony, the numbers are not absolute, because after 8–10 recrudescences many men lose count of the exact number. However, in a group of this size the percentage of error is a small one. Of interest are three men who have experienced their first malarial attack on the station. Their admission diagnosis was filariasis. One of the men had this first attack 8 months following withdrawal from the endemic area and discontinuance of suppressive atabrine. This has been the longest noted in any of many on our station, although there is another authentic instance of a 13 months' period without history of malaria overseas.

TABLE IV

Monthly relapse rate of personnel on station with malarial histories

MONTH	NUMBER OF MEN	NUMBER OF RECRUDESCENCES	RATE
June	29	2	6.9
July	184	19	10.3
August	411	30	7.3
September	569	66	11.6
October	802	89	11.1
Average			10.3

The complement fixation reaction as a diagnostic aid has been employed intensively in many military installations in the past two years. This test was first employed by Kingsbury (3) most successfully a decade ago when he employed infected vivax and falciparum blood as an antigen. It was discarded because this source of antigen was unsatisfactory. Eaton and Coggeshall (4), in 1937, showed that a non-human malaria parasite, *Plasmodium knowlesi*, could be used just as successfully and thereby excluded the chief disadvantage of obtaining antigen from ill human subjects. In therapeutic malaria induced by infected blood

where relapses practically never occur, the findings were very promising. We have used the test for the past several months in an attempt to detect hidden infections or to delineate the duration of the disease acquired in the South Pacific. There is no doubt as to its specificity, as a positive test indicates infection. However, in the majority of positive cases, proven by subsequent relapses, we have found that the test is an unreliable one, as it is too frequently negative in these known positives. These results have occurred with all the various types of antigens recently described.

As one observes the clinical picture in several hundreds of these repeating vivax infections, one is impressed by several points. The first is the absence of the picture of malaria cachexia so frequently described with chronic malaria. This is particularly true in the men who have been back a few weeks. Either malarial cachexia is only evident when associated with other infections and malnutrition or the manifestations as seen in South Pacific malaria are different than those encountered elsewhere. Likewise, splenomegaly is noted in less than 5% of the men, even after 20 to 30 recrudescences. Immediately after the acute attack, palpable spleens are present in about 8% of the individuals, most of them have barely palpable spleens, three finger enlargement has been the maximum. This information is summarized in Tables II and III. Anemia is also conspicuous by its absence, after six weeks at our station with mile high altitude, the red blood count averages 5,300,000. Except for a persistent headache in a few individuals there is nothing to indicate that an individual is suffering any discomfort between his acute episodes of fever.

When ill, the response to therapy is prompt, within 72 hours. This can be accomplished by administering orally 0.2 gm. atabrine every six hours and then 0.3 gm. daily for five days. Any greater amounts in a short time or prolongating therapy has had no influence on the subsequent relapse rate. Quinine behaves similarly and shows the same fundamental inability to effect a permanent cure. Plasmochin, now in general disrepute because of its toxicity, has not yet been shown to influence the relapse rate. Likewise, arsenicals or other heavy metals, sulfonamides, penicillin, dyes or other types of compounds are in general of little or no avail.

Among the individuals on the station, the recrudescence rate has averaged 10.3 per cent per month. This figure is obtained from the number with a malarial history and relapses each month (Table IV).

Considerable controversy has arisen as to whether the vivax malaria originating in the South Pacific area represents a strain differing from the same variety seen in this country. No immunological studies have been conducted on our station but there is considerable inferential data to support the thesis that they do differ. In the first place, the frequency of periods of clinical activity following the initial infection is far in excess of that seen in this or any other country. As shown in Table I, 57% of the men under observation have had in excess of 14 acute attacks, some of whom experienced as many as 40. This is in contrast to the picture observed in vivax malaria of the States, where it is unusual to have a fraction of this number of clinical breakdowns.

Also in the overseas group, one is impressed with the rhythm of the recrudescences. Many men can predict within a week when their next bout will occur. A common statement is that, "my malaria was much more regular than the pay check".

Another point of differentiation is the previously referred to lack of splenomegaly, high blood counts, general well-being, even in men with persistent parasitemia, and frequent recrudescences.

Not observed on the station, but another point of differentiation is that Negroes are very refractory to the vivax malaria of the United States. As a matter of fact, institutions using therapeutic malaria for C.N.S. lues resort to the quartan type. In the Pacific area, American Negroes were as susceptible to vivax malaria as whites. Butler and Sapero (5), (MC), U.S.N., conducted an epidemiological study on three battalions of colored troops from South Carolina who contracted malaria, and 90% of readmissions were diagnosed vivax malaria. Actually, the relapse rate for vivax malaria was slightly greater than in white troops serving in the same area. There is much more inferential evidence that there are strains within species of malaria plasmodia and that contracted in the South Pacific is the most tenacious yet encountered. If this impression is confirmed the greatest danger of introducing malaria into this country probably is not that sweeping epidemics will occur, but the implantation of a strain immunologically different from those indigenous to this country, and one that will incapacitate for long periods all those who contract it.

The activities of the station are concerned with the assimilation of information with considerable emphasis in investigation. For the most part it concerns evaluation of new therapeutic compounds, the results of which cannot be disclosed at the moment.

It is possible, however, to describe the program of therapy, although it is non-specific and has been in force only a few months, there is no doubt that much is being accomplished. When a man has returned from furlough he is placed on a full duty status. This includes military training, recreational activities and educational and vocational exercises. It is noted that the men gain weight, the red cell count and hemoglobin increases and there is a rapid improvement in their general physical condition. Approximately 85% of our men come from overseas and the remaining 15% have been transferred from continental hospitals or limited duty stations. Men who have been in this country for some time and only able to perform two or three hours' work daily soon are able to undergo a full day's activity.

The abuse of rest is very apparent during the convalescent period from this disease, as it is being observed in many other infections or disabilities, and certainly any man with malaria needs very little encouragement to make him a permanent mental and physical cripple. If, by careful study, the future course of these infections of several hundred men with malaria can be more clearly defined, it will be of real value to all those concerned, and during the course of these studies if the ideal drug should happen to be disclosed which would more rapidly terminate the course of this infection, the effects would be so far reaching that one would hardly be able to visualize its importance. These two possibilities remain in the future, but this accomplishment can be definitely stated at this time, namely, there is no doubt that the program designed to keep men occupied mentally and physically during their convalescent period from tropical infections is real preventive medicine in that it is preventing the inception of hundreds of cases of "hospitalitis". Thus, in the absence of curative drugs and with diseases that are gradually being eliminated by the defense mechanism of the host, our rationale of treatment is based on the concept that a physically fit body is equipped to throw off an infection more quickly than the one that is permitted to deteriorate mentally and physically by long periods of hospitalization.

Finally, there seems to be no doubt that even this South Pacific malaria is a self-limited disease and will eventually disappear. Actually, within a relatively short six months period, we are noticing that a curve representing the rate of recrudescences has a definite downward trend in this malaria that is still manifesting itself in the third year after inception, and a program of physical fitness is precipitating the fall of the curve.

FILARIASIS

When filariasis made its appearance among servicemen stationed in the South Pacific, a little more than a year and a half ago, it was a cause of considerable concern to medical men. This concern, more than anything else, had as its genesis the picture of elephantiasis seen in the natives, who have carried their infections throughout their life-time. Filariasis is especially prevalent in the Samoan area. Actually, it exists there in epidemic form, although it is not correct to refer to its existence as epidemic, even where the incidence is so uniformly high. Epidemics occur when large groups of uninfected populations immigrate into an infected area. This is what happened early in 1942, when several thousand American Marines were staging in British and American Samoa, Wallis and Ellice Islands. The causative organism is *Wuchereria bancrofti*, which is the most prevalent of the four species of the filarial organisms. The life history of this nematode worm is fairly well understood. It is transmitted to man by an infected mosquito, which injects sexually immature microfilaria into the blood stream. These embryos make their way to the lymphatic channels and thence to the lymph glands, where they mature into adult organisms. The male wraps itself around the female and fertilization occurs. After the female becomes gravid she expels microfilaria into the blood stream. The microfilaria are thus available to the bite of a susceptible mosquito. The microfilaria, in themselves, are non-pathogenic and non-infective to man. Actually, the circulating microfilaria can be transferred by transfusion to a normal individual without harm. They can only complete their development by passing through the mosquito and thence back to man. This is an important point from the standpoint of the infected serviceman. For example, if infected by mosquitoes which inject a definite number of microfilaria, it is impossible to ever have more than that number of adult worms, regardless of how long the individual lives. In other words, the adult worms are unable

to reproduce themselves in the body and thus do not continue to accumulate.

The pathological and clinical manifestations seen in the serviceman are undoubtedly stirred up by the irritation of developing worms in the lymph glands. Three predominate findings are noted in the early infections, namely, lymphangitis, lymphedema and lymphadenopathy. The lymphangitis is always retrograde, usually starting in the axilla, elbows or groins and then slowly descends. The extremes vary from the length of the extremities to a few centimeters. Although somewhat painful, it does not compare to the pain encountered in a streptococcic lymphangitis. Systemic toxic manifestations are practically absent. There may be a temperature of 101° to 102°F., which usually lasts about 48–72 hours. There still exists considerable controversy as to whether this lymphangitis, which is probably an allergic manifestation producing a lymph blockage, is associated, primarily or secondarily, with a streptococcus. The supporting evidence is not good for this theory, and the administration of sulfonamides or penicillin has no apparent effect on the lymphangitis. Lymphedema usually tends to be localized, although occasionally it is generalized, involving the entire arm or leg. An important point is that thus far it has been temporary, as no permanent swellings indicative of elephantiasis have been noted at this station in several hundreds of men over a period of eight months.

The picture of filariasis as it exists in Marine personnel from the Pacific can best be furnished from an analysis of some of the cases seen to date. In a large series of cases, 96% were stationed in the Samoan group of islands, and only 4% have contracted the infection elsewhere, Guadalcanal or Bougainville. This has occurred in spite of the fact that surveys on natives in the two general areas show intensities of infection that are not too different. The reasons for this disparity may be accounted for by the living habits of the natives, opportunities for contact, vectors and the periodic appearance of the microfilaria. In Samoa, the average length of stay was 12.5 months, with a variation of 1 month to 27 months. The incubation period, dated from the time of the first possible exposure to the appearance of initial symptoms, averaged 9 months. When seen in the States there was little differentiation in the degree of involvement in the men who were in the endemic areas a few months as compared to those who were present two or more years. The anatomical involvements as lymphedema, lymphadenopathy and lymphangitis are noted in the sites and frequency as follows: Neck—2%, upper extremities—30%, lower extremities—9%, scrotum—1%, cords—15%, and testes—18%. It was interesting to note that the right upper extremity was involved initially in 54% of the instances, while the left was only involved in 37% of the instances. For the lower extremities, the right exceeded the left, but the difference was not so marked; more use of the right arm might provide an explanation. However, for the genitalia the opposite was true; 33% on the right and 55% on the left.

From the picture of filariasis as it now exists in the serviceman, it is quite apparent that the current manifestations are extremely mild. The laboratory examination of the infected individual shows no abnormalities of the blood with the exception of an occasional instance of eosinophilia, which is rarely sustained. Thus far, three patients have come to our attention who have had high total white blood cell counts and unusually high eosinophile counts. Other than a chronic cough, there were no symptoms. Temperatures were within the normal range. The clinical histories and maximum blood counts were as follows:

Patient B., L. Cough 5 months, WBC, 36,150, Eosinophiles 72%;

Patient L., L. Cough 4 months, WBC, 14,600, Eosinophiles 48%;

Patient, R., A. Cough 16 months, WBC, 16,550, Eosinophiles 45%.

No microfilaria have been seen in the blood of any man on our station. There are a few verified instances when they have been observed in Army personnel following the concentration of large amounts of blood. Removal of enlarged lymph nodes for biopsy has been done and adult worms were revealed on histological examination, and in some instances microfilaria were detected *in utero*. In others, the adult worm was undergoing degeneration or calcification. This is not a recommended procedure from a therapeutic standpoint. However, it has provided valuable information in that it is now known that the body is gradually eliminating the infection. As yet there is no chemotherapeutic agent that is known to destroy the infection. H. W. Brown (6) has stated that a pentavalent antimony compound, known as anthiomaline, will decrease the microfilaria count in Virgin Island natives, a finding of doubtful importance unless it can be demonstrated that the

adult worm is also destroyed. The use of heat, cold, X-ray, non-specific proteins, etc., has not been shown to be beneficial.

There is a very prominent psychic element in the picture, as could be expected with an infection that involved the genitalia plus the reaction after seeing the grotesque deformities in the natives with elephantiasis. Men are concerned about sterility and the possibility that continued assaults on the lymphatic system will leave a permanent lymphedema. We now have had many hundreds of men under constant observation for several months. Upon returning from overseas, many want to get married, do, and have already started families. In 249 married men questioned there were 45 instances where the wife was pregnant. This disposes of the sterility factor. As far as the possibility of servicemen developing elephantiasis is concerned, this is an extremely unlikely possibility. Elephantiasis, in natives, usually appears late in life and rarely involves more than 5% of the population, even in the most highly endemic areas. They have been continuously exposed to the bites of infected mosquitoes from the moment of their birth until this complication appears. Elephantiasis and filariasis are not synonymous terms, but elephantiasis is a complication that arises after many years where the assaults on the tissues have been constant throughout that period. The differences in the intensity of infection are quite plain when one examines the blood, as the natives show 60% or more having high concentrations of microfilaria in the blood, whereas, in the serviceman it is a very unusual find to observe it in any individual. The secondary cases of filariasis which appeared in Charleston, South Carolina, a focus of infection which has now disappeared, were rarely associated with elephantiasis, because, like the serviceman, they were also very lightly infected. Brigadier N. H. Fairley (7), in Australia, reports that in North Queensland, 10% of the white population in 1920 had circulating microfilaria. This focus has also disappeared and no case of elephantiasis ever developed.

Of interest to all physicians and public health officials is the question as to whether filariasis is likely to gain a foothold in this country from the infected cases. It is the opinion of the author that this likelihood is extremely remote if not *nil*. In the first place, circulating microfilaria, if present, have been observed so infrequently and so few in number that transmission by mosquitoes would be impossible. Actually, no one has been able to infect artificially any local mosquitoes. Secondly, climatic conditions in this country, with the exception of a coastal strip in Southeastern United States, is not conducive to the maintenance of the disease. Finally, the infection as manifested in diagnosed cases is becoming more and more mild. Therefore, the future as regards the secondary transmission of filariasis in the United States should hold no cause for alarm.

This brings us to a consideration of the type of care best suited to these men returning with questionable or positive clinical symptoms. The term "questionable" is used because the clinical picture is the only means of establishing the diagnosis. It has been our policy to interview each man as he returns and explain to him very carefully the status of his infection. The following points are brought out. Since the microfilaria must continue their development in the mosquito, there is no possibility that the adult worms in the human body can reproduce themselves and thus they are not accumulating. Also the body is constantly destroying them. Therefore, the end result almost certainly has to be a good one and another year or two should see the disappearance of practically all symptoms in most cases referable to this disease. The man is then placed on a full duty status in a post where the terms "recreation" and "convalescent" have been purposely omitted, as there is no better way of convincing a man that he belongs to a misfit group. He is given a series of gradually increasing physical exertion exercises in combination with a program encouraging outdoor recreation. There is an immediate response, especially on the mental side, and it can now be stated that the majority of all men are not apprehensive about their infection. They do continue to have occasional flare-ups of edema, lymphangitis, and muscular soreness, but this persists only for a few days, and the following attacks become less and less frequent. Actually, it has been necessary to hospitalize only one man in 800 for filariasis, and the average stay has been five days. Less than 5% report to sick call with objective findings and 12% with subjective symptoms. There is one factor which remains to be assessed, namely, the time factor, but all the accumulated evidence to date indicates that filariasis will not result in permanent disability as has been feared and postulated by many. The abuse of rest is very apparent during the convalescent period from this disease, as it is being observed in many other infections or disabilities, and certainly

any man with filariasis needs very little encouragement to make him a permanent mental and physical cripple. Without curative drugs the program of care has been directed toward mental and physical rehabilitation. A daily program of directed military and recreational activities has been instituted. Some of these activities are very strenuous and serve as objective demonstrations that filariasis is not a crippling disease. After several months' observation of several hundreds of cases, it now seems that the problem of filariasis is not a serious one and that the vast majority of individuals now infected will shortly experience their final difficulty. In the interim between inception of symptoms and recovery, the most important procedure is the prevention of "hospitalitis" by a sane and interesting program of mental and physical activity.

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