

VENEREAL DISEASE PROBLEMS

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The Navy has watched the development of this Association in recent years with great interest. We have had many problems that were of mutual concern to us and that were met during the war years by joint action in a spirit of good fellowship and friendly cooperation. We want you to know that we are not unmindful of this and that we greatly appreciate the cooperation and assistance you gave us during the war. But we also want you to know that our interest is not lagging now that the war is won. On the contrary, we should have a little more time now to devote toward cementing the friendly ties that have developed during the war and toward the development of a more permanent relationship and a long-range program of accomplishment. As evidence of our continued interest and good intent, the Navy has sent me on this long journey from Washington that we might have the pleasure of meeting you and gaining the benefits of your advice.

Venereal diseases and their control have been a very serious problem with us, just as they are with our neighbor in the South and indeed, with most of the world today. In the Navy prior to World War II, venereal diseases have usually held first or second place as a cause of morbidity and as a cause of loss of manpower due to illness. However, during the war by great effort on the part of all organizations dealing with this problem, both civilian and military, we were able to reduce this drain on our manpower to the lowest point in the history of the Navy.

Early in the war we were losing the services of a great many men as a result of infections contracted along the border here. Those men were very badly needed to help fight the war. Your association was asked to assist us in this problem and through the splendid cooperation we received and the great effort you made, this drain on our manpower was materially reduced. We realize the difficulties you encountered in helping us. Some of the concepts of control were new and untried and some were contrary to the belief of the people. Yet they were instituted and, above all, they were successful.

Today we are facing a new era in the field of venereal disease control. Our concept of what constitutes a good venereal disease control program is changing and, as our knowledge of these diseases increases, undoubt-

* The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

edly it will change even more radically than it has in the past. With the advent of the sulfonamide drugs, we were presented with a weapon that seemed to offer the solution to the problem of gonorrhea. We went after it whole-heartedly even to the point of using these drugs as a prophylactic agent. We know now that it was not the perfect weapon we thought it to be. We know that sulfonamide-resistant strains of the gonococcus can be and were produced. We succeeded in killing off most of the non-resistant strains, thus propagating and spreading only the strains that were resistant to these drugs. Thus we defeated our purpose—or, should we say that we were thoroughly defeated by that ubiquitous diplococcus that continues to harass us today.

Now we have a new weapon that seems to offer even greater promise than the sulfonamides—we have the antibiotics and of this group the one most promising so far is penicillin. Tomorrow, there will undoubtedly be others of this character that will enter the field. This offers us an entirely new concept of therapy and possibly of venereal disease control. We are using great quantities of penicillin to treat our patients and we are constantly striving to improve the product and learn more of the basic character of these drugs. We have learned that our original drug was very crude, that it varied in character as well as effectiveness without our being able to detect it at the time. We have learned that we are dealing with a mixture of drugs and that the fraction called "G" seems to be the most effective one for the venereal diseases of the fractions so far isolated. We have now seen fractions "F", "X", and "K" isolated in addition to "G", and we hear that there are probably several more present and including an active substance that is apparently not a species of penicillin. Thus our new weapon is very complex and therefore difficult to evaluate. The Syphilis Study Section of the National Institute of Health has been attempting to evaluate penicillin in its effect on the venereal diseases. They held a symposium in Washington, April 17, 1947, in which it was reported that the results so far obtained with penicillin in early syphilis were not as striking as we had hoped. They reported that the failure rate with penicillin was somewhere between 30 and 40 per cent and that there was little if any difference between the failure rate with doses of 2.4 million units and 4.8 million units given in $7\frac{1}{2}$ days for early syphilis. This is somewhat disappointing and contrasts with the failure rate of 5 to 10 per cent using arsenic and bismuth according to previous schedules. It shows us that penicillin is not quite the miracle drug we thought it to be. However, the relative safety of penicillin as contrasted to arsenic makes it still the drug of choice. There are other factors in its favor also. The course of treatment may be repeated in larger dosage or for a longer duration in a very short time compared to a course of arsenical therapy. Penicillin

lends itself to better public health usage since it quickly sterilizes the infectious lesions and the course of treatment can be quickly finished. This factor was responsible for the establishment of the rapid treatment centers. From a public health standpoint it is not necessary to cure every case of a disease to control its spread. It is only necessary to render a sufficient percentage of the cases non-infectious to break the chain of infection and stop its spread. Penicillin lends itself to this procedure.

The Syphilis Study Section is presently engaged in studying the various fractions of penicillin, especially crystalline penicillin "G" which seems to be the most promising in the therapy of syphilis and gonorrhea. This is very fortunate because crystalline "G" does not need to be kept at a low temperature to retain its potency. It can be shipped anywhere and kept at room temperature. This means that we can send it to tropical climates and not worry about whether it can be kept at a constant temperature or not. The crystalline material has been given an expiration date by our Food and Drug Administration of 3 years. However, there is some evidence that this material deteriorates much more slowly than this and that it may retain its potency for many years.

Much experimental work is also being done on penicillin in oil and wax in an attempt to develop a satisfactory method of treating syphilis on an ambulatory basis. It is too early yet to properly evaluate this, but the work done so far indicates that one dose of 600,000 units or two doses of 300,000 units each a day works as well as the multiple doses of the aqueous preparations. This will be a great boon to the treatment of syphilis by the private practitioner of medicine. Here too, crystalline "G" is being used more and more. Preparations of crystalline "G" in oil and wax do not need refrigeration and have a potency date of 18 months as opposed to 12 mo. for the amorphous preparations. It can also be heated repeatedly and any remaining in the vial need not be thrown away after one heating as is the case with the amorphous preparation. New preparations of this containing the same amount of oil and wax will remain liquid and not require heating. It will therefore be much easier to administer.

Recent experimental work on animals using these delayed absorption preparations indicates that while there is a minimum blood level of penicillin that must be maintained, the total dosage is no more important than the time element. It apparently takes a certain length of time for penicillin to kill off the spirochetes and they are killed off at a definite rate—the time depending upon how many spirochetes are present. Twenty million units given in one day will effect only a very small percentage of cures but this dose spread over a week or even longer will effect a large percentage of cures.

Eagle and his co-workers¹ have shown that syphilitic infection in rabbits may be aborted by penicillin and that the dosage necessary to do this is very small if given within the first 4 days after inoculation. The dosage of penicillin necessary to abort the infection when given 4 days after inoculation increases progressively, however, with the size of the inoculum. After an intramuscular inoculum of 200,000 spirochetes it required 15 to 50 times as much penicillin to abort the disease as was necessary with an inoculum of only 20 organisms. The converse of this was also demonstrated when a fixed dosage of penicillin was used, no infections were observed with inocula of up to 2,000 organisms but a significant proportion of animals developed syphilitic infection after inoculation with 20,000 or 200,000 organisms. The size of the dose of penicillin necessary to abort a syphilitic infection in rabbits remained the same for the first 4 days after inoculation. By the end of the second week, however, it had increased 5 to 14-fold; and by the end of the 6th week, the curative dose, averaged 30 to 40 times that which would have sufficed to abort the infection if given within the first few days. It is a reasonable surmise that this reflects the multiplication of organisms.

This then brings us to where we were with the sulfonamides a few years ago and raises the question of whether syphilis and gonorrhea may not be prevented by using penicillin as a prophylactic agent. If these experiments on rabbits can be translated to man on an equal dosage per kilogram basis, then it might be possible to abort early syphilitic infection in man by 15 to 50 thousand units of penicillin given as a single intramuscular injection in peanut oil and beeswax to the average adult if given within the first 4 days after exposure. Or a single injection of 10 times this if given within the first 1 or 2 weeks after exposure. If the natural disease in man involves the penetration of the skin or mucous membranes by small numbers of organisms, then a single injection of penicillin or perhaps even tablets of penicillin given by mouth may suffice to abort an infection. Since the blood levels obtained by giving penicillin by mouth are one-third to one-fifth those obtained by injection, larger doses would be needed. It is possible that this would be in the neighborhood of 100,000 to 300,000 units. However, there are other difficulties encountered in giving penicillin by mouth. The blood levels obtained by the oral route of administration vary widely in the same individual from day to day and they vary widely in different individuals using the same dose schedule. How far we can get with this only the future can tell. As you can realize, there are many unanswered problems in such

¹ Relation of the Size of the Inoculum and the Age of the Infection to the Curative Dose of Penicillin in Experimental Syphilis, with Particular Reference to the Feasibility of its Prophylactic Use. Eagle, Magnuson, & Fleischman—*Jour. Exper. Med.*, 1 April 1947, Vol. 85, No. 4.

a study. The question of asymptomatic infections must be considered as well as the possibility of producing penicillin-resistant strains of the spirochete just as happened in the case of gonorrhoea although no penicillin resistance has been demonstrated so far.

In addition to the studies that are being carried out on syphilis and gonorrhoea, studies are also being made on the so-called minor venereal diseases including chancroid, lymphogranuloma inguinale, and granuloma venereum. Much effort has been exerted in the past on clinical studies and valuable lessons have been learned. However, we, in public health, must look toward prevention and not cure. To this end, we must do our utmost to foster basic laboratory work on the venereal diseases and to develop new concepts of their control. We must learn more about the motivation of the patients with whom we deal. We must see if there are new ways that can be developed to influence these people or to prevent the promiscuous from rapidly spreading their infections from person to person, state to state, and country to country. We must realize that modern transportation affects the spread of the venereal diseases just as it does other contagions. We are all in this work together and our actions taken locally influence the incidence of disease in other localities and in other countries. In short, we must develop teamwork and cooperation between the doctors and public health officials of all countries just as this Association has developed here. You, by your fine example of international cooperation have shown that doctors, public health officials and scientists can get together for the common good. God grant that our statesmen will be as successful.

ENFERMEDADES VENÉREAS (*Sumario*)

Con anterioridad a la Segunda Guerra Mundial, las enfermedades venéreas representaban generalmente la primera o segunda causa de morbilidad en la Marina de los Estados Unidos. Durante la guerra, estas enfermedades alcanzaron el nivel más bajo en la historia de la Marina. Al repasar la historia de la sulfanilamidoterapia, se expresa que la penicilina ofrece nuevas esperanzas aunque los resultados en la sífilis indican un índice de fracasos de 30 a 40% comparado con 5 a 10% de fracasos con los arsénicos y los bismutos. Sin embargo, la relativa seguridad y la repetición del tratamiento con relativa impunidad, hacen de la penicilina la droga de elección. Se repasan las ventajas de emplear las fracciones "G" cristalinias. Opina el A. que la penicilina en cera de abejas ofrece grandes posibilidades. Se discuten las posibilidades del empleo profiláctico de la penicilina en dosis de 14 a 20 millones de unidades durante los primeros cuatro días o diez veces esa dosis si se administra una o dos semanas después de la exposición. Se insiste en el valor de la prevención, la rápida diseminación de las enfermedades venéreas debido a los modernos medios de transporte, y el control de la promiscuidad.