## GORDON WILSON LECTURES

1937—WARFIELD T. LONGCOPE, M.D. "Some Observations on the Course and Outcome of Hemorrhagic Nephritis."

1938—HENRY A. CHRISTIAN, M.D. "A Glomerular Dominance in Bright's Disease."

1939—GEORGE R. MINOT, M.D. "Anemias of Nutritional Deficiency."

1940—ROLLIN T. WOODYATT, M.D. "On the Theory of Diabetes."

1941—ALFRED BLALOCK, M.D. "Shock or Peripheral Circulatory Failure."

1946—RENE J. DUBOS, Ph.D. "The Experimental Analysis of Tuberculous Infections."

1947—CECIL JAMES WATSON, M.D. "Some Aspects of the Porphyrin Problem in Relation to Clinical Medicine."

1948—HANS SELYE, M.D. "General-Adaptation-Syndrome."

1949—JOSEPH E. SMADEL, M.D. "The Changing Status of the Rickettsioses."

1950—WILDER PENFIELD, M.D. "The Mechanism of Memory."

1951—ANDRE COURNAND, M.D. "Clinical and Physio-Pathologic Considerations in Certain Types of Pulmonary Granulomata and Fibroses."

THE GORDON WILSON LECTURE

# VIRAL HEPATITIS

BY JOSEPH STOKES, JR., M.D.

PHILADELPHIA

I feel greatly honored in being asked to present the Gordon Wilson Lecture before this Association. Altho I have not been familiar with all of the aims of the Association, I am aware that in creating a yearly lectureship which bears such a distinguished name, your major objective remains clearly defined—namely, the maintaining of a high level of clinical craftsmanship—a level not necessarily dependent upon the laboratory.

Almost a decade has now passed since the opportunity became available for the group at the Children's Hospital of Philadelphia to use volunteers who are still the basis for all work on viral hepatitis. It is almost a challenge to fate to mention that no deaths have occurred in the total group of volunteers who have helped us—well over 1500—but it would hardly seem necessary to mention that in this same decade a pediatrician can name a number of special reasons for being personally interested in geriatrics—growing older suddenly comes so often when dealing with severely ill volunteers. This review of certain features of viral hepatitis is necessarily in part a tribute to these hundreds of men and women, without whom there would have been little progress.

I should like to outline certain findings in viral hepatitis obtained primarily from clinical observation, which may well prove to have broad significance in several fields of investigation, beyond the study of hepatitis alone.

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From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and The Children's Hospital of Philadelphia.

These investigations were conducted under the sponsorship of the Commission on Liver Disease, Armed Forces Epidemiological Board, and were supported by the Office of The Surgeon General, Department of the Army.

First, however, before one may consider application of knowledge in this field to other areas of medicine, it is necessary to establish more clearly a point of view concerning the nature of viral hepatitis itself, namely, as to whether it is one or more disease entities.

It is not necessary to consider serum hepatitis, or viral hepatitis B,* as a new disease entity. During our early experience over a number of years with viral hepatitis, it was rare that the attending physician thought of relating jaundice to the use of a needle or to a parenteral injection occurring months previously. The possibility of a two to four month incubation period had been completely overlooked in the past in the same manner that the possibility of rubella in the first trimester of pregnancy causing cataracts in newborns had been overlooked, and there was far less excuse for the latter because rubella is a distinct disease entity, while jaundice has many causes, including epidemic hepatitis. Certainly as injections for diabetes and syphilis increased from 1920 to 1930, an infectious cause for jaundice related to the injections was suspected. It was when transfusions, large pools of plasma, and vaccines buffered with blood products came into broad usage that Hepatitis B became a more obvious entity, and certainly a far more frequent one.

Often the belief that there are antigenic differences in the etiologic agents of viral hepatitis depends not so much upon the facts but rather upon the minds which receive the facts. Just as attitudes in politics depend often far more upon geographical location of the voters, meaning essentially the family background, so

*The use of the letters A and B in viral hepatitis was initiated in England to designate respectively infectious (epidemic) hepatitis (IH) and serum hepatitis (SH) and the letters A and B were also adopted by the World Health Organization. Although viral hepatitis under field conditions, broadly speaking, would fall into these two categories, A and B, key studies on cross immunity, etc., have been carried out with only a few viral strains. While these studies also support to an extent the separation into these two categories, until serologic tests are available there is no certain means of determining the accuracy of classification into A and B. Despite these difficulties the studies, as indicated here, point clearly to certain antigenic differences in the virus strains.

also background and position in a school of medicine deeply influence the avenues of investigation and the acceptance of data, even though similar data may be obtained by a number of investigators in more than one institution.

Also, by exciting so much interest and controversy, and by covering so many departments in medical schools, the liver has collected over recent decades a far more impressive family background, resulting in many firm beliefs.

For example, viral diseases of the central nervous system—in particular the viral encephalitides—in many instances have clinical and histological pictures which in general are indistinguishable from each other, and yet little question is raised by the pathologists or internists when viral cross-immunity studies or neutralization studies show that they are completely different etiologically—it is left to the virologists to decide. They decide they are different and the decisions stand.

Similarly, epidemic influenza A and B are indistinguishable in incubation periods, in clinical picture, and histologically, but here again the original demonstrations of lack of cross-immunity or cross-neutralization by the virologists is accepted. Not so viral hepatitis. Viruses may be considered as relative newcomers to the pedigreed liver family—during the inevitable upheavals affecting medicine in war-time.

In viral hepatitis, as in the encephalitides and in epidemic influenza, the clinical and histological pictures of epidemic hepatitis and serum hepatitis are essentially indistinguishable.

However, a well demonstrated lack of cross-immunity both under epidemic conditions and experimentally in volunteers[1, 2, 3] of what have been termed virus IH or A, and virus SH or B (the letters A and B are simpler and more acceptable)—these proven facts still appear to be unacceptable to a considerable number of internists, pathologists, and those interested in certain metabolic functions of the liver.

To an extent such doubts may be the result of the limited number of volunteers available for cross-immunity studies under experimental conditions, but such limitations were not present in studies of the disease under natural conditions such as obtained in North Africa in the studies by Gauld.[4] In these studies not only was there no immunity to epidemic hepatitis as a result of previous attacks of serum hepatitis (yellow fever vaccine jaundice) but actually the previous serum hepatitis had produced an increased susceptibility to the epidemic disease.

Dr. Havens carried out cross-immunity studies between A and B in one direction, while at the same time in Philadelphia we carried out reciprocal cross-immunity studies, namely, starting first with A and later testing the volunteer's resistance with B and vice versa. The fact that the two groups of workers obtained a strikingly similar lack of cross immunity between A and B is all the more important because the subject at test was man himself.

It may appear that this is belaboring a point of view already well established. It would not appear to be so when as well-known a worker as Sir John McNee, in his recent Harveian Lecture,[5] strongly advocated the view that these viral agents were antigenically the same. This point of view appears to be more readily accepted by those who have worked for many years in the numerous metabolic or pathologic aspects of liver disease and thus may look upon the more recent viral studies with jaundiced eyes. In fact, the jaundiced eye is often quite evident in liver disease.

Altho lack of cross-immunity appears to be the most important criterion for distinguishing the viral encephalitides and the epidemic influenzas, one from the other, the viruses of hepatitis have intriguing differences in addition to lack of cross-immunity.

The gamma globulin fraction from the Red Cross pools of plasma has been highly successful in stopping epidemics of hepatitis[6] thruout the country as well as abroad, whether used in controlled or uncontrolled studies, and recently in doses as little as .01 ml. per pound body weight.[7] Most of these studies have been conducted by our own group of workers, but a sufficient number of

corroborative studies have come from all parts of the country to overcome whatever jaundiced mote there may be in our own eyes. After all, studying jaundice so closely we cannot always be sure of having cast the jaundiced beam out of our own eyes in order to see clearly to cast out the motes elsewhere. In contrast to the epidemic disease, Red Cross gamma globulin in serum hepatitis, with a single known exception,[8] has not prevented the disease under natural conditions or in volunteers; nor has it neutralized the virus B,[9] even though recently in such studies with Dr. Drake et al[10] we have used gamma globulin, collected from volunteers, convalescent 4 months to 6 years from jaundice caused by the Ft. Bragg strain of virus, and fractionated by Sharp and Dohme Company for this particular purpose. It is still possible that the neutralizing antibodies are in another fraction of the globulin than the gamma fraction, or they may rise and fall during the first three months of convalescence. However, a previous neutralization test with convalescent plasma (2 ml. of infective serum mixed with 10 ml. of convalescent plasma)[9] did not suggest that antibodies were present. The same convalescent plasma was also injected in 20 ml. amounts at 3 successive monthly periods after parenteral inoculation of the mixture of infective plasma and convalescent plasma without evidence of protection.

Another constant difference is the presence of virus of the epidemic disease in the stools, with consequent ease of cross-infection by contact or by the milk, food, or water-borne routes. We have been unable to produce serum hepatitis even by parenteral injections of filtrates of stools from such cases obtained during the early disease period, and the general lack of epidemics starting from hepatitis B is obvious. The types of influenza do not have nor appear to need substantiation of their separation by such characteristics.

The incubation periods of viral hepatitis A and B on occasion are similar and with the same strain of virus A there may be prolongation of the incubation period to the length seen in some cases of B, but if one calculates the mean incubation periods of

both diseases in large numbers of volunteers and in field epidemics, A will average 20-30 days, while B will average 60-90 days. When the incubation periods are longer, in many instances of both A and B, our experience also strongly suggests that the infecting dose contained fewer viral bodies, namely, was of low titer, or was attenuated in some way, even the individual variation in resistance must play an important part.

This is well illustrated in our studies on A in 3 instances, (1) when contaminated water from a summer camp had stood at room temperature for a considerable period before being ingested by volunteers (about a 60-day incubation period),[11] (2) when artificially infected water was treated by flocculation and filtration, resulting in a marked increase in the incubation period of the volunteers ingesting it, as compared to the incubation periods of the control volunteers receiving the untreated water (a 30-40 day incubation from the treated water, and a 20-25 incubation in the controls),[12] and finally (3) when a single individual had ingested water from a well which had apparently been contaminated a considerable time previously and in which case a large part of the contaminated water must have been used and the remaining portion considerably diluted before he ingested it (a 56 day incubation period).[13] Ingestion of contaminated food or direct contact were also possible, though less probable, sources of infection in this case.

Altho the last individual may have had a chance infection from some other source, the origin seemed fairly clear because he was the only one in his rural area who had the disease at that time and when and where he was infected could apparently be localized to a single day and place. The reciprocal relation of number of viral particles to the length of the incubation period in virus B or its attenuation is also suggested by the results both our group and Dr. Roderick Murray's[14] group have been obtaining in studies on an artificially infected pool of plasma originally prepared by the late John Oliphant and containing the Ft. Bragg strain of virus B from our laboratories. This pool which was shown by

Dr. Murray to have a titer of at least $10^{-4}$, not only produced longer incubation periods in its higher, than its lower, dilutions, but when irradiated by apparatus which apparently had been effective in sterilizing commercial pooled plasma with possibly less virus, again produced longer incubation periods than in the control volunteers who received the unirradiated plasma. For instance, this infected pool irradiated on a cylinder type of apparatus used by Sharp and Dohme produced hepatitis with jaundice in only one of our six volunteers injected parenterally, the one case having an incubation period of 108 days. Experience of Dr. Murray's group[14] with this material covering 43 subjects who developed hepatitis shows that while the mean incubation period of those subjects who received untreated plasma was 84 days; that for those who received plasma which had been treated in some manner (such as by ultraviolet irradiation, heating or extreme dilution) was 99 days.

I have outlined at some length the factors which appear to have changed the length of incubation of viruses A and B since in particular the lengthening of the incubation period of virus A up to 40-55 days has been considered by some as suggesting the identity of the two viruses. If such factors have already been shown to alter the incubation periods both under natural and experimental conditions with virus strains known to produce no cross-immunity, the attempt to unify these two agents, under a single antigenic type, on the primary basis of incubation periods appears clearly to be based on attitude and not on facts. It would be as sensible to unify influenza A and B antigenically because they have the same incubation period, while in viral hepatitis A and B the mean incubation periods as mentioned above of the vast majority of cases are farther separated than almost any other two infectious diseases now known.

A fifth difference which accords well with the above evidence concerning gamma globulin is the common tendency for a high incidence of B to occur in later life, while epidemics of A rarely strike older individuals when they sweep through a community.

In hepatitis A this immunity appears usually to be permanent and adds its antibodies when collected to the general pools of plasma for fractionation, while virus B either is a relatively infrequent cause of disease or does not produce a very solid immunity. In the original studies on homologous immunity with Neefe,[3] the test of resistance by using the same virus parenterally in volunteers who had had jaundice from the Ft. Bragg strain previously, resulted in questionable hepatitis in at least 5 of 9 men.

It seems appropriate to add to the above 5 differences 2 others which are not as clear-cut and which still require an amount of study that already promises to be highly fruitful.

The carrier state, altho well recognized for a number of years in hepatitis virus B with respect to the blood, has only recently been studied in volunteers. Nothing is known concerning the presence or absence of a blood-borne carrier state in hepatitis A, altho this virus has been found in the stools of two children chronically ill with mild hepatitis without jaundice for 5 and 15 months respectively, in an endemic infection in a Chicago orphanage studied together with Drs. Capps, Bennett, Drake, Ettinger, and Mills.[15] Apparently the carrier state in hepatitis virus B, if one accepts the long incubation period as a general indication of the presence of this virus, has been found in at least 7 individuals, all with no history of jaundice. Since the carriers of hepatitis virus B were discovered chiefly by the resultant jaundice in recipients of their blood, and since individuals who have a history of jaundice are usually rejected as donors, it is not strange that most of the carriers thus far detected gave no history of the disease. Several of the carriers have had chronic hepatitis as shown both by biopsy and by positive liver function tests.[16,17,18] At least two have been chronic alcholics, thus raising the question of a possible relation between hepatitis virus B and alcohol in the production of chronic fibrosis of the liver.

I am mentioning hepatitis virus B in relation to the carrier state because again there appears to be a disinctly higher incidence of the carriers of this virus than of carriers of hepatitis

virus A, altho this difference is based on as yet inadequate evidence, and could not be considered as an important distinguishing feature between the two viruses.

A final point of differentiation is of increasing importance as the data accumulate, namely, the use of a skin test developed chiefly by the Drs. Henle at The Children's Hospital of Philadelphia, which consists of irradiated amniotic fluid from embryonated eggs infected with hepatitis virus A.[19] The irradiated amniotic fluid is injected intradermally in doses of 0.1 ml. of undiluted fluid or diluated 1 :10, with a control in the opposite forearm of irradiated non-infected amniotic fluid. Previous experience of the tested individual with virus A is generally indicated by a red and usually indurated reaction above 10 x 10 mm. in diameter at 24 hours. When the test material is adequate the accuracy of the test as conducted in several thousand individuals appears to be about 80 to 90%, a percentage approaching that of the Schick test.[20] The test material is not commercially available on account of its lack of stability, altho lyophilization has aided considerably in this respect. There have also been many false positive tests in control materials and adequate material has been difficult to produce. Recently use of the lyophilized material in large outbreaks in various part of the country has furnished valuable epidemiologic data to both our own group of workers and to a few others who have used the test in conjunction with our workers. One difficulty also lies in determining that all of the virus in the test material has been inactivated by irradiation, since studies with the test suggest that immunity to hepatitis A may be produced by the skin test itself.[21]

Thus far the studies with the test serve our purpose here in distinguishing between viral hepatitis A and B in that individuals who have had the latter disease react positively to the test in the same percentage one would expect for a random sample of the population of the same age range and not at all in conformity with the tests in individuals who have had epidemic hepatitis. However, hepatitis B occurs so often in older individuals who

already are likely to have had some experience with hepatitis A, that a considerable percentage of these individuals have positive tests.

If the test fulfills its early promise of high percentage of positivity in epidemics thus far studied,[15] it again should aid in clearly separating the viruses A and B.

The necessity of limiting the studies to volunteers, since no other animal is susceptible, emphasizes the importance of developing serologic tests for both viral agents. Usually the skin test material when diluted 1:10 has no longer sufficient antigen to be active, thus indicating by its low titer the chief reason apparently for the lack of adequate serologic tests by the use of infected amniotic fluid.

The accompanying Table I recapitulates the points above outlined.

TABLE I

CONTRAST BETWEEN VIRAL HEPATITIS A (IH) and B (SH)

| | *A* | *B* |
|---|---|---|
| Cross-immunity | 0 | 0 |
| Protection by gamma gloublin* | + | ?0 |
| Virus in stools | + | 0 |
| Incubation (days) | 20-30± | 60-90± |
| Usual age range | Below 30 years | All ages |
| Blood carriers | ?0 | + |
| Skin test** | + | 0 |

*From Red Cross pools of plasma by ethanol fractionation method.

**Chick embryo amniotic fluid infected with hepatitis virus A (Akiba strain) and irradiated with ultraviolet light. Still in the experimental stage.

I have outlined the differences in some detail because they review some of the more important recent findings in viral hepatitis and unless these findings are thoroughly understood it is too easy to theorize about the antigenic unity of viral hepatitis. Most of the work to date and particularly in the last few years the skin test, as used in epidemics widely separated in time and space,

suggest that hepatitis virus A may be a single antigenic entity similar to measles, to which one attack gives immunity, and for which antibodies remain in the blood during life in considerable quantities. On the other hand, the information is certainly incomplete concerning the unity or multiplicity of antigenic types in viral hepatitis B. Obviously there may be strain differences in both A and B which only the devolpment of serologic tests could clarify.

The 7 differences outlined offer conclusive evidence that there is an antigenic distinction between hepatitis viruses A and B. That these are apparently greater than mere strain differences, such as those found among the strains of influenza A, appears quite probable, because of the lack of immunity and of serum antibodies in the older groups of the population to hepatitis virus B.

Gledhill and Andrews[22] have recently described a viral hepatitis with jaundice of mice which apparently has no immunologic relation to the human viral hepatitis, but which includes two agents, the one being susceptible to aureomycin or terramycin, and the other resistant—the compound infection requiring both agents for its full activity in the liver. Only one of these is a virus, while the other is an organism, larger than a virus and endemic in mice—eperythrozoon coccoides.

In human viral hepatitis, since the liver actually appears to be sensitized by hepatitis virus B, so that it is more susceptible to infection with virus A and vice versa, there may be a synergistic reaction between the two viruses. No susceptibility to aureomycin, terramycin, or other autibiotics has been demonstrated. Certainly human viral hepatitis does not appear to be a compound infection of two viral agents A and B.

These considerations lead to an important point in chronic viral hepatitis which may have broad significance in other diseases. When we began to study the effect of aureomycin on both acute and chronic viral hepatitis A, it became apparent that a beneficial effect occurred in some of the chronic cases but not in the acute

cases when moderate doses of this antibiotic were used. Theoretically this was originally explained by a possible sparing action of the aureomycin as a result of reduction in bacterial action in the intestine—in the bacteria, themselves, the products of the bacteria, or the reduction in absorption of materials produced by bacteria as a result of their action on intestinal contents. This theoretical concept was first studied in viral hepatitis of man with Shaffer, Farquhar and Sborov at the Army Hepatic and Metabolic Center,[23] Valley Forge Hospital, and later more thoroughly with Dr. Gyorgy[24] in hepatic necrosis of rats on diets deficient in the sulfhydryl amino acids and vitamin E, with British yeast as the only source of protein.

A large proportion of rats are partially protected from such hepatic necrosis when fed aureomycin and penicillin. These results have been carried over by Dr. Gyorgy[25] to the study of hepatic cirrhosis of rats produced by choline deficient diets, and aureomycin in a similar manner has protected most of them from cirrhosis.

The results at present suggest an important area of interaction between intestinal bacteria and a damaged liver—whether damaged by viruses, deficient diet, or radiation injury (as indicated in radiation injury by Dr. Philip Miller[26] and his group in Chicago). It is possible that the outbreaks of diarrhoea so often preceding epidemic hepatitis may either spread the hepatitis virus from an early case or from an intestinal carrier, or by absorption of bacteria or their products thru the liver may render it a more fertile soil for the later hepatitis virus. The interaction of intestinal viruses and bacteria is essentially an unexplored field. Our studies with aureomycin, terramycin, and penicillin afford one approach to this field. Infections of the respiratory tract illustrate one type of interaction between viruses and bacteria. It appears that compound infections which include the interaction of viruses and bacteria may occur in varied forms in the intestinal tract. The liver may well aid in the study of such compound infections because it represents, particularly in its left lobe, which in con-

trast to the right lobe absorbs more of the products of the large intestine, a sensitive filter for detection of viral or bacterial products or for the micro-organisms themselves. As in hepatic necrosis of rats, altered livers may be used in animals as sensitive indicators of intestinal flora. Viral hepatitis of animals could well be used also for similar purposes.

The follow-up of cases of chronic viral hepatitis and of carriers would strongly suggest that chronic fibrosis of the liver is far more closely related to these viruses than has previously been realized. The possible compounding of such factors as chronic amebic infections, carriers of such organisms as *S typhosa* or *S cholerae suis,* virus carriers or chronic cases of viral hepatitis, alcoholism and nutritional deficiencies, and chronic poisoning from various chemicals or metals must be considered. Since viral hepatitis—at least in its A form—may strike most individuals, its possible relation to such compound effects is particularly important. Does it remain in the liver at times as the virus of herpes simplex remains in the skin and is it excreted with the bile into the intestine? Does it remain in the intestinal tract mucosa in the same manner and cause digestive disturbances which are reflected in the liver by direct extension or by absorption products? If continuously a hazard, does it interact in the liver with bacteria or their products over a period of years?

Altho it has been only a decade, as mentioned, since the viruses of hepatitis have been actively investigated—and in only a few places because of the requirement of volunteers—we have means at least of controlling completely sharp outbreaks of epidemic hepatitis, and the complete control of the hepatitis virus (or viruses) B, in plasma at least, appears imminent. When one compares such progress in the practical field of control with the progress in such a viral disease as poliomyelitis, which has been now studied more widely with a number of species of animals other than man, for at least 4 decades, the advances in knowledge of viral hepatitis appear to be relatively rapid. There is at present the greatest hope that the volunteer may be replaced by the chick

embryo, by tissue cultures, or by some other susceptible animal, so that even more rapid progress may be made without the attendant risks.

To those colleagues who, by their major contributions, have initiated or made possible much of the work reported here, I wish to express my great debt—Dr. Gertrude Henle, Dr. Werner Henle, Dr. John R. Neefe, Dr. Sydney S. Gellis, Dr. Paul Gyorgy, Dr. John G. Reinhold, Dr. Mercer C. Blanchard, Dr. John D. Farquhar, Dr. G. Robert Wade, Dr. Albert W. Kitts, Dr. Miles E. Drake, Dr. Winslow Bashe, Dr. Jeremiah A. Barondess, and Dr. Robert Garber. Able technical assistance has been furnished over the period of these studies by Charles and Mary Ming.

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