

depend on the specialty of cardiologists more than seems perhaps necessary.

I have given this rapid survey of certain fields in medicine with the purpose of indicating that medicine is ever changing and that the relations between the general practitioner and the specialist are always in a state of flux. The drift is not always away from the general practitioner but sometimes definitely at any given moment in his direction. These are the factors that must be evaluated in determining what is adequate medical care.

It will be noted that even if and when the general practitioner is furnished with proper and adequate x-ray equipment and interpretation, which means specialists' services, that is in some fields not sufficient. The supplementary use of certain technics or gadgets, as the electrocardiograph, in a goodly number of instances at this time does not seem to be always satisfactory.

I have not touched on the surgical specialists at all. This is largely because it seems to me at this moment that surgery is becoming a profession in itself and indeed has its own specialists. I have mentioned lung surgery, which actually is not within the province of a general surgeon. The neurologic surgeon is another example of a limited specialist within the profession of surgery.

I have deliberately omitted the relationship of psychiatry to the general practitioner and to adequate medical care. Obviously the custodial care of the manifestly insane is a problem for specialists. As the general practitioner meets this part of the problem, it is often the question of having the insane person committed to an institution.

But there are implications and imponderables far beyond the scope of this paper and indeed my ability to discuss them. The war has focused attention, too long postponed, on what is known as psychoneurosis. That problem is far too large for the number of physicians who may be regarded as having special training or interest in the field. The whole situation is rather chaotic. We have rather taken much of it for granted, as we once did the poor. And, like the weather, everybody talks about it but does nothing about it. Somehow or other in this vast field the general practitioner must play an important role. He obviously has certain advantages of familiarity with human behavior under usual family conditions and of individual relationships and actions.

DIAGNOSTIC SURVEYS IN DIAGNOSTIC CENTERS

It will be observed that I have not spoken particularly of hospitals, diagnostic centers, laboratories or clinics. Obviously major surgery will be done in a hospital. Specialized surgery, like chest surgery and neurologic surgery, will not be done in every small hospital. Adequate medical care demands not just the case and a hospital. It may demand a special hospital and a specialist within the profession of surgery. Furthermore, the x-ray equipment also obviously necessary in a hospital may be in a clinic or a diagnostic center. I have pointed out frequently that most patients who visit the Mayo Clinic never get to the hospital. In other places well known clinics are quite separate entities. In the clinic most of the diagnostic work is carried out and, if necessary, hospitalization is arranged. It is argued by some of the clinic advocates that such an arrangement is tremendously money saving. Hospital residence is apt to be expensive and, if utilized for a diagnostic survey which may be time consuming, ties up hospital space designed

for quite another purpose. Perhaps hospital trustees will devise some new types of buildings within the hospital areas so that diagnostic surveys can be carried out economically for the patient and conveniently for the diagnostician.

I have not in these remarks attempted to reevaluate adequate medical care. It has been my purpose rather to make random comments on the problem and once more to express the hope that other hands will develop something far better and far more comprehensive than the pioneer effort of over ten years ago.

NEED FOR CONTINUOUS REEVALUATIONS

I appreciate the changing conditions as medical science advances with its seven league boots. I appreciate too that our social standards change. But these considerations to my mind only make such studies more imperative. There should be constant and continuing evaluations of the changing conditions. We must know what place the general practitioner and the specialist has in adequate medical care. At the moment there are trends toward specialism within specialties, particularly in surgery. Yet insulin, liver therapy, the sulfonamides and penicillin tend to return many patients to the general practitioner. Likewise there are trends in the utilization of hospitals which must be considered in evaluating medical care. Social conditions both in the home and in industry create changes to which adequate medical care is always a goal, but as we move forward we push the goal ahead.

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POST-TRANSFUSION HEPATITIS IN BATTLE CASUALTIES

AND A STUDY OF ITS PROPHYLAXIS BY MEANS OF
HUMAN IMMUNE SERUM GLOBULIN

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It has recently become increasingly well recognized that parenteral administration of whole blood or blood products to susceptible individuals may be followed by the occurrence of a disease which is clinically indistinguishable from common acute infectious hepatitis.¹ During the latter part of 1944 a large and increasing number of cases of acute hepatitis were seen at a large army general hospital within the continental limits of the United States which serves primarily as a center

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This investigation was carried out in collaboration with the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, Washington, D. C.

1. Probert, S. A.: Hepatitis After Prophylactic Serum, *Brit. M. J.* **2**: 677, 1938. Homologous Serum Jaundice, Memorandum prepared by medical officers of the Ministry of Health, *Lancet* **1**: 83, 1943. Beeson, P. B.: Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma: Report of 7 Cases, *J. A. M. A.* **121**: 1332 (April 24) 1943. Morgan, H. V., and Williamson, D. A. J.: Jaundice Following Administration of Human Blood Products, *Brit. M. J.* **1**: 750, 1943. Turner, R. H.; Snively, J. R., Jr.; Grossman, E. B.; Buchanan, R. N., and Foster, S. O.: Some Clinical Studies on Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, *Ann. Int. Med.* **20**: 193 (Feb.) 1944. Neefe, J. R.; Stokes, Joseph, Jr.; Reinhold, J. G., and Lukens, F. P. W.: Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, *J. Clin. Investigation* **23**: 836, 1944.

for amputation and neurosurgical cases. During the six month period from Nov. 1, 1944 to April 30, 1945 a series of 108 cases of acute hepatitis came under the care of one of us (E. B. G.). Of these cases 103, or 95 per cent, occurred in men who had recently been wounded in action in either the European or the Pacific theater of operations. The fact that the high incidence of the disease in this group of patients was not merely a reflection of the selected population of this hospital is demonstrated by the data included in table 1.

The clinical history in the battle casualty group was strikingly uniform. The patient had been wounded in action from 44 to 167 days prior to the development of symptoms of hepatitis, with a median latent period of 91 days and an average of 92.6 days. In 84 per cent of the group the onset of the disease occurred between the 8th and the 17th week after injury. The large majority had received whole blood transfusion, blood plasma or both, shortly after injury. A number of the patients in whom the latent period was long (more than four months) had received multiple blood transfusions, some as long as two months after injury. Other factors, such as severity of injury, early amputation, previous administration of sulfonamide drugs or penicillin, extensive infection and general clinical condition of the patient at the time of onset of hepatitis, appeared to play no contributory role in the incidence of the disease. Common sources of infection and secondary contact cases were not recognized. The clinical course of the disease was that seen in the usual case of infectious hepatitis. The fatality rate was 2 per cent (two deaths).

The investigation here reported was undertaken with two purposes: (1) to test the validity of the hypothesis that the hepatitis-causing agent was transmitted by blood or plasma transfusion and (2) to extend the previously reported studies of one of us² on the prophylaxis of infectious (epidemic) hepatitis by injection of human immune serum globulin (gamma globulin) to this group of patients.

During the three month period from Feb. 1 to April 30, 1945 information was obtained on all battle-casualty patients admitted to this hospital. These patients were then divided into five groups: (1) those who had received neither plasma nor whole blood, (2) those who had received plasma but not whole blood, (3) those who had received whole blood but no plasma, (4) those who had received both plasma and whole blood and (5) those concerning whom adequate infor-

TABLE 1.—Hepatitis in Battle Casualties and in Other Patients During Period from Nov. 1, 1944 to April 30, 1945

	Number	Per Cent of Total
1. Hepatitis cases:		
Battle casualties.....	103	95.4
Others.....	5	4.6
2. Total hospital admissions:		
Battle casualties.....	...	44.1
Others.....	...	55.9

mation was unobtainable because clinical records were incomplete and because these patients had been rendered unconscious for variable periods following injury.

The patients in group 1 were not given immune serum globulin injections. Groups 2, 3, 4 and 5 were each again subdivided into three subgroups, designated by the subscripts a, b and x in table 2. The x series are

composed of those who had sustained their injuries more than four months prior to admission to this hospital or who presented evidence of acute hepatitis on admission and therefore were eliminated from the test and control series. Of the remaining patients, alternate men were given injections of 10 cc. of human immune

TABLE 2.—Battle Casualties Admitted to the Hospital Between February 1 and April 30, 1945

	1	2	3	4	5	6
	Series	Globulin Injection	Total Number	Number with Hepatitis	Hepatitis Occurring Less Than 7 Days After Assignment to Control or Test Series	Per Cent with Hepatitis
No plasma or blood	1	0	322	1	—	0.3
Previous plasma only	2 a	+	53	1	1	1.9
	2 b	0	52	4	1	7.7
	2 x	0	17	0	—	0
Previous blood only	3 a	+	35	0	0	0
	3 b	0	35	3	1	8.6
	3 x	0	16	0	—	0
Previous plasma and blood	4 a	+	251	10	5	4.0
	4 b	0	251	33	7	13.1
	4 x	0	167	11	—	6.6
History not clear	5 a	+	45	0	0	0
	5 b	0	46	4	1	8.7
	5 x	0	29	1	—	3.4
Total.....			1,319	68		5.2

a. Patients given globulin.
b. Alternate controls who received no globulin.
x. Patients eliminated from test and control series.

serum globulin (obtained from the U. S. Army Medical Supply Depot) on admission and again in one month. No other selection of cases for globulin injection or control series was used. It was found that selection of alternate cases resulted in random sampling of battle casualties in these two groups. Of the globulin injected group, 10.5 per cent of the patients came from the Pacific theater, 35.5 per cent had been in the Mediterranean theater and 54 per cent had been in the European theater of operation but not in the Mediterranean. For the control group the figures for the geographic distribution were 7.5 per cent from the Pacific theater, 38.5 per cent from the Mediterranean theater and 54 per cent from the European theater of operation.

Periodic icterus index determinations on blood serum and methylene blue tests of urine for bilirubin³ were done. All patients showing abnormal laboratory findings or manifesting symptoms of hepatitis were examined by one of us. No patient was considered to have hepatitis on the basis of laboratory findings alone, but the diagnosis was made only when the laboratory findings were corroborated by the clinical evidence of manifest jaundice or hepatic enlargement accompanied by the usual subjective symptoms of the disease without frank clinical jaundice. Six patients (9 per cent of the cases of hepatitis developing in this group) were diagnosed as having hepatitis without jaundice. These 6 cases were proportionately distributed among the several series that have been described.

Results of these studies are summarized in table 2. The studies are still incomplete for the reason that an appreciable proportion of the cases included in this tabulation have been under observation for an insufficient period at the time of writing.

3. Franke, K.: Methylene Blue, a Very Simple Practical Reagent for the Detection of Bilirubin, *Med. Klin.* **27**: 94, 1931. Fillinger, K., and Menkes, K.: Quantitative Bilirubin Determination in the Urine with the Methylene Blue Method, *Wien. klin. Wchnschr.* **46**: 133, 1933. Myers, C. P.: Use of Methylene Blue in Testing for Bilirubin in the Urine, *J. Indust. Hyg. & Toxicol* **27**: 52, 1945.

2. Stokes, Joseph, Jr., and Neefe, J. R.: The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin, *J. A. M. A.* **127**: 144 (Jan. 20) 1945.

The data on incidence of hepatitis as related to previous blood transfusion or blood plasma administration are given in table 3. In line 1 are given the data for patients who had received no blood or plasma, in line 2 the data for patients who had been known to have received blood or plasma, and in line 3 the data for those patients to whom it is believed, but not definitely known, that blood products were given. The conclusion that the hepatitis-causing agent was blood transmitted appears inescapable.

The preliminary results of the study of prophylaxis of hepatitis by gamma globulin injection are summarized in table 4. In line 1 are given the total figures for the incidence of hepatitis to date of writing (July 25, 1945) in the a (globulin) subgroups of series 2, 3, 4 and 5 of table 2, and in line 2 the corresponding data for the b (control) subgroups. Of 384 patients who received globulin injections, 11 developed hepatitis. Two of these had clinical manifestations of the disease prior to globulin administration, and 4 developed obvious evidence of the disease 4, 5, 5 and 6 days after injection, respectively. It is possible that the immune serum globulin was administered to those patients too late in the incubation period to be of value. There was no significant clinical or laboratory evidence of attenuation of the disease in these patients. Five patients developed hepatitis more than one week after globulin injection. In all of these, although frank jaundice developed, the clinical course was very mild, suggesting that the disease may have been attenuated by globulin administration. The 44 cases (11.5 per cent) of the control series of 384 patients represents the minimum incidence of the disease in this control group. A number of these patients have been under observation for an insufficient period, and cases of hepatitis are continuing to appear in this control group.

COMMENT

The reporting of this series of cases appears important in view of the high morbidity and mortality recently experienced both in England and in the United States from hepatitis secondary to the administration of blood products in battle casualties. Also the primary reason for such a report lies in the highly significant protection against hepatitis obtained by the use of gamma globulin. Previous experience with the use of gamma globulin in three epidemics of hepatitis obtained by one of us⁴ in collaboration with Capt. John R. Neefe, Capt. Sydney S. Gellis and others had clearly indicated its

TABLE 3.—Incidence of Hepatitis Among Battle Casualties Admitted to Hospital from Feb. 1 to April 30, 1945 as Related to Previous Transfusion

	Total Number	Hepatitis	
		Number	Per Cent
1. Received no blood or plasma.....	322	1	0.3
2. Received blood or plasma; no globulin given.....	538	51	9.5
3. Insufficient data; no globulin given.....	75	5	6.7

protective and attenuating effect in the epidemic disease, but its value had not been determined in the hepatitis resulting from blood products used in battle casualties. The cases occurring in the injected group were mild, indicating probably some degree of attenuation as a

4. Gellis, S. S.; Stokes, Joseph, Jr.; Brother, G. M.; Hall, W. M.; Gilmore, H. R., and Beyer, E.: The Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operations: I. Studies on Prophylaxis in Two Epidemics of Infectious Hepatitis, to be published. Stokes and Neefe.

result of the gamma globulin, despite its injection at the end of an incubation period of several months. The protective effect of the gamma globulin suggests either that the agent from these blood products producing hepatitis is the same agent as that occurring in the epidemic hepatitis in which gamma globulin previously

TABLE 4.—Prevention of Hepatitis by Human Immune Serum Globulin (Gamma Globulin)

	Total Number	Total Hepatitis		Hepatitis Occurring More Than 1 Week After Assignment to Control or Test Series	
		Number	Per Cent	Number	Per Cent
1. Total given globulin	384	11	2.9	5	1.3
2. Total control series	384	44	11.5	34	8.9

had been effective or that antibodies protective against more than one agent producing hepatitis have been concentrated in the globulin from the large pools of plasma.

Although some evidence, as yet inconclusive, suggests that more than one agent or more than one strain of the same agent may produce a type of hepatitis which possesses in general the same clinical and pathologic picture, the data here reported would neither support nor contradict such evidence. The history of a long incubation period in the casualties included in this report and in those investigated in other hospitals in the zone of interior is probably due to the fact that those having short incubation periods were hospitalized in the European and Mediterranean theaters of operation. Short incubation periods of approximately 20 to 30 days have been noted following parenteral injection of homologous blood products in the European and Mediterranean theaters of operation and in injected volunteers in the zone of interior, but such reported occurrences have been relatively few. Further studies of these phenomena in such casualties and in human volunteers will be necessary before an understanding of the problem of single or multiple etiology can be obtained.

SUMMARY

1. A series of 103 cases of post-transfusion hepatitis occurred within a period of six months at one United States Army general hospital.
2. Data indicate that the hepatitis-causing agent was transmitted to these patients through the medium of blood plasma or whole blood transfusion.
3. Evidence indicates that the early administration of human immune serum globulin was effective in this series of cases.
4. This series of cases is to be further studied and reported at a later date.

ADDENDUM

A study similar to the one reported was initiated somewhat later at another general hospital (to be reported by Col. G. G. Duncan, A. U. S., Lieut. Col. H. A. Christian, A. U. S., and Joseph Stokes Jr.). The procedure differed only to the extent that a single injection of gamma globulin was given as compared with the use of a second injection one month after the first in the present study. In this second study the use of gamma globulin appeared to have no effect on the incidence of homologous serum hepatitis in battle casualties who had received transfusions of blood or plasma. Recently an experimental study of the neutralizing effect of one preparation of gamma globulin on one causative agent of serum hepatitis has been conducted by Capt. Sydney S.

Gellis, M. C., A. U. S., Capt. John R. Neefe, M. C., A. U. S., and one of the present authors (J. S. Jr.). Under these experimental conditions (to be reported) neutralizing antibodies for this causative agent of serum hepatitis apparently were absent, the gamma globulin having no effect on the incidence of hepatitis in human volunteers injected with this agent. Thus the results of the use of gamma globulin for prevention of homologous serum hepatitis have been conflicting to date, the globulin having been very effective under the circumstances described in the present report but apparently ineffective under other conditions. Although no explanation of the conflicting results is at hand, the following factors may have been influential: (1) the possibility that immunologically different agents were concerned, (2) the possible variation in antibody content of different preparations of gamma globulin and (3) the possible beneficial effect of repeated injections of gamma globulin in view of the long incubation period of the disease (two to four months). Further studies obviously are necessary to clarify these points and to establish the place of gamma globulin in the prevention of homologous serum hepatitis.

THE RECOGNITION OF PRIMARY HYPERPARATHYROIDISM

AN ANALYSIS OF TWENTY-FOUR CASES

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The discovery that hyperparathyroidism is the cause of generalized osteitis fibrosa cystica has led to a widespread assumption that hyperparathyroidism manifests itself only as a disease of bone.¹ Because osteitis fibrosa cystica is a great rarity, it has been assumed that hyperparathyroidism is equally rare. Both of these assumptions have been proved to be false but they have nonetheless persisted.

In 1934 Albright and his associates² at the Massachusetts General Hospital reported 17 proved cases of hyperparathyroidism, most of which they had observed during a period of two years. Analysis of these cases led them to conclude that (1) hyperparathyroidism can occur without evident disease of bone, (2) involvement of the urinary tract is a more common and more important manifestation of hyperparathyroidism than involvement of the skeleton, (3) hyperparathyroidism is relatively common and (4) it is the etiologic factor in the formation of renal calculi in an appreciable number of cases. Subsequent experience of this group of investigators has amply substantiated these conclusions.³ By 1942 Cope⁴ was able to report the remarkable total of 67 proved cases of hyperparathyroidism which had been observed at the Massachusetts General Hospital over a period of ten years. Classic osteitis fibrosa

cystica had been encountered in about a third of these and minimal or atypical osseous changes had occurred in another third, while in the remainder of the cases evidence of skeletal involvement was altogether lacking.

The experience of the investigators at the Massachusetts General Hospital has been unique with regard both to the remarkably large number of patients proved to have the disease and to the frequency with which it was encountered in the absence of skeletal involvement. By contrast, there have been few case reports from other sources describing hyperparathyroidism without classic bone disease.⁵ The great majority of published reports have continued to deal with patients having classic generalized osteitis fibrosa cystica, usually of severe degree.⁶

The first case of hyperparathyroidism to be observed at the Mayo Clinic was reported by Wilder⁷ in 1929. For many years the diagnosis was made infrequently.⁸ Alexander, Pemberton, Kepler and Broders⁹ were able to collect data on only 14 cases of proved hyperparathyroidism which had been observed at the clinic between 1929 and September 1942. Considering the much greater incidence which had been encountered by Albright and his colleagues, it appeared reasonable that here as well as elsewhere the diagnosis was being overlooked. Accordingly, early in 1943 a deliberate attempt was made to improve diagnostic accuracy. To this end the collaboration of internists, urologists and surgeons was solicited.

In approximately two and a half years (Sept. 30, 1942 to Jan. 30, 1945) in 24 additional cases hyperparathyroidism has been proved at operation at the Mayo Clinic, in contrast to 14 cases observed during the preceding fourteen years. Our experience with these patients confirms fully the observations made much earlier by the Boston workers. It is our purpose in this report to analyze the diagnostic features presented by this group of cases and to emphasize again the frequency and importance of this disease.

The increase in the frequency with which hyperparathyroidism was recognized was due in part to deliberate search, particularly among patients having renal calculi and in part to careful adherence to the diagnostic

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