ment with the early work of MacLeod and Stone[7] who showed that mice infected with strains of pneumococcal types I, II, or III could be effectively treated with penicillin when the total daily dose (for each of 4 days) was restricted to only 3 injections within an 8-hour period. It is of interest to note, also, that Tillett, McCormack, and Cambier[8] have concluded that in the treatment of pneumococcal pneumonia with penicillin, repetition of injections continuously throughout each 24-hour period was in many cases not necessary or advantageous. Further experimental evidence indicating that there is no advantage in splitting daily penicillin dosage into a series of small frequently repeated doses has recently been reported by Zubrod[9] who investigated penicillins G and K in mice under conditions similar to those of the present report.

In the present investigation, the comparison of single and divided dosage schedules has been confined to a maximum treatment period of only 24 hours. That different results may be obtained under other experimental conditions, is indicated by the data of MacLeod and Stone.[7] For example, these workers found that treatment with penicillin for a 4-day period could be much more effective than giving an equivalent amount of drug for a single day. In mice infected with a type I pneumococcal strain, recovery of only 74% could be obtained with a total of 600 Oxford units when treatment was restricted to a single day, whereas, recovery of 100% resulted from treatment with a total of only 60 units divided into 4 daily amounts of 15 units each. With type II pneumococcus, about the same degree of recovery (60 to 70%) was produced by a total of 300 units, regardless of whether it was administered in a single day or divided into 4 daily amounts of 75 units each.

Conclusion. From 4 to 8 times as much penicillin was needed for oral, as for subcutaneous administration, to obtain the same degree of therapeutic effect in a streptococcal infection in mice.

In this infection, the administration of daily penicillin dosage in a series of small equally spaced doses was not more effective than giving an equivalent amount of drug in 1 or 2 doses per day.

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Effect of Passive Sensitization and Anaphylactic Shock on Rabbit Bone Marrow.*

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Concepts relating the plasma cell to hyperglobulinemia, globulin formation, immune mechanisms, hypersensitivity, and anaphylactic shock have a firm basis in both clinical and experimental literature.[1-10] Beginning with

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the interest of Bing and Plum[11] in the relationship of bone marrow plasmacytosis to hyperglobulinemia there has accumulated a recent literature which clearly demonstrates that in man and animals reticular organ plasmacytosis occurs concomitant to the development of hyperglobulinemia in a great variety of conditions. Kolouch,[12,13] studying myelograms of animals sensitized to and shocked with bacterial antigens, discovered a cytomorphic cycle initiated by sensitization and fired by anaphylactic shock that led to bone marrow plasmacytosis. The development of plasma cells, from the plasmacellular reticulum of Rohr,[14] Kolouch found to be associated with rising serum antibody titer. Since this publication, a number of investigators have become interested in the plasma cell of reticular organs and experiments have been performed which indicate that this cell is the source of abnormal globulin and especially antibody globulin.[15–19] In a series of experiments Kolouch, Good, and Campbell[20] clarified the morphological mechanisms of reticular organ plasma cell genesis as previously pointed out by Kolouch and showed that the plasma cell content of bone marrow and spleen could be increased following active sensitization and shock with simple protein antigen (egg white) as well as with bacterial antigen. The phenomenon is one, then, of general hypersensitivity and shock and is not limited to bacterial antigens.

The possible relations of plasmacytosis to passive sensitization and shock have never been investigated. Bjoerneboe and Gormsen[17] have shown that passively induced hyperglobulinemia does not bring about reticular organ plasmacytosis. Bjoerneboe, Gormsen and Lundquist[21] as well as Fagraeus[18] also conducted experiments which seemed to indicate that increased plasma cell formation does not occur during heightened normal globulin formation. Further experiments carried out in our laboratory[22] indicate that local plasma cell formation, under some circumstances at least, is a function of tissue hypersensitivity and antigen-antibody interaction. In these experiments the plasma cells in the acute inflammatory reaction were shown to be a cytological accompaniment of hyperergic inflammation.

In order to test whether or not plasma cell formation is secondary either to passive sensitization and shock the following experiments were performed. Twenty-four young adult albino rabbits were actively sensitized to a simple protein antigen by injecting egg white on alternate days in the following dosages: 1 cc i.v., .5 cc i.v., and 1 cc i.m. A period of 18-30 days was then allowed to elapse before these rabbits were used as blood donors in the following experiment. Blood was obtained by cardiac puncture under aseptic precautions and allowed to clot. The antibody-rich serum was then separated carefully from the clot and that from several donors pooled to provide the serum used for the passive sensitization.

Six young adult albino rabbits weighing 4.0 to 5.3 lb were used for this experiment. Bone marrow biopsies were made after the

TABLE I.

No. 1055	severe	shock
" 1058	moderate	"
" 1057	mild	"
" 1061	moderate	"
" 1062	mild	"
" 1063	no	"

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TABLE II.*

No. 459	Cells	Plasma cells	Plasmacellular reticulum cells	Reticulum cells
Effect of Active Sensitization and Shock on Bone Marrow.				
Control	1000	9.50	2	9.75
Pre-shock	1000	15.50	37.4	8.20
24 hrs post shock	1000	34.20	10.5	9.20
4 days post shock	1000	36.20	11.75	10.50
Effect of Passive Sensitization and Shock on Bone Marrow.				
No. 1058				
Control	1000	5.25	1	9.50
Pre-shock	1000	9.0	2.5	10.2
24 hrs post shock	1000	6.7	1.5	7.2
4 days post shock	1000	6.2	2.5	1.0
No. 1055				
Control	1000	7.0	5.5	12.2
Pre-shock	1000	8.5	5.25	13.5
24 hrs post shock	1000	6.5	2.75	14.5
4 days post shock	1000	7.75	4.25	11.50

* Each figure is the mean of four 1000 cell counts.

method of Kolouch.[12] Each rabbit was given an injection of 15-30 cc of rabbit serum obtained from the actively sensitized rabbits described above. Eighteen hours later imprints were made of the bone marrow. Six hours later (24 hours after the injection of serum from the hypersensitive rabbits) each rabbit was injected with .4 cc egg white intravenously. All animals save one showed some degree of anaphylactic shock.

Each animal which showed shock was subjected to rib biopsy 8, 24, and 96 hours after the shock, and a large number of 1000-cell differential counts was made.

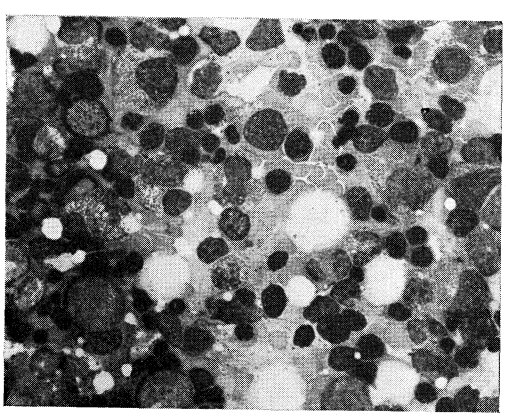

FIG. 1.

Bone marrow imprint from passively sensitized rabbit illustrating the presence of normal bone marrow. Note lack of plasma cells and plasmacellular reticulum cells. *Cf.* Kolouch, Good, and Campbell,[20] Fig. 2.

Results. The effect of passive sensitization and shock on bone marrow may be compared to that of active sensitization and shock in Table II.

While in active sensitization numerous plasmacellular reticulum cells flooded the bone marrow and following anaphylactic shock the bone marrow became filled with true Marschalko plasma cells, in passively sensitized and shocked rabbits no comparable changes were to be noted. The photo-micrograph, Fig. 1, illustrates this relationship. It is apparent that the cytomorphic cycle culminating in bone marrow plasmacytosis following active immunization or active sensitization and shock is due to factors other than reticular reaction secondary either to the presence of altered globulin in the form of antibody protein in the blood or tissues or factors related to the local or general effect of anaphylactic shock *per se.*

Summary. Studies of serial bone marrow biopsies of passively sensitized and shocked animals reveal: 1. Passive sensitization to a foreign protein does not activate the reticulum as does active sensitization. 2. Anaphylactic shock in passively sensitized rabbits is not followed by the development of bone marrow plasmacytosis as is the case with anaphylactic shock in actively sensitized animals.