Effects of Hyaluronidase Administration on Myocardial Ischemic Injury in Acute Infarction

A Preliminary Study in 24 Patients

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The effect of hyaluronidase on myocardial ischemic injury was examined in 13 patients with acute myocardial infarction, and the results were compared with 11 patients who did not receive hyaluronidase. A 35-electrode precordial mapping method was used to assess the rate of resolution of ST segment elevations. In the 11 control patients, the sum of ST segment elevations (ΣST) fell after 2 hours to an average of 93.5% ± 17.3% (SEM) and after 24 hours to 89.6% ± 7.6% of the initial values, while the number of electrodes exhibiting ST segment elevations exceeding 0.1 mV (NST) fell to 98.0% ± 12.3% and 94.3% ± 10.4% of the initial values respectively. In the hyaluronidase-treated group, at the same time ΣST fell significantly more ($P < 0.05$), to 54.1% ± 5.0% and 51.3% ± 11.8% and NST was also more markedly reduced ($P < 0.05$) to 50.7% ± 7.8% and 50.1% ± 12.4%, thus indicating that hyaluronidase can accelerate the reduction of myocardial ischemic injury in patients with acute myocardial infarction.

In a series of studies using a model of coronary occlusion in the dog, reduction in the extent of ischemic injury and subsequent necrosis was achieved with several interventions (1); these investigations have recently been reviewed (2, 3). It was found that the administration of a number of agents, including hyaluronidase, decreases the magnitude and the extent of electrocardiographic myocardial ischemic injury and subsequent necrosis in dogs subjected to coronary artery occlusion (4). In addition, a noninvasive electrocardiographic method was developed that evaluates changes in ischemic injury that could be used in patients in rapidly assessing changes in the extent of myocardial damage as a consequence of therapeutic interventions (5, 6). In view of the apparent lack of toxicity of hyaluronidase and the impressive experimental results with this agent, a pilot study was undertaken to examine its effectiveness in patients with acute myocardial infarction.

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Methods

TOXICOLOGICAL STUDIES

Six dogs and six rabbits received hyaluronidase, 500 National Formulary units/kg body weight, in a bolus intravenously three times daily, and three rabbits and three dogs received this dose six times daily for 2 weeks. At the end of the 2 weeks, all experimental animals and six dogs and two rabbits in the control group were autopsied and their organs examined for both gross and microscopic changes. Specifically, there were no pathologic changes observed by light microscopy in the brain, heart muscle or valves, lungs, aorta, liver, spleen, gonads, eyes, crystalline lens, or interlumbar discs.

After obtaining informed consent, we administered hyaluronidase to nine hospital volunteers without myocardial disease. Six patients received 500 National Formulary units/kg body weight, in a bolus intravenously three times daily, and another three received this dose five times daily for 48 hours. There were no adverse clinical reactions and there were no changes in vital signs, blood creatine phosphokinase, lactic dehydrogenase, serum glutamic oxalacetic transaminase, electrolytes, bilirubin, blood urea nitrogen, urinalyses, complete blood counts, the standard 12-lead electrocardiograms, or chest roentgenograms.

STUDIES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION*

Twenty-four patients who had suffered typical transmural myocardial infarctions determined by history, enzyme changes, and electrocardiographic criteria were studied. The 11 patients who did not receive hyaluronidase served as controls and the 13 patients who received the drug constituted the experimental group. Although these patients were not assigned to one of the two groups in a randomized manner and the design of the study was not blind, there was no attempt to preselect the patients on the basis of the severity of complication of their disease. All patients had acute myocardial infarction involving the anterior or lateral walls of the left ventricle, and the onset of the chest pain occurred less than 8 hours before the beginning of the study. Patients more than 75 years of age and others with disease of kidney or liver, pregnancy, neoplasms, or infections were excluded.

The control group consisted of seven men and four women, averaging 56 ± 4 years (SEM) in age, who entered the study an average of 4.7 ± 0.5 hours after the onset of chest pain.

* This study was approved by the Committee on Human Research and was carried out under IND #8352.

The experimental group consisted of 12 men and 2 women, averaging 50 ± 2 years in age, and they entered the study an average of 4.3 ± 0.5 hours after the onset of chest pain. After obtaining informed consent, we gave an intradermal test dose of 150 units of hyaluronidase before intravenous administration. Each patient then received hyaluronidase 500 National Formulary units/kg body weight intravenously in a bolus, followed by additional identical doses at 2 and 6 hours, and then every 6 hours until 42 hours after the initial dose.

ELECTROCARDIOGRAPHIC METHOD

The precordial electrocardiograms were recorded with 35 unipolar leads, as described previously (5). The precordial leads were standard chest electrodes (Hewlett Packard #14058*) in a fixed position in a blanket covering the precordium distributed in five rows of seven electrodes each. The right uppermost electrode was always located in the second intercostal space and the right parasternal line and thus in general the precordial map extended laterally to the left midaxillary line and inferiorly to the sixth intercostal space. The electrodes were connected to a switch box, which in turn was connected to the V lead of a clinical electrocardiograph, standardized so that 1 mV = 10 mm deflection. ST segment deviations were analyzed independently by two observers without knowledge of the time sequence in which they were taken. The data were analyzed using Student's *t* test when comparing data between the control and experimental groups and the paired *t* test when comparing data obtained at different times in the same group.

Results

CONTROL GROUP

The average sum of ST segment elevations (ΣST) at the time of the first map was 65.3 ± 9.2 mm (Figure 1, Panel I) and the number of sites exhibiting ST segment elevations greater than 1 mm (NST) was 20 ± 2 (Figure 1, Panel II). ΣST 2, 6, 12, and 24 hours after the initial tracing fell, on average, to 93.5% ± 17.3%, 86.4% ± 12.8%, 84.5% ± 8.3%, and 89.6% ± 7.6% (Figure 1, Panel I), while NST during the same period fell, on average, to 98.0% ± 12.3%, 96.5% ± 17.5%, 86.7% ± 7.7%, and 94.3% ± 10.4% of the initial values respectively (Figure 1, Panel II). Three of the 11 patients developed heart failure and eventually died.

HYALURONIDASE GROUP

The average ΣST before hyaluronidase administration was 62.0 ± 3.5 mm (Figure 1, Panel I), and NST was 17 ± 2 (Figure 1, Panel II). After the electrocardiographic map, the first dose of hyaluronidase was administered, and 2, 6, 12, and 24 hours later the ΣST fell, on average, to 54.1% ± 5.0%, 46.4% ± 4.9%, 39.7% ± 7.3%, and 51.3% ± 11.7% of the initial values respectively, while the NST during the same period fell, on average, to 50.7% ± 7.8%, 37.2% ± 7.4%, 35.6% ± 9.9%, and 50.1% ± 12.4% (Figures 1, 2, and 3). Average ΣST and NST levels before hyaluronidase administration in this group were not statistically different from the control group. However, at all times after treatment with hyaluronidase, average ΣST and NST were significantly lower ($P < 0.05$) than in the control group (Figure 1). One patient in the treated group died 10 days after hospitalization due to ventricular arrhythmias. At postmortem examination, there was no sign from gross or microscopic examination of thinning of the ventricular wall or any abnormality of healing of the infarction. Two patients showed signs of ventricular failure, one of them overt pulmonary edema; both survived. No toxic or allergic side effects were observed in any of the patients who received hyaluronidase.

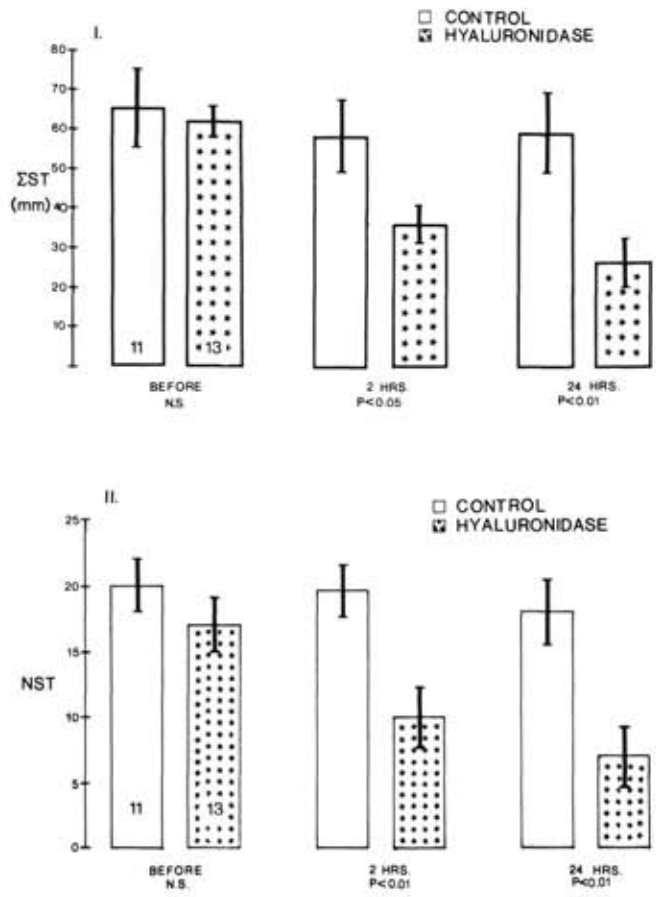

Figure 1, Panel I. The sum of ST segment elevations (ΣST) in control patients and in hyaluronidase-treated patients at zero time (before treatment), and at 2 and 24 hours after treatment. Note that before treatment both groups had similar values of ΣST. However, in the treated group, ΣST dropped significantly more rapidly than in the control group. **Panel II.** Number of electrodes showing ST segment elevations exceeding 1 mm (NST) in control patients and in hyaluronidase-treated patients at zero time (before treatment), and at 2 and 24 hours after treatment. Note that before treatment both groups had similar values of NST. However, in the treated group NST dropped significantly more rapidly than in the control group.

Discussion

Of all interventions shown to reduce infarct size experimentally, hyaluronidase seemed of most immediate interest for clinical evaluation because its effectiveness in decreasing infarction in experimentally produced coronary occlusion compared favorably with other interventions (2). In addition, its application requires no special instrumentation or invasive procedures, and its toxic and unwanted effects are minimal (7, 8). The lack of toxicity was confirmed in the present investigation, which showed that dogs and rabbits treated for 2 weeks with doses of hyaluronidase comparable to those administered to the patients in this study did not show any changes attributable

* Hewlett Packard Corp., Lexington, Massachusetts.

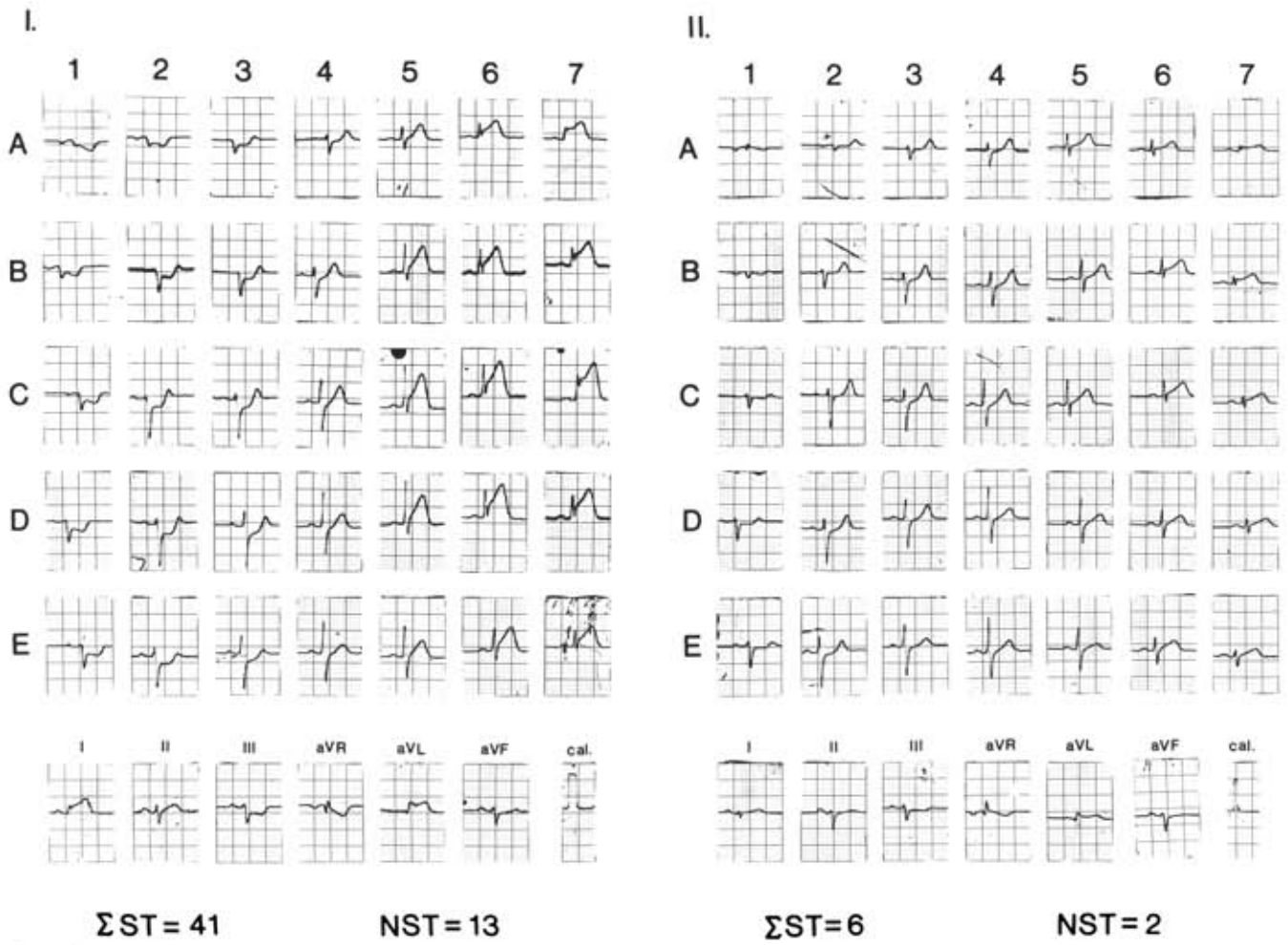

Figure 2. An example of the 35 precordial leads and the 6 classical electrocardiograpical leads in a patient with acute myocardial infarction of the posterolateral wall before treatment (*Panel I*) and 2 hours after hyaluronidase administration (*Panel II*). Note the reduction in ST segment elevations over the lateral wall (*sixth and seventh columns*) as well as the diminution of ST segment depressions in the right precordial leads.

to hyaluronidase. The clinical use of hyaluronidase in a variety of conditions has been associated with only minimal toxic and allergic reactions (9-11). In this study we did not observe any abnormal reactions or changes in patients' laboratory tests that could be attributed to the hyaluronidase either in normal volunteers or in the patients with acute myocardial infarction.

The effectiveness of hyaluronidase in diminishing infarct size after coronary occlusion was initially demonstrated in the experimental animal by electrocardiographic, enzymatic, and histologic methods (4). Also, hyaluronidase did not alter left ventricular function in normal anesthetized dogs or dogs with regional myocardial ischemia due to occlusion of the midportion of the left anterior descending coronary artery. Moreover, in dogs with generalized left ventricular ischemia, hyaluronidase appeared to protect the left ventricle from the development of heart failure (12). Therefore, considering the apparent low toxicity of this drug, both in experimental animals and in man, and its effectiveness in reducing infarct size in the dog, it was selected for study in patients with acute myocardial infarction.

This pilot study was undertaken only to investigate the possible role of hyaluronidase therapy and its suitability for more extensive clinical investigation; the patients were not selected in a prospective or random manner and the trial was not conducted in a blind fashion in that the investigators knew to which group each patient was assigned. On retrospective analysis, however, the control and experimental groups were well matched for time after onset of pain at which they entered the study. It is also noteworthy that before treatment the sum of ST segment elevations (ΣST) and the number of sites showing ST segment elevations greater than 1 mm (NST) were similar in the two groups; thus the extent and magnitude of ischemic injury, as assessed by the precordial electrocardiographic methods, were comparable in both groups. This method has been used by several investigators (13-15) and its rationale explained in detail elsewhere (2, 5, 16, 17).

The results of this study show that the reduction in the magnitude and extent of ST segment elevations was greater in the experimental than in the control group at each time interval during the 24 hours after treatment. This more

rapid decline in the electrocardiographic indexes of injury was already evident 2 hours after drug administration. These results support previous observations that hyaluronidase lowers ST segment elevations in the 12-lead electrocardiogram in patients with acute myocardial infarction (18-20). Also, although several patients in the control group exhibited an increase in ST segment elevation on sequential electrocardiograms, suggesting an extension of the infarction, this situation did not occur in any of the hyaluronidase-treated patients. Therefore, based on studies in experimentally produced coronary occlusions, it is suggested that this reduction in acute myocardial ischemic injury produced by hyaluronidase may reflect a reduction in the quantity of myocardium that eventually becomes necrotic.

It must be emphasized, however, that this study is preliminary in nature and a larger, prospective, randomized, double-blind study will be necessary to establish the clinical effectiveness of this agent in the treatment of acute myocardial infarction. Accordingly, consideration of the routine use of hyaluronidase in the treatment of acute myocardial infarction should be deferred until its effectiveness is validated in a rigorous clinical trial.

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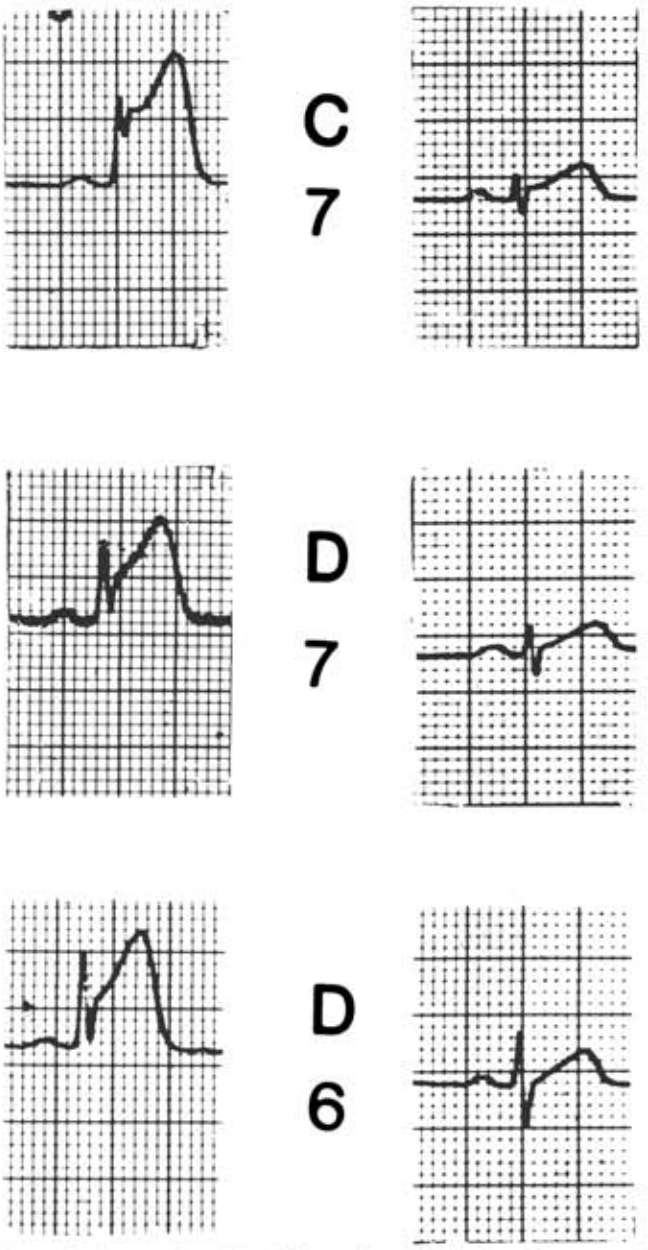

Figure 3. Three enlarged leads from Figure 2 showing ST segment elevations in these leads before hyaluronidase administration (*left*) and the striking reduction in ST segment elevation 2 hours after its administration (*right*).

References

1. Maroko PR, Kjekshus JK, Sobel BE, et al: Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 43:67-82, 1971
2. Maroko PR, Braunwald E: Modification of myocardial infarction size after coronary occlusion. *Ann Intern Med* 79:720-733, 1973
3. Braunwald E, Maroko PR: The reduction of infarct size—an idea whose time (for testing) has come. *Circulation* 50:206-209, 1974
4. Maroko PR, Libby P, Bloor CM, et al: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46:430-437, 1972
5. Maroko PR, Libby P, Covell JW, et al: Precordial S-T segment elevation mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. *Am J Cardiol* 29:223-230, 1972
6. Maroko PR, Bernstein EF, Libby P, et al: The effects of intraaortic balloon counterpulsation on the severity of myocardial ischemic injury following acute coronary occlusion. Counterpulsation and myocardial injury. *Circulation* 45:1150-1159, 1972
7. Seifter J: Studies of the pharmacology and toxicology of testicular hyaluronidase. *Ann NY Acad Sci* 52:1141-1155, 1950
8. Tislow R, Chase JF: Subacute and chronic toxicity experiments with hyaluronidase. *Ann NY Acad Sci* 52:1156, 1950
9. Britton RC, Habif DV: Clinical uses of hyaluronidase; a current review. *Surgery* 33:917-942, 1953
10. Moore DC: An evaluation of hyaluronidase in local and nerve block analgesia: a review of 519 cases. *Anesthesiology* 11:470-484, 1950
11. Schwartzman J: Hyaluronidase. A review of its therapeutic use in pediatrics. *J Pediatr* 38:491-502, 1951
12. Maroko PR, Libby P, Braunwald E: The effect of pharmacologic agents on the function of the ischemic heart. *Am J Cardiol* 32:930-936, 1973
13. Pelides LJ, Reid DS, Thomas M, et al: Inhibition by β-blockade of the ST segment elevation after acute myocardial infarction in man. *Cardiovasc Res* 6:295-301, 1972
14. Krotkiewski A, Gajewska-Lipka J, Szelemetko J, et al: Multi-lead electrocardiogram in relation to serum enzymes in acute myocardial infarction. *Br Heart J* 35:991-996, 1973
15. Reid PR, Taylor DR, Kelly DT, et al: Myocardial-infarct extension detected by precordial ST-segment mapping. *N Engl J Med* 290:123-128, 1974
16. Muller JE, Maroko PR, Braunwald E: Evaluation of precordial ST segment maps in assessment of myocardial ischemic injury. *Circulation*. In press

17. MAROKO PR: Assessing myocardial damage in acute infarcts (editorial). *N Engl J Med* 290:158-159, 1974
18. OLIVEIRA JM, CARBALLO R, ZIMMERMAN HA: Intravenous injection of hyaluronidase in acute myocardial infarction: Preliminary report of clinical and experimental observations. *Am Heart J* 57:712-722, 1959
19. TRANCHESI J, BOCCALANDRO I, EBAID M, et al: O use da hialuronidase no enfarte recente do miocardio, estudo electrocardiografico. *Arq Bras Cardiol* 13:1-6, 1960
20. EBAID M, CARAMELLI Z, NETO SM, et al: The effects of large intravenous doses of hydrocortisone or hyaluronidase on the electrocardiographic pattern of acute myocardial infarction. A comparative clinical and experimental study. *Arch Inst Cardiol Mex* 35:3-10, 1965

"The Common Impulse Droops"

It is the common character of large societies to suffer heavily from the restrictive effect on personality of the social instinct, and at the same time to suffer in the highest degree from the debilitation of the common social impulse. Only in the smallest groups, such as perhaps was early republican Rome, can the common impulse inform and invigorate the whole society. As the group expands and ceases to feel the constant pressure of an environment it no longer has to fear, the common impulse droops, and the society becomes segregated into classes, each of which a lesser herd within the main body and under the reciprocated pressure of its fellows now yields to its members the social feeling which the main body can no longer provide. The passage of the small, vigorous, homogeneous and fiercely patriotic group into the large, lax, segregated and ultimately decadent group is a commonplace of history. In highly segregated peoples the restrictive effect of the social instinct upon personality has usually been to some extent relaxed, and a relatively rich personal development has been possible. Such an amplification has always, however, been limited to privileged classes, has always been accompanied by a weakening of the national bond, and a tendency of the privileged class to the sincere conviction that its interests are identical with those of the nation. No nation has ever succeeded in liberating the personality of its citizens from the restrictive action of the social instinct and at the same time in maintaining national homogeneity and common impulse. In a small community intercommunication among its individual members is free enough to keep common feeling intense and vigorous. As the community increases in size the general intercommunication becomes attenuated, and with this common feeling is correspondingly weakened. If there were no other mechanism capable of inducing common action than the faint social stimulus coming from the nation at large, a segregated society would be incapable of national enterprise. There is, however, another mechanism which we may call leadership, using the word in a certain special sense. All social groups are more or less capable of being led, and it is manifest that the leadership of individuals, or perhaps more usually of classes, has been a dominant influence in the expansion and enterprise of all civilizations of which we have any knowledge. It is only in the small communities that we can detect evidence of a true common impulse shared alike by all the members acting as the case of expansion. In larger groups, autocracies and dynasties, Pharaohs and Nebuchadnezzars have imposed the impulse of expansion upon the people, and by virtue of human susceptibility to leadership have secured a vital, though only a secondary, common purpose.

W. TROTTER
Instincts of the Herd in Peace and War
London, T. Fisher Unwin Ltd., 1916, pp. 246, 247