Massive Myocardial Necrosis with Calcification

Report of Two Cases of Possible Hypokalemic Etiology

By Margaret S. Littman, M.D., and W. R. Meadows, M.D.

In recent years there has been considerable interest in the effects of potassium deficit on the myocardium, kidneys, and the gastrointestinal tract. Shrader and associates were the first to produce potassium deficiency in rats. They cited in detail the changes in the gastrointestinal tract and briefly noted "diffuse tubular nephritis." They described "massive erosions" of the endocardium and myocardium of both ventricles but gave no further details or illustrations. Cardiac lesions have subsequently been described in cats, calves, mice, rabbits, monkeys, and rats. However, despite severe tissue depletion of potassium no myocardial lesions have been produced in dogs, although lesions of striated muscle have been observed. Cannon, Frazier, and Hughes established the need for potassium in tissue protein synthesis. In the protein-depleted adult rat, when potassium was removed from the salt mixture of a repletion ration of calories, vitamins, and amino acids, there was a loss of appetite, poor food consumption, failure to gain weight, development of cardiac lesions characteristic of potassium deficiency, and early death. When small amounts of potassium were added to the repletion diet, effective protein repletion and survival occurred.

Cannon et al. and French et al. have described the heart lesions clearly and chronologically. Severe myocardial lesions developed 14 to 18 days after potassium depletion was begun. The earliest changes appeared in the ventricular subendocardial muscles affecting initially only small muscle groups in the papillary muscles and columnae carneae. Later these lesions became massive, involving large areas in the inner half of the myocardium. Although both ventricles were apparently affected with equal severity, the lateral wall of the right ventricle was more frequently involved. The atrial myocardium was affected least, except when the heart was diffusely involved. The microscopic changes were those of primary degeneration of muscle fibers, beginning with the sarcoplasm and sparing the sheaths. Interstitial edema and a few round cells were present. As necrosis advanced, the nuclei became pyknotic and resembled myogenic cells. Phagocytosis of dead muscles by macrophages was seen. Blood vessels and connective tissues were not altered. Healing of the lesions took place with complete recovery of some muscle fibers and hypertrophy of apparently unaffected fibers. Attempted or abortive regeneration represented by masses of sarcolemmal nuclei was not seen. The areas of fibrosis apparently represented condensation of pre-existing interstitial tissue and sarcolemmal sheaths, with only slight fibroblastic proliferation. Calcification was not observed.

The synergistic effect of sodium, adrenocorticotropic, deoxycorticosterone, and other corticoids in accelerating potassium excretion and producing severe and rapid myocardial necrosis has been reported by many authors. Selye et al. and Selye and de Saedec re- garded sodium salts and the corticoids as "conditioners" of the myocardium. In both rat and monkey "infarctoid cardiopathies" were produced consistently when stress was applied after pretreatment with monobasic or dibasic sodium phosphates and corticoids. When calcium salts were used instead of sodium salts, calcification occurred in the "infarctoid" areas. Selye asserted that the "infarctoid" cardiopathies without calcification were similar to acute myocardial infarcts seen

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in man and differed only by the absence of vascular occlusion.

Myocardial necrosis believed to be due to potassium deficiency has been reported in patients with adrenal cortical insufficiency treated with excessive doses of desoxycorticosterone,

10, 11 diabetic acidosis,

12 ulcerative colitis,

13 chronic diarrhea,

14 idiopathic steatorrhea,

14 and chronic renal disease without anuria or oliguria.

10, 15

Recently we encountered two instances of myocardial necrosis with calcification associated with subacute membranous and proliferative glomerulonephritis. In one case the myocardial lesions were massive, and in the other they were numerous but small. To our knowledge, massive cardiac lesions with calcification of the muscle fibers only, as in our first case, have been reported twice. Camerini et al.16 reported one case of a 21-year-old man as an unusual cardiopathy, and Lanco and Toth17 described an 8-year-old girl with chronic glomerulonephritis and necrosis and calcification of the myocardium.

Case Reports

Case 1

A 32-year-old white male steel worker entered Hines Veterans Administration Hospital on September 27, 1960, with swelling of the legs, buttocks, serosan, and abdomen. His illness began about 9 months before with sore throat, hoarseness, nasal congestion and discharge, and frontal headaches in the morning. He had frequent sore throats since childhood.

Because of increasing malaise, ankle edema at the end of the day and blurred vision, he sought advice from his family physician, who found a blood pressure of 160/120 and albumin in the urine. In August he was hospitalized for 20 days and received large doses of an unknown adrenocortiroid with little benefit.

The blood pressure was 110/80. Funduscopic examination was normal. There were edema of the sacrum and lower extremities and large abdominal ascites. The urine contained a few red blood cells, many white blood cells and granular casts, and four plus albumin. Specific gravity was 1.018, the highest value obtained during hospitalization. Total serum cholesterol was 509 mg. per 100 ml. Table 1 summarizes the biochemical tests.

Hemoglobin varied between 16.8 and 19.5 Gm. per 100 ml. during the first month of hospitalization but had fallen to 9.1 Gm. per 100 ml. on November 17. White blood-cell count was 7,199 on admission. Two lupus erythematous cell preparations, a serologic test for syphilis, blood volume determinations, bromsulfalein excretion, serum transaminase, prothrombin activity, blood glucose, sedimentation rate, and C-reactive protein were normal or negative. Chest x-ray was not remarkable. An intravenous pyelogram showed poor excretion of dye.

During the first 2 weeks of hospitalization he was given chlorothiazide, 500 mg. twice daily, for 12 days and intramuscular injections of Mercuhydrin, 1.5 ml. daily, for 4 days. Fluids were urged, and his sodium chloride intake was limited to 500 mg. daily. On this regimen his weight fell from 224 pounds on October 4 to 213 on October 18. Subsequent therapy included Mercuhydrin, 1 ml. twice daily, from October 19 to November 1 and Aldactone, 100 mg. four times daily, from November 1 to November 8. Potassium chloride, 1,200 mg. daily, was started October 26 and continued until November 8.

The first complaint of back pain occurred on October 19, 22 days after admission, and 9 days later was associated with pain and tenderness in the right groin and hip and difficulty in raising his legs. An electrocardiogram showed sinus rhythm, rate 86; axis +30°; P-R = 0.14 second, QRS = 0.05, QT = 0.36; low voltage of QRS and T in limb and precordial leads; and slight sagging of ST segments in lead II. It was interpreted as suggestive of hypopotassemia. By November the erythema over the right hip was noted, and headache and backache were severe. He complained

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<td><strong>Biochemical Determinations</strong></td>
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of increasing weakness, nausea, dizziness, and “fever.”

Six days later he awoke with a shaking chill followed by severe epigastric pain and vomiting. His temperature rose to 104 F., and the white blood-cell count was 20,500 per mm.³, with 96 per cent neutrophilic leukocytes. The abdomen was diffusely tender with rebound. Continuous gastric suction was begun because of persistent vomiting. His blood pressure fell to 80/60 but responded to intramuscular metaraminol. A blood culture was taken and later reported positive for Diplococcus pneumoniae. Fluid obtained by abdominal paracentesis contained 2,000 white blood cells per mm.³, with 92 per cent neutrophils. Total protein was 0.4 Gm. per 100 ml. Numerous pneumococci and alpha hemolytic streptococci were cultured. During the next 6 days 800 ml. of plasma, serum albumin, vitamin B complex with C, glucose, and chloramphenicol were given intravenously.

Dyspnea began on November 9. The heart rate ranged from 100 to 120. He was given oxygen and a digitalizing dose of Cedilanid. The electrocardiogram now showed elevation of ST segments in leads I and aVL and depression of ST segments in leads II, III, and aVF. It was interpreted as compatible with acute infarction of the lateral wall of the left ventricle. Chest x-ray was consistent with pneumonia in the right lower lung field. This cleared considerably by November 12, when an infiltrate was noted in the left base.

Fever and abdominal symptoms subsided over the next 5 days, but right chest pain, epistaxis, and frequent, occasionally bloody liquid stools appeared. His condition steadily worsened, and death occurred on November 18. During the last 4 days of life erythromycin was given in large doses. A blood culture taken during that time was reported negative.

**Significant Autopsy Findings.** Pedal edema was moderate. Each pleural space contained 2,000 ml. of clear fluid. The lungs were intensely hyperemic and edematous. The pericardial sac contained 100 ml. of clear fluid. The heart weighed 450 Gm., and was flabby. All chambers were dilated. Circumferences of the valves were normal. The right ventricular wall measured 3 mm. Through the endocardium irregular bright yellow areas were seen in the interventricular septum (fig. 1). Small gray patches were seen within the papillary muscles. The left ventricular wall measured 14 mm. In the mid-layer of muscle of the septum, posterior, lateral, and anterior walls there were large irregular bright yellow areas that projected slightly above the adjacent muscle. The transition from brown myocardium to the yellow zones was sharp, but the continuity of muscle fibers from one zone to the other was maintained. There was a gritty feeling on sectioning and on palpation of the yellow zones. Identical smaller areas were scattered in the subendocardial and subepicardial areas and throughout the left ventricular myocardium and papillary muscles. Small gray streaks were occasionally seen. The coronary ostia were patent, and the coronary arteries, aorta, and major arteries were elastic and free from arteriosclerosis.

The right kidney weighed 250 Gm.; the left, 300 Gm. They were swollen and uniformly pale tan. The capsules were removed easily. The surface made by cutting was moist; the cortex and medulla bulged. The pelves, calyces, ureters, and bladder were normal.

The abdominal cavity contained 200 ml. of cloudy yellow fluid from which pneumococci was grown. However, the peritoneum was smooth and glistening. The liver weighed 2,300 Gm. and was hyperemic. The spleen weighed 750 Gm. It was diffusent and intensely hyperemic.

**Microscopic.** The coronary arteries were the seat of minimal subintimal thickening composed of fibrous tissue and elastic and occasional smooth muscle fibers. Luminal narrowing was minimal.

The uninvolved muscle fibers were dilated. The nuclei were large. Nuclear polar deposition of golden-brown pigment was often strikingly increased. The interstitial tissue was edematous and contained histiocytes and an occasional lymphocyte. The most extensive changes were in the middle third of the left ventricular myocardium and corresponded to the brilliant yellow areas seen.
MYOCARDIAL NECROSIS WITH CALCIFICATION

Figure 2
Section of left ventricle showing calcification in approximate middle third of myocardium. Von Kossa technic, ×5.

grossly (fig. 2). The sarcolemma was the seat of cloudy swelling and hydropic degeneration. In many fibers there were hyaline globules of varying size giving an irregular beaded appearance. The intense hyaline change resembled coagulation necrosis. Segments of empty sheaths were often conspicuous. In some areas there was irregular swelling or shrinkage of muscle fibers with segmentation and disappearance of cross striations. Despite the profound abnormalities of the sarcolemma, the sarcolemmal sheaths were intact and their continuity could be traced through some of the areas with most severe changes. The degree of nuclear alteration was variable and could not be correlated with the degree of muscle necrosis. In some of the fibers with extensive necrosis the nuclei were swollen and the chromatin finely vacuolated. In other areas pyknosis was evident. At times the nuclei were absent or represented by amorphous basophilic masses (fig. 3).

Superimposed on the muscle necrosis, and never seen without it, was the striking deposition of uniform basophilic granules in the sarcolemma (fig. 4). The granules were identified as calcium by the von Kossa technic. Calcium was never observed in the interstitial tissues or in the blood vessels.

Most of the necrotic and calcified areas, particularly the largest, were not accompanied by a cellular reaction. Occasionally, at the periphery of the large areas there were polymorphonuclear leukocytes, lymphocytes, and histiocytes. In several small areas necrotic and calcified muscle had undergone central dissolution, where many polymorphonuclear leukocytes were seen. In other areas there were only a few histiocytes and lymphocytes and occasional Anitschkow myocytes and mast cells. Capillaries, veins, and arterioles in both the necrotic and intact myocardium were not involved. There was no perivascular reaction.

Small extravasations of blood were seen in those areas in which there was liquefaction of necrotic muscles. Between the trabeculae carneae of the right ventricle there were small recent and organizing mural thrombi, but the subjacent myocardium was uninvolved.

In some areas there was delicate interstitial fibrosis, often with interruption of a single fiber or small groups of muscle fibers, and accompanied by a few lymphocytes. Older healed areas of mus-
Focal acute chitis, calcified. Were tubules were obliterated, with obvious interruption of continuity.

Numerous sections were taken of the atria and of the ventricles. The most conspicuous and numerous lesions in recent, healing and healed stages, were found in the left ventricle, and to a lesser degree in the right ventricle. In the atria only isolated degeneration of muscle fibers and interstitial edema were seen. There were no areas of hyaline necrosis or calcification.

There was no evidence of attempted regeneration of muscle fibers. The sarcomembranous nuclei were not increased in number and at no time were muscle giant cells seen. In addition, there was no new formation of capillaries. One small mass of calcified and necrotic fibers was in the left bundle branch.

Kidneys. In all glomeruli the capillary basement membranes were thickened but there were only focal adhesions to Bowman's capsule. There were no crescents. The glomerular capillaries were relatively empty. The endothelial cells were increased in number without hyperechomiasis. Many resembled fibroblasts. Small amounts of protein were precipitated in the glomerular spaces. In the collecting tubules there were many hyaline casts, proteinaceous precipitate, and occasionally hemoglobin casts. Some of the distal tubules contained masses of polymorphonuclear leukocytes. The epithelium of the proximal convoluted tubules was swollen and often filled the lumen. In small areas the tubules were dilated; the epithelium was flattened and the cytoplasm contained small droplets and vacuoles. The cytoplasm was finely vacuolated, without any distributional pattern of the vacuoles. Doubly refractile bodies were identified in some convoluted tubules and in the lumens. Neutral fat was present in small amounts in the same areas. The cells of the distal convoluted tubules were flat or low cuboidal. Some regeneration was present. Several small collecting tubules were atrophic and occasional lining cells were calcified.

In the remaining organs there was acute bronchitis, focal acute nonspecific hepatitis, and focal fat necrosis of the pancreas. No peritonitis was seen, although many areas were studied.

Case 2
A 41-year-old cachectic and dehydrated Negro man was admitted to Hines Veterans Administration Hospital December 31, 1960, in a terminal state and died 9 hours later. He was able to tell only of abdominal pain with progressive distention and vomiting for 5 weeks.

Blood pressure was 40 mm. Hg by palpation, heart rate was 100, and temperature was 99 F. A large fixed mass was noted in the neck bilaterally but predominantly on the right. The abdomen was distended with generalized tenderness and rebound.

A plain film of the abdomen taken with the patient upright showed free air under the diaphragm. The white blood-cell count was 35,000, with a differential count of 93 per cent neutrophils and 7 per cent lymphocytes. Hemoglobin was 7.4 Gm. per 100 ml. with a hematocrit level of 28 per cent. The small amount of urine obtained by catheter contained two plus albumin, 10 to 15 white blood cells and a few granular casts per high-power field.

Treatment consisted of a blood transfusion, intravenous fluids, and massive doses of penicillin. Oxygen was given for dyspnea, which appeared 4 hours after admission. Nasogastric suction was started.

Significant Autopsy Findings. The mucous membranes and tongue were dry. The heart weighed 280 Gm. Serous atrophy of the subepicardial fat was seen. The right ventricle measured 4 mm. and the left ventricle 13 mm. The valve measurements and the valves were normal. The myocardium was friable, brown, and streaked with irregular bright yellow lines and areas of 2 to 4 mm. size. Although present in both ventricles, they were most conspicuous in the interventricular septum and posterior wall of the left ventricle, and could be seen through the endocardium. With the exception of slight arteriosclerotic narrowing of the right coronary ostium, the coronary arteries were elastic and patent. Arteriosclerosis of the aorta was minimal.

In the esophagus there was a 5 by 3 by 3 cm., fungating, squamous-cell carcinoma with metastases to the lungs, mediastinal and hilar lymph nodes, and serosa of the small and large intestines. The latter were associated with an acute fibrinopurulent exudate but no perforations were found. The right kidney weighed 140 Gm. and the left 130 Gm. The surfaces were smooth and reddish-brown.

Heart. Within the heart muscle small groups as well as isolated fibers were intensely eosinophilic and the seat of coagulation or hyaline necrosis (fig. 5). Superimposed on these changes was the deposition of calcium, which was restricted to the degenerated muscles and never seen in the interstitial tissues. Some of the fibers were the seat of a
cloudy swelling, hydropic degeneration, and dilatation. In areas of degeneration the nuclei at times appeared unchanged, or were enlarged and contained a delicate chromatin. In other areas they were shrunken and deeply basophilic, so that chromatin details were obscured. The interstitial tissues, both in areas of degeneration and in apparently healthy muscle, were edematous and contained a few histiocytes and occasional lymphocytes. Mast cells were sparse. At times in small zones there were empty muscle fibers whose continuity was still maintained by intact sarcolemmal sheaths. At the periphery of occasional groups of necrotic and calcified muscle fibers there were polymorphonuclear leukocytes. There were no lesions in the blood vessels. Small scattered areas representing healed lesions were characterized by delicate fibrous tissue interrupting the continuity of muscle fibers (fig. 6). Although only a few calcified fibers were seen in the right ventricle, there were many areas of hyaline necrosis and many healed scars (fig. 7). In the atria only a few small areas of minimal muscle degeneration were seen.

**Kidneys.** The glomeruli were uniformly involved by subacute membranous and focally proliferative glomerulonephritis. The epithelium of the proximal convoluted tubules were swollen, finely vacuolated, and at times desquamated into the lumens. Some of the tubules were dilated and the epithelium was shrunken. Within the distal convoluted tubules, degeneration and regeneration of the epithelium was present. Only a few small calcified spherules surrounding still recognizable cells, filled the tubules. Other calcified masses were acellular. Protein, hyaline, and hemoglobin casts were seen. The collecting tubules contained some calcified masses. In some tubules degenerative changes were present.

**Discussion**

The cardiac lesions in these two cases differ in many respects from those myocardial necroses of known etiology. We considered the
calcification to be dystrophic in type, a secondary phenomenon related to cellular damage. It cannot be entirely excluded that it might be metastatic calcification. However, the absence of calcium deposits in mesenchymal tissues of other organ systems favors the dystrophic type of calcification.

Although the bright yellow color of the gross lesions suggests myocardial infarcts, certain differences are noteworthy. The color is uniform and glistening; the muscle bundles are distinct, and no marginal mottling or translucency suggestive of tissue dissolution is seen. Microscopically, only the sarcoplasm is degenerated, and the sarcolemmal sheaths, interstitial tissues, and blood vessels are intact. This picture resembles that of experimentally induced hypokalemic myocardial necrosis. Welt, Hollander, and Blythe18 do not believe that hypokalemic myocardial lesions differ in any way from those associated with diphtheria, coronary artery disease, and nonspecific focal myocytolysis. However, there are certain differentiating features. Firstly, in myocardial infarcts due to coronary occlusion there is a close parallel in the extent and severity of sarcoplasmic and nuclear abnormalities, whereas in hypokalemic necrosis there is a disparity. Secondly, healing of large myocardial infarcts is by formation of scar, while in hypokalemic lesions there is minimal fibroplastic proliferation and the major process is stromal collapse and condensation. Thirdly, unlike diphtheritic necrosis, abortive muscle regeneration with multinucleated muscle giant cells as described by Warthin19 has not been seen in the hypokalemic lesions in man or in experimental animals. In addition, Poché20 has demonstrated that the mitochondria of rat myocardial cells disintegrate rapidly after anoxia. On the other hand, the mitochondria remained intact even in the most severe instances of hypokalemic myocardial necrosis.

In both cases the coronary arteries were the seat of minimal arteriosclerosis without significant narrowing of the vascular lumens and no occlusions. Horn et al.21 reported myocardial infarcts in the absence of significant coronary artery disease. However, the lesions described by them were restricted to the subendocardial muscle bundles of the left ventricle and were associated with the classical gross and microscopic features of acute infarction, namely, hemorrhage, necrosis, and peripheral cellular reaction. This picture is not compatible with the myocardial necrosis produced by hypokalemia, where the sarco-plasm is degenerated but the sarcolemmal sheaths are intact. The nuclei may appear unaffected or may vary from partial to complete necrosis. The blood vessels are intact and the cellular reaction may be minimal or absent. In our cases polymorphonuclear leukocytes, a few lymphocytes, and plasma cells around small areas of necrotic muscles are considered a reparative response to the presence of necrotic tissue.

The massive involvement of the heart in case 1 and localization to the inner half of the ventricular myocardium resembles that produced by Selye in rats and monkeys when large doses of sodium or calcium salts were given with highly active corticoids and were followed by stress. That such extensive lesions have infrequently been described in man may imply that several serious or stressful conditions must occur almost simultaneously or act synergistically as in the experiments of Selye et al. In both of our cases hypokalemia was perhaps initially the result of subacute glomerulonephritis with tubular alterations. In case 1 the patient received large doses of chlorothiazide and mercurials and developed pneumococcal bacteremia, septicemia, and peritonitis. An electrocardiogram taken because of severe dyspnea was interpreted as compatible with infarction of the lateral wall of the left ventricle. In case 2 there was a large primary carcinoma of the esophagus with a history of vomiting of unknown duration.

In case 1 the evidence is suggestive but not conclusive for potassium deficiency. One electrocardiogram was "suggestive of hypokalemia." During this interval the patient
complained of pain and tenderness in the right groin, headache, backache, increasing weakness, nausea, and dizziness. These symptoms could have reflected a potassium deficient state.

The association of subacute glomerulonephritis in our cases is provocative. In 27 fatal cases of uremia with electrocardiographic evidence of potassium deficiency, Langendorff and Pirani22 found no specific myocardial lesions. In 160 patients with acute and subacute glomerulonephritis Gore and Saphir23 saw only focal serous myocarditis in 16 patients. However, Gore and Arons24 reported 13 cases of calcification of the myocardium, in 11 of which there was renal disease. In two cases there was acute and subacute glomerulonephritis; in four, lower nephron nephrosis; in four, severe arteriolar nephrosclerosis; and in one, severe embolic glomerular disease. In all instances calcium was deposited in degenerated muscle fibers and never in the interstitium, thus resembling our cases. Potassium levels were not recorded, nor was the possibility of hypokalemia considered.

It would be presumptuous to say that our cases definitely represented hypokalemic myocardial necrosis and calcification. However, the lesions were strikingly similar to those in experimentally induced potassium deficient states and they were clearly different from those in other myocardial necroses.

Summary

The clinical and autopsy observations on two cases with myocardial necrosis and calcification are presented. In each case there also was subacute membranous and proliferative glomerulonephritis.

The myocardial lesions closely resemble those produced experimentally by potassium depletion and differ from those in other myocardial necroses.

Acknowledgment

We are grateful to Dr. Otto Saphir, Director of Pathology, Michael Reese Hospital, for review of the histologic sections of the heart and kidney. He agreed that the kidneys were the seat of a subacute membranous and proliferative glomerulonephritis. He had never seen myocardial necrosis and calcification of the degree seen in case 1 nor of the distribution and frequency of case 2, although the necrotic areas were reminiscent of those in diphtheritic myocardial necrosis. The predominant differences were the minimal and only focal cellular reaction, the absence of muscle giant cells in regeneration, and calcification.

References

Principles of Research

In the temple of Science are many mansions, and various indeed are they that dwell therein and the motives that have led them thither. Many take to science out of a joyful sense of superior intellectual power; science is their own special sport to which they look for vivid experience and the satisfaction of ambition; many others are to be found in the temple who have offered the products of their brains on this altar for purely utilitarian purposes. Were an angel of the Lord to come and drive all the people belonging to these two categories out of the temple, it would be noticeably emptier, but there would still be some men, of both present and past times, left inside. . . .

Now let us have another look at those who have found favor with the angel. Most of them are somewhat odd, uncommunicative, solitary fellows, really less like each other, in spite of these common characteristics, than the hosts of the rejected. What has brought them to the temple? That is a difficult question and no single answer will cover it. . . .

A finely tempered nature longs to escape from personal life into the world of objective perception and thought; this desire may be compared with the townsman's irresistible longing to escape from his noisy, cramped surroundings into the silence of high mountains, where the eye ranges freely through the still, pure air and fondly traces out the restful contours apparently built for eternity. With this negative motive there goes a personal one. Man tries to make for himself in the fashion that suits him best a simplified and intelligible picture of the world; he then tries to some extent to substitute this cosmos of his for the world of experience, and thus to overcome it. This is what the painter, the poet, the speculative philosopher and the natural scientist do, each in his own fashion. He makes this cosmos and its construction the pivot of his emotional life, in order to find in this way the peace and security which he cannot find in the narrow whirlpool of personal experience.—Albert Einstein. Essays in Science. New York, Philosophical Library, Inc., 1934, pp. 1-3.
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