lar eruptions occurring three and twenty-four hours after the first dose of penicillin.

Using the Schultz-Dale technic in sensitized guinea pigs, Jadassohn (quoted by Graves, Carpenter and Unangst) proved that pathogenic fungi contain a specific antigen as well as another antigen common to all of them. Could allergic reactions to penicillin, which is produced from a fungus, be attributed to such a fungus-antigen relationship? There is considerable doubt at present.

Some of the most interesting and revealing laboratory studies on the sensitizing properties of penicillin were performed by McClosky and Smith,[14] using two series of guinea pigs, both sensitized by daily subcutaneous and intraperitoneal injections of penicillin over a five day period. One group was used for intracardiac or intravenous injection of antigen after an adequate incubation period, the other for tests on the isolated uterus by the Schultz-Dale technic. Some of the animals in each group were also sensitized to horse serum to ascertain the extent of the anaphylactic state developed in the animals in the event the reactions to penicillin were negative. Sensitization was not uniform and was usually atypical. The positive reactions were also mostly atypical in that reactions (such as uterine response) were often delayed and desensitization was often ineffective. This led to the opinion that the antibody-antigen combinations of commercial penicillin lack permanence and are more readily reversible than is the case in anaphylactic reactions following sensitization with true proteins.

They concluded that anaphylactic sensitization in the susceptible guinea pig can be achieved with penicillin as it is currently prepared and marketed. They used penicillin consisting of several commercial lots of the sodium salt manufactured by five different distributors, of the same degree of purity as that used in the clinic. They could not state to what extent impurities alone were responsible; if responsible, then the impurities were inherent in the commercial products, in which they were inseparable from the active substance. It was suggested that parallel experiments with synthetic penicillin, when available, would provide the answer.

From this excellent laboratory study we have direct evidence that penicillin is capable of anaphylactic sensitization. Unfortunately there have been few clinical studies in this direction, possibly owing to the present relative infrequency of reactions to penicillin. It is suggested that one might attempt desensitization to penicillin when a reaction is encountered and the use of the drug is imperative, in the same manner as that performed for tetanus antitoxin and gas gangrene antitoxin.

Although, admittedly, corroborative experimental evidence is not yet conclusive, it is my opinion that reactions to penicillin should be regarded as the manifestation of a sensitizing substance with allergic potency and should not be merely attributed to toxic impurities resulting from the commercial preparation of the drug. The problem should not be regarded as merely a matter of switching brands, but it should be approached in the same manner in which one would approach any other allergic condition. The advent of penicillin in synthetic form will undoubtedly lead to further investigation and clarification of the present nebulous etiology of reactions to penicillin.

14. McClosky, W. T., and Smith, M. I.: Experiments on the Sensitizing Properties of Penicillin, Proc. Soc. Exper. Biol. & Med. **57**: 270 (Nov.) 1944.

SUMMARY AND CONCLUSIONS

A search of the literature revealed several reported cases of delayed reactions to penicillin of the type of urticaria and serum sickness.

The incidence of delayed, serum sickness reaction to penicillin is low; although exact statistics are not available, the incidence is probably no greater than 1 : 1,500 or 1 : 2,000 cases of penicillin therapy.

The characteristic features in 3 cases were (1) delay in appearance, (2) severe malaise, mild fever and moderately rapid pulse, (3) severe, intense spreading urticaria, (4) arthralgia with serous effusions of the joints, (5) exfoliative dermatitis of the palms of both hands, and (6) a self-limited course of seven to ten days regardless of the treatment used.

Both the preponderance of opinion and the laboratory studies point to an anaphylactic sensitization by the penicillin fraction itself in susceptible individuals, with a resultant true allergic manifestation such as is found with sensitization to true proteins as the cause.

The diagnosis of urticaria of obscure origin should always include the possibility of origin from a recently completed course of penicillin therapy.

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FATAL ANAPHYLACTIC SHOCK

Occurrence in Identical Twins Following Second Injection of Diphtheria Toxoid and Pertussis Antigen

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Deaths related to the injection of foreign protein in man are fortunately few. The exact number of such occurrences is difficult to estimate from the available literature. By 1942 Kojis [1] was able to find 61 such deaths, and he added 4 more from the Willard Parker Hospital. The most complete and most recent study of necropsies was made by Vance and Strassmann,[2] who added 7 autopsy studies from the Office of the Chief Medical Examiner to 19 taken from the literature. Park [3] in 1932 recorded the mortality from serum anaphylaxis as 0.002 per cent. Kojis [1] in 1942 found it to be just under 0.1 per cent in a series of 6,211 subjects treated for various infections. Rutstein and his associates,[4] in their analysis of pneumonia cases treated with antipneumococcus horse serum, found the mortality to be 0.45 per cent. In only 1 or possibly 2 of the 25 deaths did they assign significance to protein hypersensitivity as a cause. They state that all these persons who died had vascular collapse, that only 2 had asthmatic breathing and that only 1 had hives. No characteristic change was noted in the 7 who came to autopsy other than the primary pneumonia from which all the patients suffered at the time of receiving the serum.

The inadequacy of our present knowledge of the mechanism in deaths following the administration of

The photomicrographs were taken by Mr. Julius Weber.

Read in part before the New York Pathological Society, Dec. 27, 1945.

From the Office of the Chief Medical Examiner, City of New York, and the Pathology Department of St. John's Long Island City Hospital.

1. Kojis, F. G.: Serum Sickness and Anaphylaxis: Analysis of Cases of 6,211 Patients Treated with Horse Serum for Various Infections, Am. J. Dis. Child. **64**: 93 (July); 313, (Aug.) 1942.

2. Vance, B. M., and Strassmann, G.: Sudden Death Following Injection of Foreign Protein, Arch. Path. **34**: 849 (Nov.) 1942.

3. Park, W. H.: Deleterious Effects from Serum Injections, Am. J. Pub. Health **18**: 354 (March) 1928.

4. Rutstein, D. D.; Reed, E. A.; Langmuir, A. D., and Rogers, E. S.: Immediate Serum Reactions in Man, Arch. Int. Med. **68**: 25 (July) 1941.

foreign protein is evident from Kojis's [1] summary of the 24 necropsies among the 61 he found in the literature. "3 . . . showed nothing; 6, only an enlarged thymus; 1, subacute nephritis; 1, a dilated left ventricle, congested kidneys and a slightly enlarged and pulpy spleen; 7, the guinea pig type of anaphylactic death; 3, the canine type; 1, the rabbit type; 1, a combination of the guinea pig and rabbit type; and 1, a combination of the guinea pig and canine types." It is evident that the interpretation of some published cases must remain in doubt because of the absence or incompleteness of pathologic study.

The cases reported as exhibiting harmful effects from the administration of foreign proteins fall into two groups: In one the reinjection of antigen appears to have induced the same state of susceptibility [5] as obtains in the experimental animal; in the other the development of sensitivity is considered spontaneous because it is unassociated with a history of prior parenteral injection.

Coca and Cooke [6] considered the mechanism of natural sensitivity in atopic individuals as separate from the one which underlies experimental anaphylaxis. Ratner and Gruehl [7] believed that the demonstration of transferable reagin in the blood of asthmatic persons and guinea pigs made such a distinction untenable. The possibility that some naturally sensitive individuals may have had previous contact with an antigen subsequently found capable of producing shock was suggested by the successful sensitization of guinea pigs to inhaled horse dander.[8] Of the 65 cases summarized in Kojis's [1] review 16 gave a history of asthma or chronic respiratory disease, and 17 had injections from one day to ten years previously. Vance and Strassmann [2] noted a striking resemblance between the asthmatic and the presumably nonasthmatic patients. There was similarly no fundamental difference either in clinical symptomatology or in pathologic findings in those who had no history of prior parenteral injection.

Although the symptoms and lesions of anaphylaxis are constant for a given animal species [9] irrespective of the antigen, available information discloses no such uniformity in the human being. Conditions that surround the clinical occurrence of hypersensitive states in contrast with the experimental are far from standard. Among the variables that explain the wide differences in the allergic responses observed clinically are dosage, route of absorption, period in the development of sensitivity, concurrent disease and individual predisposition. Dependent on these various conditions and on the site of antigen antibody reaction we may see [10] the Arthus phenomenon, urticaria, eczema, asthma, hay fever, serum sickness, periarteritis nodosa, food or drug idiosyncrasy, the "tuberculin type" of reaction to microorganisms and their products, and sudden collapse and death.

With the increasing use of immunotherapy, it is important that serious reactions be made known. Where death has occurred, the postmortem investigation should consider (1) the possible primary toxicity of the product in the dosage used, (2) possible contamination of injection materials, (3) symptomatology and pathologic findings, with special attention to the role of associated disease, and (4) possible demonstration of passively transferable reagin.[11]

REPORT OF CASES

On June 19, 1945, the death of identical [12] twins after a second injection of diphtheria toxoid and pertussis antigen, alum precipitated,[13] was reported for investigation.

History.—D. M. and G. M., boys aged 10 months, were brought to St. John's Long Island City Hospital (service of Dr. James M. Dobbins) on June 19, 1945 at 7:15 a. m. D. M. was pronounced dead on arrival; the condition of G. M. was described as critical. He was cyanotic and dyspneic; respirations were shallow, rapid and labored. Oxygen was given by mask; suction was applied for aspiration of mucus; 4 cc. of nikethamide was given at 8 a. m., 3 minims (0.18 cc.) of epinephrine at 8:15 and 2 cc. of caffeine with sodium benzoate at 8:45. At this time the temperature was 99 F. Cyanosis continued to be present at intervals. One cc. of

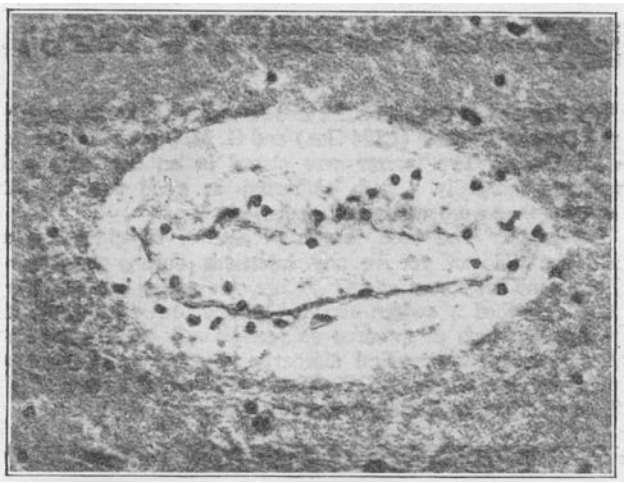

Fig. 1 (D. M.).—Section of brain showing fibrin clot in vein, perivascular edema and cellular infiltrate. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 300 diameters.

picrotoxin was given at 9:30; respirations were then noted as being 38. At 10 and 10:30 3 more minims of epinephrine were given, and at 10:45 infusion of plasma was begun. Before 40 cc. was given the subject was pronounced dead.

The family physician stated that nothing untoward was noticed immediately after the injections except that 1 twin bled slightly from the site, necessitating the application of an additional cotton pledget. The parents stated that following the first injections one month before (from another ampule of the same product) D. M. vomited, had a temperature of 101 F. and cried considerably. One-half grain (0.032 Gm.) of acetylsalicylic acid was given and by evening he was apparently well. G. M. remained symptom free after the first injection.

After the second immunizing injections, both infants cried considerably on reaching home; they vomited and consumed excessive amounts of water, each taking about two full bottles. They then "fell asleep" and when next noticed by their parents appeared "lifeless." Their position in the cribs remained unchanged, and they could be aroused only by loud noises. D. M. had a "staring" expression; his temperature was 99 F.

5. Longcope, W. T.: Susceptibility of Man to Foreign Proteins, Am. J. M. Sc. **152**: 625 (Nov.) 1916.
6. Coca, A. F., and Cooke, R. A.: Classification of Phenomena of Hypersensitiveness, J. Immunol. **8**: 163 (May) 1923.
7. Ratner, B., and Gruehl, H. L.: Identity of Animal Anaphylaxis and Human Allergy (Protein Hypersensitiveness), Proc. Soc. Exper. Biol. & Med. **27**: 574 (March) 1930.
8. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Anaphylactogenic Character of Horse Dander and Its Crossed Relationship to Horse Serum, Proc. Soc. Exper. Biol. & Med. **23**: 16 (Oct.) 1925.
9. Doerr, R.: Allergie und Anaphylaxis, in Kolle, W.; Kraus, R., and Uhlenuth, P.: Handbuch der pathog. Mikroorganismen, Jena, Gustav Fischer, 1929, vol. 1, p. 759.
10. Rich, A. R.: The Different Forms of Hypersensitivity to Foreign Protein, in the Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 330.
11. Lund, H., and Hunt, E. L.: Postmortem Diagnosis of Allergic Shock, Arch. Path. **32**: 664 (Oct.) 1941.
12. The physician in attendance at their birth stated that they had a common placenta.
13. The product of a reliable pharmaceutical manufacturing company whose name is withheld.

At 11:30 p. m., when his diaper was changed, he was found to be "ice cold and wringing wet with perspiration." The parents explained that they regarded these symptoms as expected effects of the injections and therefore did not summon medical aid until 5:30 a. m., when D. M. appeared to be dead and G. M. gravely ill.

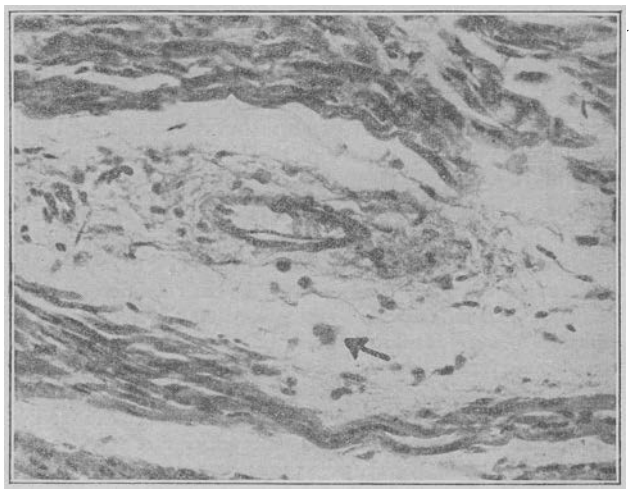

Fig. 2 (D. M.).—Section of heart showing paravascular mononuclear cellular infiltration. Note the binucleated cell. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 275 diameters.

The twins were born at eight months gestation, D. M. weighing 2 pounds 8 ounces (1,134 Gm.) and G. M. 5 pounds 4 ounces (2,381 Gm.). The former was placed in an incubator and developed normally. Both continued in good health. At 6 months they were vaccinated against smallpox.

The mother had been inoculated against diphtheria as a child but did not receive any injections during pregnancy. There is no history of allergy on her side of the family. The father described a sudden swelling of the lower lip while in the Army, which disappeared as precipitously as it came on. After receiving his medical discharge he experienced another similar episode, which was diagnosed as "allergic" by a medical officer who happened to be present at the time.

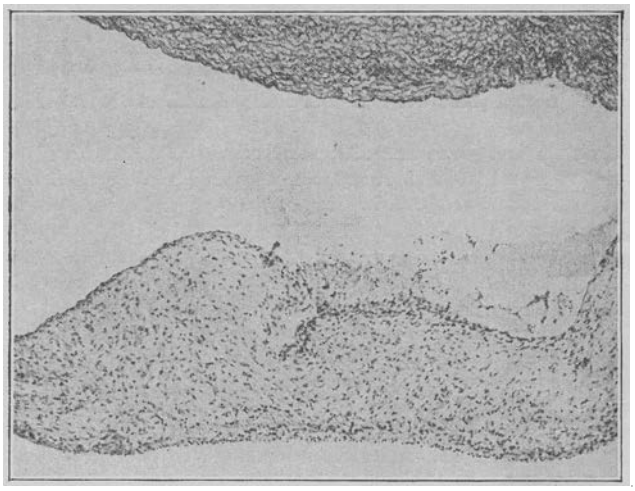

Fig. 3 (D. M.).—Section of aortic valve showing endothelial swelling and increased cellularity of leaflet. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 60 diameters.

Postmortem Study.—At autopsy both twins [14] were well nourished and well developed. The sites of recent inoculation in the deltoid region were marked by minute puncture wounds of the skin and a small amount of hemorrhage in the underlying fat. There was no gross evidence of significant inflammatory reaction. The brain in each case felt softer than usual. The subarachnoid space contained excess fluid. The meninges, mastoids, middle ears and tonsils showed no evidence of infection. There was no regurgitation or aspiration of stomach contents. The thymus of D. M. weighed 28.4 Gm. and showed numerous petechiae; that of G. M. weighed 34.1 Gm. The adrenals of D. M. weighed 3.0 Gm. and those of G. M. 3.2 Gm.; they showed no gross abnormalities. The heart contained both clotted and fluid blood in each instance. There were epicardial and pleural petechiae. The lungs were salmon pink and air containing for the most part. In G. M. the parenchyma on section showed edema; in D. M. there were conspicuous focal hemorrhages in the dependent portions. The mucosa of the larynx, trachea and bronchi was pale and free of exudate. The bronchopulmonary lymph nodes were not enlarged. The liver of D. M. weighed 350 Gm., that of G. M. 370 Gm. In D. M. it showed extreme congestion. The spleen and kidneys were moderately congested. The gastrointestinal tract showed no gross lesions. The lymphatic follicles were normally conspicuous, as were the mesenteric nodes. The pancreas, biliary passages and genital organs were natural. There were no skeletal abnormalities. Postmortem lung cultures were made and found sterile in each instance, and in addition a sterile postmortem culture was obtained from the spleen of D. M.

Postmortem serum was tested on four members of the laboratory staff for the presence of reagin after the prior

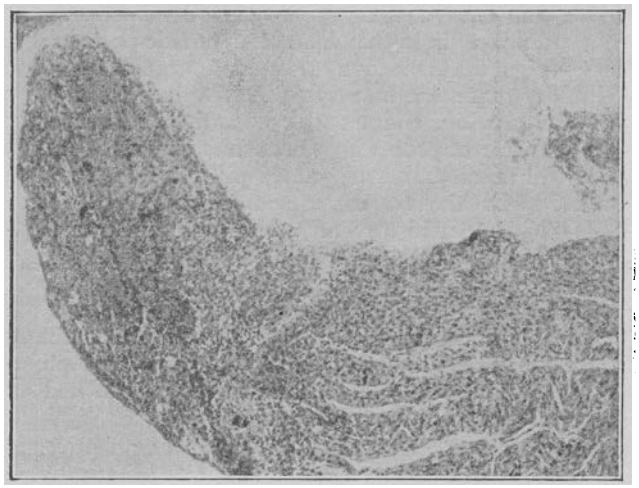

Fig. 4 (G. M.).—Section of cardiac papillary muscle showing necrosis and hemorrhage. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 80 diameters.

intracutaneous injection of the biologic product, with negative results.[15] This contrasts with the success of Lund and Hunt [11] in eliciting a Prausnitz-Kustner reaction for the first time with postmortem serum. It is noteworthy in this connection that negative reaction to passive transfer was also recorded by Walzer [16] in a case of shock following injection of horse serum. The attempt [17] to effect passive transfer from postmortem serum in these cases to guinea pigs was also unsuccessful.

The contents of the vial used in immunizing the twins, and of the vials bearing the same lot number submitted by the manufacturer, were examined by Dr. Jules Freund of the Bureau of Laboratories, Department of Health, City of New York, and the following results were obtained: "The vaccine was found to be sterile; that is, the sterility test required by the National Institute of Health for biological products was satisfactory. The microscopic picture showed formed elements of the size and shape and staining qualities of Bordet-Gengou bacilli. Tests carried out on the skin of rabbits showed that there was no free diphtheria toxin in the vaccine. The identity test showed that the vaccine contained diphtheria toxoid, that is, combined with the diphtheria antitoxin, 0.5 cc. amounts of the vaccine injected into the peritoneal cavities of white mice

14. Unless otherwise stated, the pathologic descriptions apply to both subjects.

15. Dr. Bret Ratner examined the sites of injection in the 4 volunteers.

16. Walzer, M.: New Diagnostic Methods in Asthma, Long Island M. J. **60**: 85, 1932.

17. Dr. Jules Freund, Bureau of Laboratories, City of New York.

did not cause obvious toxic reactions. (The latter test is routinely done on biologicals for harmlessness.)"

The histopathologic study disclosed lesions consistent with death in anaphylactic shock. The skin at the site of inoculation (studied in G. M.) showed swelling and acute degeneration of collagen, arteriolar degenerative changes, thrombosis and hemorrhage. Bacterial stains showed numerous forms resembling Hemophilus pertussis. The follicles of the spleen, lymph nodes and gastrointestinal tract showed conspicuous macrophages containing abundant nuclear particles and cytoplasmic débris. There were numerous eosinophils in the lymphatic tissues. The thymus showed foci of hemorrhage and necrosis, and extremely constricted arteries whose walls showed edema, eosinophilia and endothelial swelling and proliferation.

The brain showed capillovenous engorgement, perivascular hemorrhages, arteriolar narrowing and diffuse degenerative changes of some arterial walls, with cellular infiltration of the vessels and the surrounding space; this was mainly mononuclear, with occasional polymorphonuclears and eosinophils. Many nerve cells showed acute degenerative changes.

Heart sections showed focal necrosis of muscle, more accentuated beneath the epicardium and endocardium. Constricted lumens, edema and necrosis of some arterial walls were observed, as were swelling and some proliferation of the endothelium. Perivascular hemorrhages were frequent in relation to such

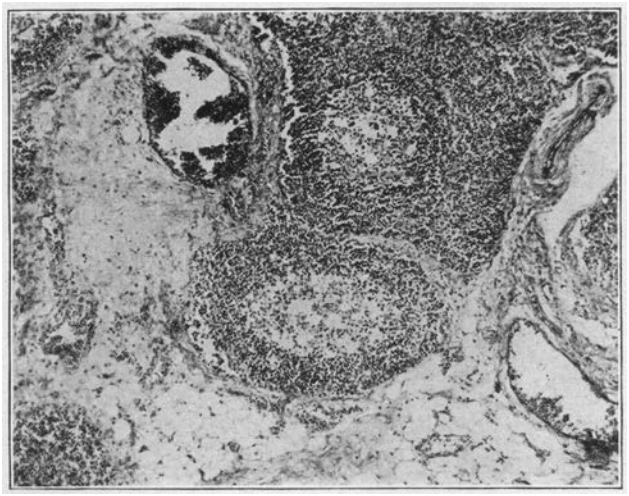

Fig. 5 (D. M.).—Hilus of lung, showing macrophagocytic activity in lymph follicles, constricted artery, dilated veins and interstitial edema. Hematoxylin and eosin. Slightly reduced from a photograph with a magnification of 60 diameters.

areas. Sections of aortic and mitral cusps showed endothelial swelling and increased mononuclear cells throughout the leaflets.

The respiratory epithelium showed excellent preservation with intact cilia. (Fulminating respiratory infection, the most common cause of unexpected death during infancy, was thereby excluded.[18]) Extreme narrowing of some bronchial and many arterial and arteriolar lumens was conspicuous. Mononuclear, slight polynuclear and slight eosinophilic infiltration occurred in both bronchial and pulmonary arterial walls. The pulmonary veins and alveolar septal capillaries were deeply engorged. The lymphatics were dilated with abundant protein precipitate. There were foci of pulmonary edema, both interstitial and intra-alveolar, and foci of hemorrhage and early intra-alveolar exudate, mainly polymorphonuclear, especially in the case of D. M. Fibrinous exudate and bacteria were not seen.

The liver sections showed extensive parenchymatous degeneration, most evident in the central two thirds of the lobule; this took the form of granular and hydropic change, with pyknosis of nuclei and chromatolysis. The sinusoids contained abundant leukocytes, with a moderate number of eosinophils. Occasional focal necrosis was seen, mononuclears filling the parenchymatous defect; some multinucleated hepatic cells occurred in peripheral portions of some lobules.

18. Werne, J.: Postmortem Evidence of Acute Infection in Unexpected Death in Infancy, Am. J. Path. **18**: 759 (July) 1942. Werne, J., and Garrow, J.: Sudden Deaths in Infancy, Bull. New York Acad. Med. **21**: 445 (Aug.) 1945.

COMMENT

The widespread visceral lesions encountered seem adequate to explain the profound shock observed clinically. The histological appearances point to acute vascular injury as the underlying cause. This results from the basic physiological disturbances that seem

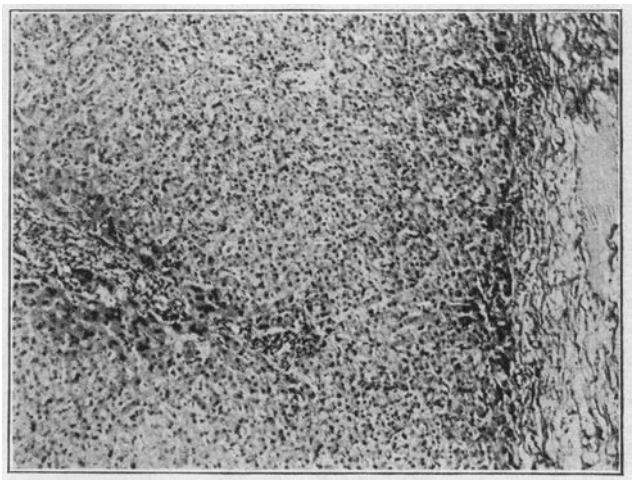

Fig. 6 (D. M.).—Section of liver showing parenchymatous degeneration, increased leukocytes in sinusoids and capsular edema. Note multinucleated hepatic cells. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 60 diameters.

adequate to explain the apparently diverse manifestations of the anaphylactic state: contraction of smooth muscle and increased capillary permeability.[19] The former, if severe enough in bronchiolar or pulmonary arteriolar muscle, is believed to cause death by asphyxia or dilatation of the right ventricle, as in the guinea pig [20] and the rabbit [21] respectively.

In 14 of the 19 autopsies taken from the literature and in the 7 they added, Vance and Strassmann [2] noted either a clinical history of dyspnea or the postmortem

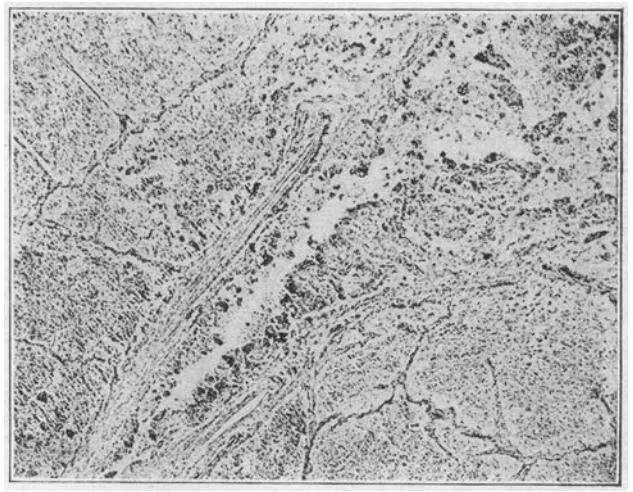

Fig. 7 (D. M.).—Section of thymus showing constriction of artery, hemorrhage and necrosis. Reticulum stain. Slightly reduced from a photomicrograph with a magnification of 40 diameters.

finding of emphysema. This they interpreted as indicating asphyxial death by bronchospasm. In the cases

19. Seegal, B. C., in Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C Thomas, Publisher, 1935, chap. 6.

20. Gay, F. P., and Southard, E. E.: Further Studies on Anaphylaxis: III. The Relative Specificity of Anaphylaxis, J. M. Research **19**: 5, 1908. Auer, J., and Lewis, P. A.: The Pathology of the Immediate Reaction of Anaphylaxis in the Guinea Pig, J. Exper. Med. **12**: 151, 1910.

21. Coca, A. F.: The Mechanism of the Anaphylaxis Reaction in the Rabbit, J. Immunol. **4**: 219 (July) 1919. Drinker, C. K., and Bronfenbrenner, J.: Pulmonary Circulation in Anaphylactic Shock, ibid. **9**: 387 (Sept.) 1924.

reported here there was neither clinical nor pathologic evidence for significant bronchial obstruction as a cause of death. Increased capillary permeability, as emphasized by Manwaring and his associates [22] and by Moon,[23] among others, may lead to reversible shock, protracted shock or instantaneous death. Collapse

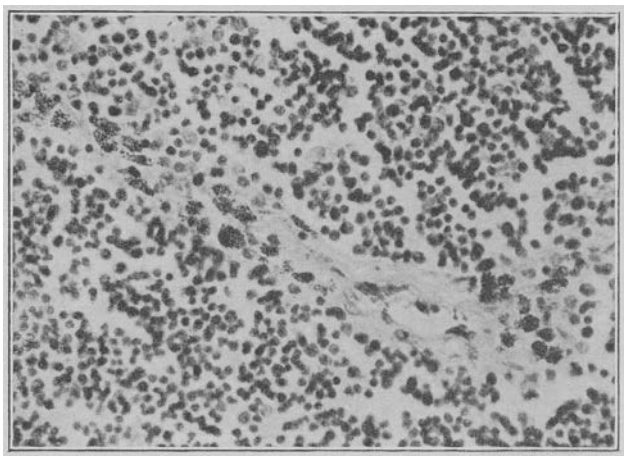

Fig. 8 (D. M.).—Section of thymus showing vascular edema and eosinophilia. Giemsa stain. Slightly reduced from a photomicrograph with a magnification of 300 diameters.

referable to this widespread vascular disturbance is the usual expression of anaphylaxis in the dog and was the conspicuous feature in the cases presented here. With respect to the clinical appearance of shock, rather than respiratory difficulty, as with respect to some of the visceral lesions, particularly the hepatic, these cases recall the one reported by Dean,[24] in which death occurred seventy minutes after the fourth injection of tetanus antitoxin.

The morphologic appearances are in accord with the direct observations of Abell and Schenck [25] in shocked

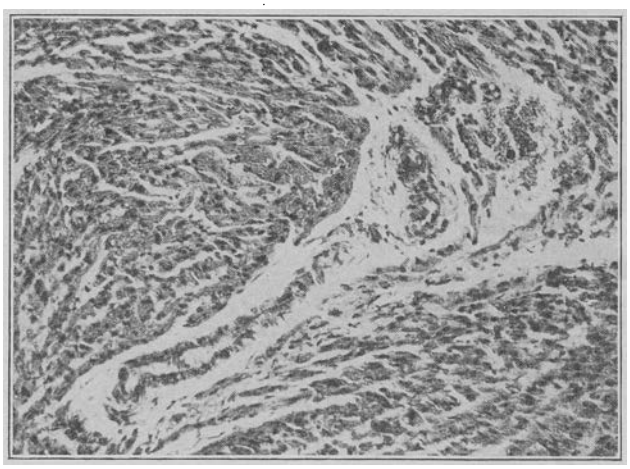

Fig. 9 (G. M.).—Section of heart showing constriction of arterioles and focal hemorrhage. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 150 diameters.

rabbits. They describe arteriolar contraction with obliteration of lumens and margination and migration of leukocytes, which formed obstructive clumps, thereby stopping circulation. Endothelial destruction with hemorrhage was seen in the most severe reactions. McMaster [26] similarly observed vascular spasm as a local effect of the introduction of antigen in a previously sensitized mouse. Arteriolar spasm has been emphasized by Ratner [27] as explaining the characteristic allergic phenomenon of wheal formation.

The sixteen and twenty hour intervals elapsing between the shocking injection and death in the cases reported here contrast with the short interval in the majority of recorded instances. In the 26 necropsies reviewed by Vance and Strassmann [2] only 5 of the patients lived from one to twenty-three hours.

Waldbott [28] reported 3 cases of allergic shock in which the acute symptoms were followed by signs of bronchopneumonia. Recovery occurred in 2. The third showed at autopsy congestion and edema of cerebral and meningeal blood vessels, few cerebellar petechiae, areas of solidification in both lungs, congestion and emphysema; on microscopic study, patchy bronchopneumonia, massive intra-alveolar hemorrhage and edema; necrosis of alveolar epithelium, and emphysema were noted. In this case dyspnea, cough and

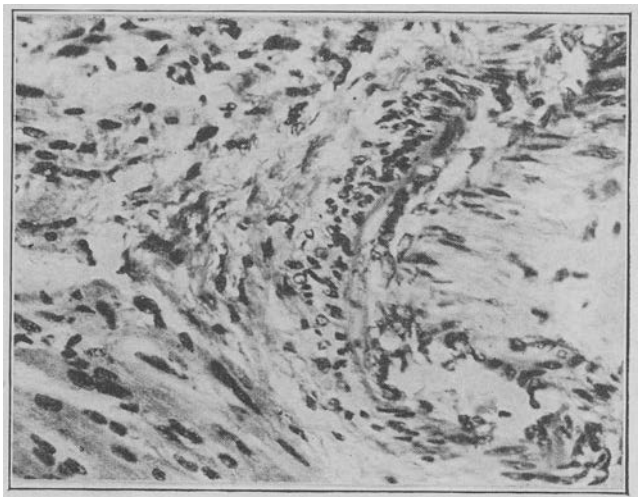

Fig. 10 (D. M.).—Section of heart showing extreme narrowing and edema of arteriole. Hematoxylin and eosin. Slightly reduced from a photomicrograph with a magnification of 300 diameters.

unconsciousness had developed four hours after the intravenous injection of typhoid vaccine, and death occurred on the third day. The possibility of delayed reaction should be considered whenever foreign protein is administered. Prompt recognition of untoward signs may avert a fatal outcome. Successful treatment of anaphylactic shock was reported by Blotner [29] with saline solution and by Raynolds [30] with plasma. These important aids in the management of shock should therefore be routinely employed, in addition to such routine therapy as epinephrine.

In view of the high mortality that accompanies both diphtheria and pertussis during infancy, it is hoped that the publication of a report of these two fatalities will not deter the profession from continuing to practice immunization. It will be recalled that the family history was positive for allergy; the father suffered from what appeared to be episodes of angioneurotic edema.

22. Manwaring, W. H.; Chilcote, R. C., and Hosepian, V. M.: Capillary Permeability in Anaphylaxis, J. A. M. A. **80:** 303 (Feb. 3) 1923.
23. Moon, V. H.: Pathology and Mechanism of Anaphylaxis, Ann. Int. Med. **12:** 205 (Aug.) 1938.
24. Dean, H. R.: Histology of Case of Anaphylactic Shock, J. Path. & Bact. **25:** 305 (July) 1922.
25. Abell, R. G., and Schenck, H. P.: Microscopic Observations on Behavior of Living Blood Vessels of Rabbit During Reaction of Anaphylaxis, J. Immunol. **34:** 195 (March) 1938.
26. McMaster, P. D.: Peripheral Vascular Reactions in Anaphylactic Shock of the Mouse, Am. J. Path. **17:** 457 (May) 1941.
27. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, Williams & Wilkins Company, 1943, p. 632.
28. Waldbott, G. L.: Allergic Death: Protracted Shock, Arch. Int. Med. **54:** 597 (Oct.) 1934.
29. Blotner, H.: Anaphylactic Shock with Hemoconcentration Treated Intravenously with Saline Solution, J. A. M. A. **118:** 219 (Jan. 17) 1942.
30. Raynolds, A. H.: Plasma Treatment of Severe Near-Fatal Anaphylactic Shock, J. Allergy **14:** 495 (Sept.) 1943.

That heredity is dominant in the anaphylactic state has been emphasized by Ratner and his associates.[31] Landsteiner and Chase [32] and Chase [33] demonstrated experimentally the role of heredity in both local (cutaneous) and general hypersensitivity. Allergic manifestations in seven pairs of identical twins were reported by Criep.[34] It would seem that the influences of heredity and twinning deserve weight as determinants of individual predisposition in the cases reported here. A search of the literature disclosed no other fatalities following inoculation with pertussis antigen and diphtheria toxoid, whether separately or combined.

After being notified of the deaths, the manufacturer recalled the entire batch from which the biologic product had been dispensed. A search of all records of complaint was immediately instituted. To date no reports of serious reactions have been received, and all tests on the lot in question were found satisfactory.

Kendrick,[35] in a field study of alum-precipitated combined pertussis and diphtheria toxoid, found among records of local and general reactions in 900 children only a few that were described as pronounced. Of further interest in connection with the degree of possible hazard attached to some immunizations is the experience of Friedman,[36] who gave 109 allergic children tetanus and diphtheria toxoid without untoward reactions. Bigler and Werner [37] observed but 2 instances of allergic response in 300 children receiving tetanus toxoid or combined diphtheria and tetanus toxoids. Cooke and his associates [38] reported generalized urticaria following the second injection of tetanus toxoid in an asthmatic patient, and Cunningham [39] reported the occurrence of anaphylaxis following a second injection of toxoid in an adult who had previously had serum sickness. The first patient gave positive skin tests to Gerna and Witte peptone, and the second to Witte peptone; both recovered. Deaths following the intravenous injection of typhoid vaccine have been recorded.[40]

SUMMARY

Identical twins died in delayed anaphylactic shock. The widespread occurrence of lesions referable to arterial spasm and increased endothelial permeability contribute further evidence to the basic role of vascular injury in the hypersensitive state.[41]

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REMISSIONS IN THYROTOXICOSIS AFTER DISCONTINUING THIOURACIL

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A review of the literature has failed to reveal information which might serve to evaluate thiouracil as a possible form of treatment for permanent cure of thyrotoxicosis. The main reason for this is that too few patients have been followed for a sufficiently long period to warrant definite conclusions. The drug is now released for general distribution, and most physicians have the impression that it has no other use than as a preoperative form of therapy. Since a review of our series of 80 patients treated with thiouracil for over two months revealed a very definite pattern of behavior, we considered that enough data were now at hand to justify a few important tentative conclusions that might be helpful as a guide in the treatment of thyrotoxicosis with this preparation.

REVIEW OF THE LITERATURE

Apparently Palmer [1] is the only author who has differentiated the nodular from the non-nodular toxic goiters when determining the effect of thiouracil in the production of a therapeutic remission in patients with thyrotoxicosis. It is our opinion that this differentiation is an important one, first because the nodular goiters respond less satisfactorily to thiouracil treatment, second because, although the toxic clinical manifestations of nodular goiters are more insidious, they possess less tendency to natural remissions, and third because of the recognized possibility that a certain number of adenomatous goiters will develop carcinoma. It was observed by Palmer [1] that all the 9 cases of thyrotoxicosis observed by her in which there was no evidence of a recurrence of the disease after the medication had been discontinued for six months were of the diffuse hyperplastic type. She also stated that thus far no patient with a nodular thyroid had experienced a remission of more than four months after treatment with thiouracil was discontinued. No other information concerning these patients was supplied.

Williams and Clute [2] reported 98 cases of thyrotoxicosis treated with the drug for more than four months. Thiouracil was administered continuously for more than a year in 10 of these, for more than eight months in 36 and for more than four months in 52. In only 5 was the administration of the drug discontinued and their subsequent course observed during the time when all therapeutic measures were omitted. One of these had been treated for six months and the rest for one year. One had remained normal for a period of six months and 4 for two to three months. Another patient experienced a relapse after two months. Other details, such as the type of goiter and the initial basal metabolic rate were not given. The 20 per cent relapse in this group was not of statistical significance. One other observation of theirs also coincided with the experience of others, namely that at least 2 patients who discontinued treatment of their own accord, on three

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