The results of administering amiphenazole to 16 patients are given. Carbon dioxide tension was lowered significantly in eight cases, and this was associated with an increase in ventilation.

It is suggested that amiphenazole has a place in the treatment of carbon dioxide retention. Although the effects are noted with smaller doses, it is advisable that 150 mg. should be given intravenously, and the results suggest that there might be a place for continuing the drug intramuscularly for some time.

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REFERENCES

- Berman, L. B., O'Connor, T. F., and Luchsinger, P. C. (1960). *J. appl. Physiol.*, **15**, 393.
 Campbell, E. J. M. (1961). *Brit. med. J.*, **1**, 286.
 Galdston, M. (1955). *Amer. J. Med.*, **19**, 516.
 Manfredi, F., Sieker, H. O., Spoto, A. P., and Saltzman, H. A. (1960). *J. Amer. med. Ass.*, **173**, 999.
 Naimark, A., Brodovsky, D. M., and Cherniack, R. M. (1960). *Amer. J. Med.*, **28**, 368.
 Riley, R. L., Campbell, E. J. M., and Shepard, R. H. (1957). *J. appl. Physiol.*, **11**, 245.
 Shaw, F. H., and Bentley, G. (1952). *Nature (Lond.)*, **169**, 712.
 Simpson, T., and Hawkins, W. (1959). *Brit. med. J.*, **1**, 508.
 Wégria, R., Capeci, N., Kiss, G., Glaviano, V. V., Keating, J. H., and Hilton, J. G. (1955). *Amer. J. Med.*, **19**, 509.
 Westlake, E. K., and Campbell, E. J. M. (1959). *Brit. med. J.*, **1**, 274.

THROMBOCYTOPENIC PURPURA AFTER SMALLPOX VACCINATION

BY

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Vaccination against smallpox is rarely complicated by severe reactions. Some of these so-called post-vaccination reactions have contributed to a temporary suspension of compulsory vaccination in some European countries. Other countries demand a certificate of a recent vaccination or revaccination before allowing entry. Fortunately, these reactions are not often encountered. Nevertheless it may be useful to report some of these rare complications. For this reason the case histories of two patients who suffered from "idiopathic" thrombocytopenic purpura after vaccination against smallpox are here recorded.

Case 1

A man aged 58 was revaccinated against smallpox on July 20, 1949. Primary vaccination had been performed when he was 1 year old. A slight rise in temperature, up to 37.7° C., occurred on July 29. On August 4, while on holiday abroad, he noticed that his gums were bleeding. Next day the tendency to bleed had increased, a haemorrhagic blister appeared in the mouth, and petechiae were noticed on the arms and legs. He returned home and was first seen on August 15.

On examination his general condition was fair. Some small petechiae were noticed in the oral cavity. Large

haemorrhages were scattered over the trunk, abdomen, and lower extremities, and numerous smaller petechiae were noticed on both upper and lower extremities. Apart from

FIG. 1.—Clinical course of Case 1.

a slight enlargement of the heart and a palpable liver edge no other abnormalities could be detected. The spleen was not felt. Blood-pressure was 150/100. The tourniquet test was strongly positive.

Laboratory Investigations.—The urine contained traces of albumin and urobilinogen and an occasional erythrocyte. Indirect serum bilirubin 1.5 mg./100 ml.; E.S.R. 4 mm. after one hour; haemoglobin 13.2 g./100 ml.; R.B.C. 4,400,000/c.mm.; W.B.C. 6,700/c.mm. (eosinophils 2%, basophils 1%, metamyelocytes 1%, stabs 2%, polymorphonuclear leucocytes 66%, lymphocytes 22%, monocytes 6%); platelets 13,000/c.mm. Bleeding-time (Duke), 11 min.; coagulation time (Lee and White), 9 min. 30 sec. Clot retraction was greatly affected. The bone-marrow was active and of a normal cellularity, with normal erythrocyte: leucocyte ratio, normal reticulum activity, but a marked increase of megakaryocytes, promegakaryocytes, and megakaryoblasts. The production of platelets was deranged. This picture was compatible with idiopathic thrombocytopenic purpura.

Blood transfusions caused a transient rise in the number of platelets, soon followed, however, by a relapse (Fig. 1). After mobilization new petechiae developed. Because of a persistent thrombocytopenic purpura, splenectomy was performed in December. The operation was followed by a dramatic rise in the number of platelets, and the patient was discharged in an excellent clinical and haematological condition.

Not until 1953, when the platelet count was completely normal, could a serological examination be performed. At that time adequate antibodies against platelets could not be demonstrated. Also, incubation of serum and vaccine gave negative results.

Case 2

A 19-year-old youth was referred to the military hospital on December 16, 1957, because of a generalized petechial eruption and a haemorrhagic diathesis. On December 4 primary vaccination against smallpox was performed. Eight days later he developed fever and felt ill. After a few days he had no complaint apart from fatigue and weakness, and the fever gradually subsided. During the febrile period tablets containing aspirin, phenacetin, and caffeine were taken. On December 13 he had nose-bleedings, and two days later he noticed haemorrhages from the mouth and lips and subcutaneous bleeding in the lower extremities.

On examination mucosal haemorrhage was detected in the mouth and on the right side of the nose. Disseminated petechial eruption was noted, especially on the extremities, more numerous proximally and more on the legs than on the arms. Large subcutaneous haemorrhages also occurred in the legs. Enlarged but indolent lymph nodes were felt in the left axilla. The spleen was not palpable. Both tourniquet test and Jürgens's pinch-phenomenon were positive. There were no haemorrhages in the fundus oculi.

Laboratory Investigations.—Haemoglobin 13.9 g./100 ml.; R.B.C. 4,300,000/c.mm.; W.B.C. 7,000/c.mm. (eosinophils 2%, stabs 5%, neutrophils 52%, lymphocytes 39%, monocytes 2%); platelets 5,000/c.mm. Coagulation time, 6 min. 30 sec.; bleeding-time 14 min.; prothrombin time 14 sec. (control 15 sec.). Clot retraction was very disturbed. Vitamin C content of blood was: 4 mg./litre, calcium 9.7 mg./100 ml. The antistreptolysin titre was normal (<100 units). The urine did not contain erythrocytes. The renal function tests were normal. Bone-marrow biopsy was not performed. Complete antibodies against platelets could not be demonstrated. The results after incubation with smallpox vaccine and complement were also negative (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service).

A diagnosis of acute thrombocytopenic purpura was made and 20 mg. of prednisone was given daily. The day after therapy was started no further petechial eruption was noted. There was a rise in the platelet count to 24,000 on the second day, and to 337,000 in the second week (Fig. 2). The general condition gradually improved and the patient was discharged in excellent condition. On May 30, 1958, his platelet count was 299,000/c.mm.

FIG. 2.—Clinical course of Case 2.

Discussion

From these cases it seems conceivable that thrombocytopenia was related to the preceding vaccination. A connexion between purpura and vaccination against smallpox has been described in a few cases (Nocke, 1921; Heaton, 1940; Regamey, 1940; Veldkamp, 1952). In most of these cases it was not made sufficiently clear whether thrombocytopenia existed and if vaccination was the only aetiological possibility (see Table). Only cases of primary vaccination complicated by thrombocytopenia have been collected from the literature. The haemorrhagic diathesis is characterized by a generalized purpura. Large haematomas are seen. Epistaxis has often been reported; mucosal bleedings from mouth, tongue, lips, and conjunctivae are less frequent. In fact the clinical and haematological picture does not differ from that of so-called idiopathic thrombocytopenic purpura.

Our Case 2 is an example of the self-limited form of the disease. Case 1, however, ran a chronic course: complete cure was achieved only after splenectomy. The patient had been vaccinated against smallpox before, and, so far as is known, it was uneventful. Regamey's (1940) patient developed a chronic thrombocytopenic purpura after primary vaccination, complicated by a generalized vaccinia. Purpura was noted on the 32nd day after vaccination. Splenectomy was performed and the patient died.

Apart from infections by the vaccinia virus itself or by micro-organisms, complications after vaccination have been ascribed to hypersensitivity reactions. Even the origin of the area (the extensive inflammatory induration on the eighth or ninth day of "typical primary vaccinia") was regarded as an "allergic" one (von Pirquet, 1907). It is most likely that all kinds of exanthemas are hypersensitivity reactions. Glanzmann (1927) was the first to suggest this as a cause of post-vaccination encephalitis, as did Koster and van Tilburg (1953) for glomerulonephritis after primary vaccination. On the other hand, thrombocytopenic purpura is thought to be the result of an allergic reaction—an obvious conclusion in cases of drug-induced thrombocytopenia, like apronal ("sedormid") and quinidine purpuras. Much attention has been given to it since Ackroyd (1949) demonstrated antibodies against platelets. Miescher and Straessle (1956) suggested two possibilities by which platelets may be sensitized by autoantibodies: (1) The platelet itself or the platelet combined with another substance—for instance, apronal—acts as an antigen. (2) The platelet acts as a "shock organ"—that is, it becomes involved in an antigen-antibody reaction of totally different character. One may consider the possi-

Cases with Post-vaccination Thrombocytopenia Collected from Literature

Author	Primary vaccination (P) or Revaccination (R)	Day of Petechial Eruption after Vaccination	Acute or Chronic Course	Treatment			Outcome	Remarks
				Blood Transfusion	Corticoids	Splenectomy		
Impfbericht (1905)* ..	P	16	Acute	?	—	—	Dead	In course of generalized vaccinia
Nocke (1921)	P	10	"	—	—	—	Alive	
Heaton (1940)	P	14	"	—	—	—	"	
Regamey (1940)	P	32	Chronic	+	—	+	Dead	
Veldkamp (1952) ..	P	11	Acute	—	—	—	Alive	No information
Harrington <i>et al.</i> (1953)	?	?	?	?	?	?	?	
Case 1	R	15	Chronic	+	—	+	Alive	
Case 2	P	9	Acute	—	+	—	"	

* Cited by Lentz and Gins (1927).

bility that antibodies not only destroy platelets but also delay the maturation of megakaryocytes in the bone-marrow.

Harrington *et al.* (1953) were not able to demonstrate the presence of antibodies against platelets in the blood of a patient with thrombocytopenic purpura after primary vaccination. In both our cases demonstration of antibodies failed, even after incubation with vaccine and complement. In thrombocytopenias after other viral diseases (measles, chicken-pox, infectious mononucleosis, mumps, infectious hepatitis) antibodies could not be demonstrated. Only Ferguson (1960) found antibodies in some cases of rubella. Immunization against whooping-cough, tetanus, and poliomyelitis may be followed by thrombocytopenia, but antibodies are never found. Negative results have been published by van Creveld (1959) after vaccination against poliomyelitis. No history of hypersensitivity was known in our patients. In the period of haemorrhagic diathesis no other allergic manifestations were noted.

The frequency of thrombocytopenic purpura after vaccination against smallpox seems to be very low.

Summary

Case histories of two patients with thrombocytopenic purpura after smallpox vaccination are given; the first ran a chronic course, the second showed the acute form. Recovery was attained after splenectomy and prednisone respectively. This vaccination hazard may be explained as an allergic phenomenon.

REFERENCES

- Ackroyd, J. F. (1949). *Clin. Sci.*, **7**, 249.
 Creveld, S. van (1959). *Ned. T. Geneesk.*, **103**, 57.
 Ferguson, A. W. (1960). *Pediatrics*, **25**, 400.
 Glanzmann, E. (1927). *Schweiz. med. Wschr.*, **57**, 145.
 Harrington, W. J., Sprague, C. C., Minnich, V., Moore, C. V., Aulvin, R. C., and Dubach, R. (1953). *Ann. intern. Med.*, **38**, 433.
 Heaton, T. G. (1940). *Canad. med. Ass. J.*, **43**, 593.
 Koster, L., and Tilburg, J. Q. van (1953). *Ned. T. Geneesk.*, **97**, 17.
 Lentz, O., and Gins, H. A. (1927). In A. Czerny and H. Opitz's *Handbuch der Pockenbekämpfung und Impfung*, p. 444. Schoetz, Berlin.
 Miescher, P., and Straessle, R. (1956). *Vox Sang. (Basel)*, **1**, 83.
 Nocke, H. (1921). *Mtschr. Kinderheilk.*, **19**, 455.
 Pirquet, C. von (1907). *Klinische Studien über Vakzination und vakzinale Allergie*, p. 141. Deuticke, Leipzig, Wien.
 Regamey, E. (1940). *Schweiz. med. Wschr.*, **70**, 697.
 Veldkamp, A. L. (1952). *Ned. T. Geneesk.*, **96**, 2138.
 Wintrobe, M. M. (1956). *Clinical Hematology*, 4th ed. Kimpton, London.

"Because Government grants [in the U.S.A.] have concentrated so heavily on the encouragement of research and because medical schools have the facilities and personnel to conduct research, most of the money in the bio-medical field has gone their way. However, medical schools have other and equally important jobs to do, such as training, education and service. Research is only one cylinder in the medical school motor. As a matter of fact, medical research itself won't get very far in the future if medical schools are not kept running on all of them. With grants for research projects, grants for research facilities, grants for research trainees, grants for research equipment, grants for research personnel and grants for anything in any way, shape or form, as long as they are for research, the 'central function' (which is education) and the 'proper internal balance' (among their major responsibilities) of medical schools have been seriously distorted. At matters stand, the medical school motor is not hitting on all cylinders and is in need of a tune-up. Uncle Sam's tinkering is not helping matters very much." (1960-61 *Annual Report of the John and Mary R. Markle Foundation*, President's Report.)

Preliminary Communications

Atropine Premedication for Electric Convulsion Therapy

When modified electric convulsion therapy (E.C.T.) is given to a patient under the influence of a hypnotic and a muscle relaxant it is common to give atropine as a premedication. It is usually recommended that this should be given subcutaneously half an hour before treatment (Wylie and Churchill-Davidson, 1960), but there are theoretical and practical disadvantages to this, and a simple clinical investigation was carried out to see if the intravenous route for the atropine would be more satisfactory.

Method.—A total of 200 patients undergoing E.C.T. were investigated. All received thiopentone (200–300 mg.) and suxamethonium (30–50 mg.) before the shock was administered. After the injection each patient was ventilated with 100% oxygen for one minute. The 100 patients in group A received 1 mg. of atropine *subcutaneously* half an hour before treatment and the 100 patients in group B received 1 mg. of atropine *intravenously* immediately preceding the thiopentone. The heart rate was monitored by palpation of the radial pulse and auscultation of the apex beat. The rate was recorded for 15 seconds before the shock and for 60 seconds after it. Group A contained 76 men and 24 women, and group B 77 men and 23 women. The age distribution of the two groups was nearly identical.

RESULTS

Group A.—Twenty-two patients had complete disappearance of heart sounds and pulse for between one and a half and five seconds from the beginning of the electric shock. When the pulse returned the rate rose within a few beats to its pre-shock level, or to a higher figure if the fit was not well modified.

Group B.—One patient developed a severe bradycardia for five seconds. One patient had complete disappearance of heart sounds and pulse for four seconds (this case is discussed below).

In both these cases the pulse rate returned to its initial level a few beats after it had returned.

The only other abnormality of rhythm noted was the occurrence of extrasystoles, either during the convulsion or in the succeeding minute. These were noted 11 times in group A and eight times in group B. The particular patient, rather than the route of premedication, appeared to be the more important factor, since two patients, each treated once in group A and once in group B, developed extrasystoles on both occasions.

DISCUSSION

It is well recognized that unmodified E.C.T. can produce serious strains on the cardiovascular system. The commonest abnormality is a disturbance of cardiac rhythm, usually vagal in origin. The muscular activity of the convulsion produces a marked increase in cardiac work which not all hearts are able to tolerate, particularly if hypoxia occurs owing to inadequate preoxygenation. The blood-pressure and pulse are also modified by the alteration in intrathoracic pressure during the tonic phase of the convulsion (Richardson *et al.*, 1957).