Our departmental collection of pertussis strains included ten which were used by manufacturer C to produce vaccines in 1955, and six which were used by manufacturer B. These were likewise subjected to slide-agglutination, with the results given in Table IV.

Clearly, an individual batch of vaccine may not necessarily contain the full range of type-specific antigens.

Discussion

The results of this investigation suggest that the strains of *Bord. pertussis* frequently encountered in this country in the past, and probably used in the manufacture of pertussis vaccines, contained predominantly antigens 1, 2, and 4 and less frequently antigens 1, 2, 3, and 4. Vaccines deficient in antigen 3 may give incomplete immunity against infection by strains containing antigens 1 and 3, which appear to be causing most cases of whooping-cough in this country at the present time. Attention is drawn particularly to the three strains (all type 1, 3) isolated from vaccinated patients, one of whom had a severe infection.

The weakness of the argument lies in the relatively small number of strains and vaccines which have been examined. However, the object of this communication is to indicate the need for a fuller and more widespread investigation of freshly isolated strains of *Bord. pertussis* and comparison of their antigenic composition with that of pertussis vaccines, not only in this country but also in other countries where vaccination is less effective than may be expected (Petrilla and Barsy, 1959; Edsall *et al.*, 1962).

This investigation has been confined to the heat-labile antigens originally designated by Andersen as (major) antigens 1, 2, 3, and 4; it has not included other heat-labile (minor) antigens which are capable of producing only low titres of antibody (Andersen, 1953; Eldering *et al.*, 1957; Preston and Te Punga, 1959). Even antigen 4 has been considered a minor antigen by Eldering *et al.* (1962), and with this I would agree, for we have never produced high titres of antibody 4 in our rabbits. Moreover, no strains have been found to possess antigen 4 in the absence of antigen 2. It seems, then, that, in this country at least, investigations could be confined to the major antigens (1, 2, and 3) unless freshly isolated strains are shown to produce high titres of some other antibody.

One of the difficulties in acquiring recently isolated strains of *Bord. pertussis* at the present time is that some laboratories, having isolated an organism from a case of whooping-cough, have been uncertain about its identity. Although a strain may appear typical both morphologically and culturally, it may fail to agglutinate with standard anti-pertussis serum. It is possible, as suggested by Lacey (1957), that the anti-pertussis serum may have been produced against a strain containing antigens 1, 2, and 4, but no 3; such a serum would contain no antibody 3 and, as shown by Andersen (1958), it may also have very little antibody 1. It could not, therefore, be expected to give good agglutination of strains such as GB or LS (Table II) which are strongly agglutinated only by antibody 3. This emphasizes the necessity for diagnostic pertussis serum to contain an adequate amount of antibody 3.

Summary

A number of pertussis vaccines and strains of *Bordetella pertussis* were examined for their content of heat-labile antigens 1, 2, 3, and 4, by agglutination with specific sera.

Differences in antigenic composition were found between strains encountered in the past and those being isolated at the present time.

It is suggested that antigen deficiencies in pertussis vaccine may result in failure to give complete protection against whooping-cough if the infecting strains of *Bord. pertussis* possess antigens not present in the vaccine.

This investigation would not have been possible without the ready co-operation of medical practitioners and technicians whose help and assistance are gratefully acknowledged—namely, Sir Graham Wilson and the staff of the Public Health Laboratory Service; Salford Health Department and many general practitioners in Manchester and Salford; the staff of Fazackerley Hospital, Liverpool; the laboratory staff of the Royal Manchester Children's Hospital and of Hope Hospital, Salford; and Mrs. Pamela Garrity and Miss Joyce Crompton of this department.

REFERENCES

- Andersen, E. K. (1953). *Acta path. microbiol. scand.*, **33**, 202.
 — (1958). Thesis, Univ. Copenhagen, p. 32.
 Edsall, G., McComb, J. A., Wetterlow, L. H., and Ipsen, J., jun. (1962). *New Engl. J. Med.*, **267**, 687.
 Eldering, G., Eveland, W. C., and Kendrick, P. L. (1962). *J. Bact.*, **83**, 745.
 — Hornbeck, C., and Baker, J. (1957). *Ibid.*, **74**, 133.
 Galbraith, N. S., and Cockburn, W. C. (1963). *Mth. Bull. Minist. Hlth Lab. Serv.*, **22**, 54.
 Lacey, B. W. (1957). *Ass. clin. Path.*, Broadsheet No. 17 (new series).
 — (1960). *J. Hyg. (Lond.)*, **58**, 57.
 Petrilla, A., and Barsy, G. (1959). *Ann. Immunol. hung.*, **2**, 143.
 Preston, N. W., and Evans, P. (1963). *Nature (Lond.)*, **197**, 508.
 — and Te Punga, W. A. (1959). *J. Path. Bact.*, **78**, 209.

IDIOPATHIC RHABDOMYOLYSIS (MYOGLOBINURIA) AS AN ACUTE RESPIRATORY PROBLEM

BY

J. B. BORMAN, M.B., F.R.C.S.

J. T. DAVIDSON, L.R.C.P., D.A., F.F.A.R.C.S.

AND

S. H. BLONDHEIM, M.D.

From the Departments of Thoracic Surgery, Anaesthesia, and Internal Medicine B, Rothschild Hadassah-University Hospital, Jerusalem, Israel

A rare cause of peripheral respiratory failure is idiopathic rhabdomyolysis. This unusual disease (reviewed by Korein, Coddon, and Mowrey, 1959) is due to dissolution of striated muscle and excretion of the muscle protein, myoglobin, in the urine. Hence this syndrome, long referred to as "idiopathic paroxysmal myoglobinuria," has been renamed rhabdomyolysis (Bowden, Fraser, Jackson, and Walker, 1956). The disease is intermittent in character, the exciting factor often being physical exertion or, less often, a febrile illness. The large muscles of the extremities, usually the lower, bear the brunt of the disease. Pain and swelling in the affected muscle group are followed by the excretion of characteristically dark-red urine (myoglobinuria) which soon turns brownish-black on standing. In only very rare instances are the muscles of respiration involved so that respiratory failure dominates the clinical picture. Such a case, simulating bulbospinal poliomyelitis, is presented, together with details of its management.

Case Report

A 22-year-old married woman was admitted to hospital complaining of difficulty with breathing, talking, and swallowing

of a few hours' duration. Her past history included six episodes of passing dark urine during or immediately after a febrile illness. None followed exertion, nor were any associated with respiratory difficulty. At the age of 18 she was admitted to this hospital during an acute attack and the diagnosis of rhabdomyolysis was established. She recovered after a few days and remained well until her last relapse. Her symptoms began one month after normal delivery of her first child during acute mastitis with fever of 39° C.

On her admission the respiration was shallow, rapid, and laboured, and she was restless. The temperature was 38° C., pulse rate 128, and B.P. 120/80. She spoke in a whisper and was unable to swallow her saliva or to separate her teeth more than 1 cm. The right breast was inflamed. A tentative diagnosis of a recurrent bout of rhabdomyolysis was made, but bulbospinal poliomyelitis could not be ruled out. In addition to antibiotic therapy and intranasal administration of oxygen, an attempt was made to alkalize the urine by oral sodium bicarbonate, in anticipation of the appearance of myoglobinuria. Next morning she passed reddish-brown urine shown to contain myoglobin by a simple test described by Blondheim, Margoliash, and Shafrir (1958).

Dyspnoea was progressive and short episodes of apnoea accompanied by cyanosis, hypotension, and loss of consciousness developed. At this stage tracheostomy was performed. A cuffed rubber tube was introduced and connected direct to an intermittent positive-pressure breathing apparatus* triggered by the patient's own respiratory efforts. Tracheobronchial toilet was repeated as necessary, paying strict attention to asepsis. Each suction was preceded by the instillation of sterile saline to stimulate the cough reflex and to liquefy secretions. On this regime her condition improved markedly. Full consciousness returned and the blood-pressure rose to, and remained at, normal levels. Spontaneous breathing, however, remained insufficient and it was not possible to discontinue aided respiration. After 72 hours on the respirator marked crusting of the bronchial secretions began and it became increasingly difficult to maintain patency of the airway. This was attributable to constant technical difficulties with the nebulizer (gas humidifier) of the respirator. The patient's condition deteriorated. Cyanosis developed and she slowly lapsed into coma. Respiration became insufficient to cycle the respirator, necessitating a switch-over from "patient-cycled" to "automatic cycling."

The blood-pressure dropped, but was restored by an infusion of noradrenaline (which was continued intermittently for 36 hours). Atelectasis of the right lung followed. Despite repeated tracheobronchial suction the lung did not expand. Therefore, after hyperventilation with 100% oxygen, the tracheostomy cannula was removed and a No. 7 bronchoscope was introduced in its place. Cardiac arrest immediately occurred. The bronchoscope was withdrawn, the cannula was reinserted, and intermittent positive-pressure oxygen was manually applied. After a few seconds the heart-beat returned and the patient recovered consciousness. Her condition remained critical with total right lung atelectasis and deep cyanosis. Accordingly, the bronchoscope was reintroduced and a large plug of crusted mucus removed from the right main bronchus, but before toilet of the left side could be carried out cardiac arrest recurred. Manual intermittent positive-pressure respiration, with oxygen and external cardiac massage (Kouwenhoven, Jude, and Knickerbocker, 1960) was performed and the heart started to beat again after about one minute.

Radiological examination of the chest demonstrated complete expansion of the right lung but collapse on the left side. Further bronchoscopy was thought to be too dangerous at this stage. Controlled respiration with 100% oxygen was continued and her colour improved. About two hours later the heart again suddenly stopped. External cardiac massage produced no palpable peripheral pulse and after two minutes the chest was opened and direct cardiac massage started. After a few minutes the heart began to beat spontaneously, and the patient opened her eyes and made purposeful movements. The chest incision was closed after insertion of an underwater tube drain.

*Bennett, Los Angeles.

Hypothermia was now instituted to afford some protection against hypoxia. Surface cooling supplemented with promethazine hydrochloride and pethidine reduced the rectal temperature to 34–35° C., which was maintained for five days with fully controlled respiration, using 50% oxygen in air. Subsequently, repeated episodes of severe hypoxia occurred with loss of consciousness and hypotension, accompanied by signs of atelectasis of one or the other lung. These episodes were treated by vigorous suction, and after extraction of crusted material the condition improved and consciousness returned within a short time.

During the respiratory difficulties serious renal complications occurred. After two days of complete anuria the kidneys began to secrete small but increasing quantities of urine of low specific gravity (1008–1012), reaching a maximum of 700 ml. in 24 hours two days before death. Simultaneously the blood urea also rose, and remained fairly constant at 400 mg./100 ml. Serum potassium reached 5.8 mEq/l. However, the blood urea again rose rapidly two days before death, reaching a maximum of 790 mg./100 ml. The patient died during one of the oft-repeated attacks of severe hypoxia.

Post-mortem Findings.—The whole length of the trachea was severely involved by acute haemorrhagic tracheitis. In its

Histological section of intercostal muscle. The majority of muscle fibres have disappeared. Those remaining show atrophic changes and fragmentation of the sarcoplasm. At the site of the damaged fibres marked mononuclear infiltration is evident. (H. and E. $\times 95$.)

lower third a large pseudomembrane was found attached at the level of the carina. This necrotic mass was able to obstruct the openings of the right or left main bronchus by slipping to one or the other side of the carina and probably accounted for the alternating attacks of atelectasis. The major and minor bronchi showed acute inflammatory changes. There was confluent bronchopneumonia in the right lung. The left lung was completely atelectatic. The diaphragm and intercostal muscles were severely damaged by rhabdomyolysis (see Fig.). The kidneys showed acute tubular necrosis. In the cerebral cortex numerous neurones showed irreversible anoxic damage.

Discussion

Only four previous cases of respiratory failure due to rhabdomyolysis have been described (Buchanan and Steiner, 1951; Kaufman and Barry, 1959; Wheby and Miller, 1960). The first was diagnosed as "anterior poliomyelitis and transitory acute nephritis," and only on readmission in a second and fatal attack with respiratory failure was the correct diagnosis made. The other three cases were treated with controlled respiration for 8, 18, and 14 days respectively. The first of these three cases ended fatally, while the latter two made successful recoveries. While

respiratory failure is a rare manifestation of idiopathic rhabdomyolysis, it appears to occur more often in the toxic myoglobinuria that follows poisoning from sea-snake bite (Mardsen and Reid, 1961).

Our patient presented a clinical picture similar to bulbo-spinal poliomyelitis, but the previous history gave the clue to the correct diagnosis, which was confirmed when myoglobinuria appeared.

The patient's serious condition did not permit transportation to our special treatment unit in a distant building. Hence tracheostomy, bronchoscopy, and open-chest cardiac massage were performed under conditions of difficult access to the patient in the medical ward. The malfunctioning nebulizer of the respirator led to inadequate humidification and prevented the use of therapeutic aerosols to reduce the viscosity of the tracheobronchial secretions. As a result, inspissation and crusting of the secretions occurred necessitating repeated vigorous suction, which traumatized the tracheal epithelium, producing bleeding, infection, and further crusting, which demanded still more energetic suction.

Repeated bronchoscopy would undoubtedly have been most valuable in maintaining a patent airway, but, as the additional hypoxia attendant on bronchoscopy led to cardiac arrest on two occasions, the procedure was abandoned. We have since adopted Rogers and Erhardt's (1961) method in which the bronchoscope is passed behind a previously introduced small endotracheal tube supplying oxygen. This technique, with general anaesthesia and relaxants, permits continuous intermittent positive-pressure respiration. In retrospect, this method might have permitted repeated bronchoscopy and removal of the ball-valve carinal plug which produced the alternating atelectasis and ultimately led to our patient's death.

The episodes of cardiac arrest were caused by severe hypoxia of the heart muscle. In the first episode the heart responded to "pneumomassage" (intermittent positive-pressure respiration) (Bencini and Parola, 1956). The second arrest was treated by pneumomassage plus external cardiac massage, but open-chest cardiac massage was necessary the third time.

The patient's renal complication and other aspects of the aetiology, diagnosis, and pathology of this disease will be presented elsewhere. The renal failure probably added to the pulmonary difficulties by contributing fluid reten-

tion and electrolyte imbalance. The patient appeared to be on the way to recovery from lower nephron nephrosis, but inability to maintain patency of the airways and severe recurrent anoxia led to her death.

Summary

An extremely rare case of idiopathic rhabdomyolysis (myoglobinuria) presenting as an acute respiratory problem is described. Involvement of the diaphragm and intercostal and pharyngeal muscles resulted in a clinical picture simulating bulbo-spinal poliomyelitis. Treatment included sodium bicarbonate to alkalize the urine, tracheostomy, and intermittent positive-pressure respiration. A pseudo-membrane which formed at the carina produced alternating obstruction of the right and left main bronchi with recurring episodes of severe hypoxia which ultimately led to the death of the patient. The condition was further complicated by renal shut-down and repeated cardiac standstill. The latter responded initially to pneumomassage and external cardiac massage. However, after the third episode of cardiac arrest it was necessary to open the chest and massage the heart directly.

At post-mortem examination the typical changes of atrophy, disappearance of muscle fibres, and fragmentation of the sarcolemma were found in the diaphragm and the intercostal and other muscles.

Dr. E. Moran and Mr. H. Reuveni, of the Department of Pathology, kindly helped in the preparation of this paper.

REFERENCES

- Bencini, A., and Parola, P. L. (1956). *Surgery*, **39**, 375.
- Blondheim, S. H., Margoliash, E., and Shafrir, E. (1958). *J. Amer. med. Ass.*, **167**, 453.
- Bowden, D. H., Fraser, D., Jackson, S. H., and Walker, N. F. (1956). *Medicine (Baltimore)*, **35**, 335.
- Buchanan, D., and Steiner, P. E. (1951). *Arch. Neurol. Psychiat. (Chic.)*, **66**, 107.
- Kaufman, R. P., and Barry, P. E. (1959). *New Engl. J. Med.*, **260**, 430.
- Korein, J., Coddon, D. R., and Mowrey, F. H. (1959). *Neurology (Minneapolis)*, **9**, 767.
- Kouwenhoven, W. B., Jude, J. R., and Knickerbocker, G. G. (1960). *J. Amer. med. Ass.*, **173**, 1064.
- Marsden, A. T. H., and Reid, H. A. (1961). *Brit. med. J.*, **1**, 1290.
- Rogers, F. A., and Erhardt, K. S. (1961). *J. thorac. cardiovasc. Surg.*, **41**, 817.
- Wheby, M. S., and Miller, H. S. (1960). *Amer. J. Med.*, **29**, 599.

Preliminary Communications

Pyrimethamine and Sulphadiazine in Treatment of Malaria

The antibacterial action of diaminopyrimidine derivatives is potentiated by sulphonamides, probably because of the sequential blocking of stages in the metabolic synthesis of nucleotides. Sulphonamides interfere with the utilization of *p*-aminobenzoate by the organism, and diaminopyrimidines act as folic-acid antagonists, probably as a result of inhibition of folic-acid reductase (Hitchings, 1962). Potentiation also occurs in experimental infections of *Toxoplasma* (Eyles and Coleman, 1953), *Eimeria* (Lux, 1954), and *Plasmodium* (Rollo, 1955). Pyrimethamine and sulphadiazine are now used together for the treatment of human toxoplasmosis, and the closely related diaminopyrimidine

compound, diaveridine, is used with sulphaquinoxaline for coccidiosis in poultry.

The potentiating effect of sulphadiazine on the activity of pyrimethamine in human *P. falciparum* malaria was shown by Hurly (1959) in the Gambia, and Basu, Mondal, and Chakrabarti (1962) have shown that a combination of pyrimethamine and dapsone is more effective than either drug alone against *P. vivax* in India. Hurly suggested that the combination of drugs might possibly overcome the resistance to pyrimethamine which is sometimes observed in certain strains of the human malaria parasite.

CASE HISTORY

An African girl (age, 11 years; weight, 54 lb.—24.5 kg.) of the Mandingo tribe, reputedly receiving pyrimethamine as a malarial prophylactic at a dosage of 25 mg. a week, was observed on February 8, 1963, to be infected with *P. falciparum* (trophozoite blood density 12,025/c.mm.). As it was not possible to establish beyond doubt that the prophylactic pyrimethamine had been successfully administered, and since