dosage should preferably be continued by patients in this category until only one or two flushes are experienced daily.

Discussion

The facts given suggest that in vitamin E therapy we possibly have an alternative method to oestrogen therapy for combating menopausal flushes. If this be so—and the data are so few as to be merely suggestive—its mode of action is not clear. The changes which take place at the menopause lack uniformity and vary greatly in severity. It is unlikely, therefore, that an equal response will be obtained in all cases, and possibly one treatment will succeed where another has failed. As has been said, oestrogen is generally prescribed for menopausal flushes, the rationale being that, given in large doses, it depresses pituitary function at a time when considerable amounts of gonadotrophin are being excreted in the urine (Frank and Salmon, 1935; Jones *et al.*, 1937). The flushes are held to be an indication of oestrogen insufficiency, yet it has been demonstrated by Robson *et al.* (1934), Frank (1934), and others that in some cases oestrogens are recoverable from the blood and urine in considerable quantity for as long as 20 years after the menopause, although in other women there may be none at the end of three years.

The rationale for the employment of vitamin E in the control of menopausal flushes is all the more obscure as Shute (1939), its advocate, considers vitamin E to be anti-oestrogenic—a thesis which others, however, have failed to confirm (Drummond *et al.*, 1939).

It is always dangerous to cite effects on animals in an article dealing with the human subject, because of the similarity that such a reference tends to imply. Subject to this caution, and bearing in mind that the experimental results that have been obtained on animals do not indicate that the endocrine system is primarily responsible for the changes observed after feeding on an E-deficient diet (Mason, 1929; Drummond *et al.*, 1939), certain tangible results of E-deficiency stand out in a sphere in which many claims have too readily been made. Thus there is evidence of a reduction in the pituitary principle responsible for causing ovulation in vitamin-E-deficient rabbits (Rowland and Singer, 1936; Drummond *et al.*, 1939) and of thyroid deficiency in rats deprived of the vitamin (Singer, 1936; Barrie, 1937).

This latter finding may have some bearing on our problem, as a mild degree of myxoedema is commoner in menopausal women than states of true hyperthyroidism (Donald, 1938), and it is possible that one of the ways in which vitamin E acts is by relieving this condition, at the same time causing an improvement in the emotional and physical state. If this be so, such women are more likely to benefit by vitamin E therapy than those in whom menopausal flushes are combined with hyperthyroidism, who would benefit from oestrogen therapy rather than from vitamin E. The preferential response to stilboestrol in Case B may perhaps be explained on these lines, as she had manifest symptoms of hyperthyroidism, which were wanting in Case A, which responded well to viteolin. Relevant to this aspect is the fact that in the treatment of involutional melancholia in menopausal women Hemphill and Reiss (1940) noted that the patients who derived greatest benefit from oestrogen treatment were those in whom a lack of ovarian function was combined with a considerable degree of hyperthyroidism, whereas the symptoms seemed, if anything, to be aggravated in those with hypothyroidism. Since oestrogens inhibit the thyrotrophic action of the pituitary, their indiscriminate use may be harmful if thyroid insufficiency is present.

Arising out of this study, Reiss and Golla (1940) considered the possibility that the endocrines might have an influence on cerebral circulation, and their investigations suggest that in

trained animals the blood content in the brain is considerably lowered and can be increased by treatment with sex hormones. In our effort to ascertain if any similar action has been claimed for vitamin E we have encountered the statement by Wortis and Jolliffe (1941) that the vitamin "has a vasodilator action." If this can be substantiated we would have one property common to both substances—viz., a levelling-up of cerebral blood flow which would counteract sudden cerebral congestion.

(Side actions would be provided in a stimulus to muscular metabolism as well as a probable psychological effect.)

Reynolds (1939), on this aspect, states that the effect of oestrogens upon the venous pressure in ovariectomized women is to lower this appreciably within the short space of 6 to 8 minutes—a diminution which may be the result of a general increase in the size of the subcutaneous capillary bed, since capillary pressure diminishes coincident with the change in venous pressure. He considers it probable that the basis of the adjustment is a shift of part of the blood volume from the visceral regions to the somatic capillary bed as a moderate but extensive capillary vasodilatation takes place. Inevitably associated with this would be an alteration in the heat-regulating capacity of the individual, increasing the heat loss by radiation and conduction, and so minimizing the need for loss by evaporation. This, he avers, should minimize the amount of nervous activity of the sympathetic system which heat regulation by sweating entails. Such a peripheral vascular action of oestrogens would account for their relief of the acute menopausal disturbances on the basis of well-established physiological grounds through readjustment of normal heat-regulating mechanisms.

Conclusion

Although a case has not been made out for the alleviation of menopausal flushes with vitamin E, as claimed by Shute, the few cases described suggest lines along which patients might be selected for this mode of therapy, and it is hoped that it may be given a trial, especially where an idiosyncrasy for oestrogens exists.

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HEMIPLEGIA COMPLICATING WHOOPING-COUGH

BY

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The occurrence of a complete and permanent hemiplegia during whooping-cough is a very unusual type of neurological complication: there is, in fact, no record of such a case at this hospital in 20 years. We feel, therefore, that the following case should be recorded, especially in view of the opinion of some authorities—e.g., Nelson (1939)—that it is desirable to report all cases of whooping-cough showing permanent neurological sequelae. The present case was further complicated by subcutaneous emphysema.

Case Report

A boy aged 5 was admitted on Sept. 25, 1941, with a history of cough for a month and occasional vomiting. He had first been heard to whoop three weeks before admission. On examination the child was found to be very ill; temperature was 102.8° F., pulse 130, respirations 60. He was cyanosed, the alae nasi were working, and there were recession and signs of a patchy pneumonia at both bases. Although next day the temperature had subsided to 100°, the pulse was still rapid and signs of bronchopneumonia became more extensive, involving the whole of the right lung and the major portion of

the left. Sulphapyridine 0.5 g. was administered four-hourly. The temperature came down and gradually the bronchopneumonia began to clear, though the general condition was not greatly improved. Spasms of coughing accompanied by whooping and vomiting were still severe, cyanosis was frequent, and the respiration remained rapid, averaging 60.

On the ninth day after admission the boy suddenly developed a marked degree of subcutaneous emphysema of the upper chest, neck, and cheeks, and was severely cyanosed. The lungs showed a patchy impairment of percussion note and there were some coarse moist rales at the bases. A radiograph at this stage (see fuller report below) showed subcutaneous emphysema, hilar gland enlargement, and bronchitic changes, but no evidence of collapse. Four days later the subcutaneous emphysema had practically disappeared and the sulphapyridine was reduced to 0.5 g. six-hourly. On the fourteenth day after admission the chest was definitely clearing, the colour and pulse were much improved, and chemotherapy was discontinued. On the sixteenth day the temperature rose suddenly to 103° F. and continued raised in spite of the resumption of chemotherapy. Coarse moist sounds were heard all over both lungs.

On the night of the eighteenth day twitchings of the limbs of the left side were noticed, and later in the same day the left side of the face was similarly involved. Despite treatment with bromides and chloral the twitchings continued and spread to the left arm. The next day the whole of the left side was affected, the twitchings being of a Jacksonian character and increasing both in frequency and in duration. There was no evidence of paresis in the intervals, though the child was very drowsy and resentful of movement and painful stimuli. The pupils were equal, regular, central, and reacted briskly to light. Abdominal reflexes were absent on the left side and there was a left extensor plantar response. There was no neck rigidity; Kernig's sign was absent; tendon reflexes on both sides were difficult to elicit but not significantly unequal. There was no evidence of papilloedema.

By the twenty-first day there was a complete left hemiplegia of a flaccid type. A lumbar puncture secured about 4 c.cm. of crystal-clear fluid, not under pressure. C.S.F. examination showed protein 30 mg., no excess of globulin, sugar 57 mg. per 100 c.cm., and white cells not in excess; cultures remained sterile. Chlorides were not estimated. At this stage and before the result of the examination of the cerebrospinal fluid was available, the possibility of cerebral abscess was considered. Mr. D. W. C. Northfield (neurosurgeon, E.M.S.) saw the patient in consultation, but doubted the presence of an abscess in view of the absence of papilloedema, the normal pulse, the normal pressure of the spinal fluid, the rapid evolution, and the evidence of more widespread disturbance of cerebral function. The possibility of encephalitis or a vascular lesion was suggested. The child vomited several times during that day and remained drowsy, rapidly becoming more dehydrated and wasted, and doubly incontinent. Consciousness, however, was not so clouded. Three days later lumbar puncture was again performed and about 10 c.cm. of crystal-clear fluid, this time under pressure, withdrawn. Examination of this showed protein 20 mg., globulin no excess, sugar 68 mg., no excess of white cells, no organisms. The next day the child was much brighter and able to answer simple questions, and this improvement in his mental state continued. During the next two months the boy put on flesh, and regained a practically normal mentality, but the hemiplegia persisted and became progressively more spastic.

The patient has since been transferred to another hospital, where he has not been seen by us. A recent report received by the kindness of Mr. Northfield states that on Sept. 7, 1942, the child had an epileptiform fit restricted to the left side and starting with convulsive movements of the left leg, without loss of consciousness. Encephalography was performed, which demonstrated gross atrophy of the right cerebral hemisphere, with enlargement of the right lateral ventricle.

Radiological Appearances through the Course of the Illness

Oct. 6, 1941.—Surgical emphysema was present in the tissues of the neck, cheek, and thoracic wall—probably of some duration, as the fibres of the muscles were well outlined. The hilar glands were enlarged and there was a general increase in striae, indicating congestive and catarrhal changes. In the right midzone, at the level of the third right rib, there was an indefinite opacity, situated in the lung parenchyma.

Oct. 16.—The surgical emphysema had cleared completely. The hilar shadows and the striae had increased in extent, especially in the left upper zone. In the right midzone there was what looked like a definite cavity. In the opaque area previously noticed there were now two semi-translucent areas.

Oct. 30.—The hilar shadows were as before, and the striae had increased in extent. In the right midzone there were what now seemed to be three cavities. In the left zone there appeared to be two large cavities overlapping. In the left midzone there seemed to be a cavity, and a possible one at the left base. The lateral view showed these cavities rather well.

Nov. 13.—The cavities in the right midzone were clearing. The cavity in the right upper zone was more distinct. The cavities in the left upper and midzones were also clearing. At the left base the cavity was more delineated. Striae had decreased, but the hilar shadows were still enlarged.

Dec. 29.—Only a trace of the cavities remained on the right side and left upper zone. The hilar glands were still enlarged and the striae still prominent.

Feb. 27, 1942.—The cavities had disappeared except in the left upper zone and base, where there was just a faint trace of them.

Discussion

The occurrence of hemiplegia in the course of whooping-cough, although rare, is a recognized phenomenon. In the largest series of cases, collected over a lengthy period, hemiplegia occurred in about 50% of the cases showing neurological complications (convulsions not being included as such by the authors concerned). The hemiplegia may be transient, permanent, or associated with high mortality, particularly in the left-side paralyses (Valentin, 1901-2). The subject is reviewed by Gordon Sears (1929) and Nelson (1939).

Though we were familiar with this particular complication, our patient presented us with a diagnostic problem which still remains unsolved, though a speculative attempt has been made. There is no general agreement as to the aetiology of neurological phenomena in pertussis even when post-mortem material is available. When it is not, there is a much larger field for speculation. Perhaps the commonest tendency nowadays is to ascribe most of the neurological complications of whooping-cough, as indeed of most of the acute specific fevers, to an "encephalitis." This diagnosis, undoubtedly true in many cases, cannot be universally applied, and often rests on insecure pathological findings (Kinnier Wilson, 1941). Very often also there is a paucity of such positive findings in the cerebrospinal fluid as would tend to confirm the presence of encephalitis.

The occurrence of focal intracranial haemorrhage, and more particularly of local functional disturbances of vascular supply as shown by Hiller and Grinker (1930), cannot be excluded. Brain (1940) holds that focal symptoms are probably the result of focal vascular lesions and softening.

Neuburger (1925) advances the view, based on comparative pathological studies, that the lesions found in certain cases of whooping-cough eclampsia are strictly comparable to those produced by air embolism. The histopathology described is typical of an ischaemic necrosis; this is strikingly confirmed by the recent work of Dorothy Russell (1941). She describes the histological features of the results of fat embolism in the brains examined by her and, referring to the work of Neuburger, confirms his findings in air and fat embolism. For the histological picture presented reference should be made to the original papers by Husler and Spatz (1924), Neuburger (1925, 1926), Spielmeyer (1928), and Dorothy Russell (1941). Neuburger (1925) gives very cogent reasons for the occurrence of air emboli in whooping-cough. In two of his cases the cerebral histology was identical with that found in a case of air embolism following induced abortion, in which the embolus passed to the cerebral circulation by way of a widely patent foramen ovale. Already in 1913 Spielmeyer had obtained similar results in experimental animals.

In our case there was very marked evidence of a ruptured alveolus—a severe grade of subcutaneous emphysema which presumably originated from an acute interstitial emphysema tracking up to the neck by way of the posterior mediastinum. Furthermore, the radiological appearances are in support of the occurrence of acute emphysematous bullae. The round translucencies, distributed in a multiple fashion, appearing and disappearing quickly, and healing without fibrosis, are unlike any other lesion causing cavitation. The disappearance of the bullae may be due to rupture. Probably, therefore, volumes of air may have been liberated into the circulation at any time throughout the period of formation of these areas of parenchymatous emphysema.

It therefore seemed reasonable to correlate the phenomena. Convulsions were attributable to the early ischaemic phase, and the hemiplegia resulted from infarction of the motor area by means of the emboli. The recent finding of marked right

cortical atrophy on encephalography would certainly favour a vascular lesion and exclude encephalitis.

To speculate on the occurrence of air embolism in other cases of whooping-cough complicated by convulsions, pareses, amaurosis, etc., both in those which recover and in those which are permanent, does not seem to us to be far-fetched. Small emboli may produce ischaemic effects which result in transient symptoms, and are comparable to the transient effects seen in the milder cases of caisson disease or in the pilots of rapidly climbing aircraft (Armstrong, 1939). Larger and more numerous emboli may produce permanent lesions by means of the focal infarctions which result, as in the more serious effects of caisson disease. We would suggest that the diagnosis of air embolism be more frequently entertained in cases of neurological complications of whooping-cough, particularly those which follow severe spasms of coughing and are likely to be associated with a ruptured alveolus; furthermore, that the diagnosis of encephalitis be reserved for cases in which the spinal fluid shows some evidence of inflammatory change or the cerebral histopathology is undoubtedly encephalitic.

Summary

A case of whooping-cough complicated by hemiplegia is presented.

An interesting feature of the case was the occurrence of severe subcutaneous emphysema some days before the onset of the hemiplegia.

The two phenomena are correlated, and the hemiplegia is considered to be possibly due to air embolism.

A brief summary of the literature is given.

We should like to express our thanks to Dr. Norman Begg, medical superintendent of the Eastern Hospital, for his encouragement and critical help with this case; to Dr. T. V. L. Crichlow of the Middlesex Hospital for his advice as to radiological findings; and to the Medical Officer of Health to the London County Council for permission to publish.

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Medical Memoranda

Anaphylactic Shock after First Injection of Tetanus Serum

The following case of anaphylactic shock may be considered of enough interest to be placed on record.

CASE HISTORY

T. B., a 19½-year-old medical student, bruised his right leg just above the tuberosity of the tibia on April 15, 1943. The next day, at 9.20 p.m., antitetanus serum was administered subcutaneously. The serum was made early in the war by the Lister Institute, and no similar reaction after its use has been reported to them since the batch was issued. Twelve years ago the subject had an anti-scarlatinal injection. He has never had asthma, or any other similar disease, and there is no history of asthma in the family. He has never shown any signs of urticaria.

Having only a 1-c.cm. sterilized syringe at hand, the serum was given in two stages, with about half a minute interval. About five minutes later the first signs of allergy appeared, laryngeal constriction was felt, and there was itching over the whole body. Having realized that an anaphylactic shock had started, some adrenaline was called for. Meanwhile other symptoms developed—vomiting, desire to pass water, inability to sit up, and a bottle given to the patient fell from his hand. The pulse rate was 120 and very weak, sometimes imperceptible. The lips and finger-nails were cyanosed, great difficulty was experienced in breathing, and heavy pains were felt round the xiphisternum and angle of Louis.

Three ampoules of adrenaline 1/10,000 (a higher concentration was not available) brought temporary improvement; cyanosis remained, the blood pressure fell shortly afterwards again, and the patient vomited for the second time. As no more adrenaline was available it was imperative to arrange for removal to hospital. On arrival 1 c.cm. of adrenaline 1/1000 was given. The pulse improved, and the blood pressure was 100/70. The condition was satisfactory

at 2 a.m., five hours after the serum had been given, but the patient was restless the whole night. There was enough improvement during the following day for him to be discharged from hospital, but he remained under my observation. Progress was as follows:

April 19 (two days after discharge from hospital): pulse rate 56, temperature normal; pains in joints; veganin given with effect. April 20: pulse rate 60, temperature normal: parotid, submaxillary, and sublingual glands became swollen. April 21: pulse rate 120, temperature 99° in the morning and 101.5° in the afternoon; glands increased in size, and the site of the serum injection inflamed. April 22: temperature 99°; swelling of glands disappeared; more urticaria; swelling of arm increased and more painful. April 23: return to normal.

The antitetanus serum, made by the Lister Institute during the early part of the war, was not used before April 16, 1943.

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Sulphapyridine Anuria successfully Treated by Ureteric Catheterization

The case reported below suggests the advisability of the following measures during sulphapyridine therapy: ample fluid intake to prevent concentration of the drug in the renal tubules; daily measurement of urinary output; daily examination of urine for the presence of excess erythrocytes (ideally), or, alternatively, daily chemical tests for blood in urine. Estimation of urinary output alone, without examination for red cells, may be misleading, as for three days the patient neither complained of pain nor showed any gross diminution in output, although one ureter was completely occluded. It is worth while noting that in this case the mechanical obstruction was at the lower ends of the ureters.

The following treatment is suggested. Haematuria, renal colic, or diminution in urinary output during sulphapyridine therapy calls for cystoscopy—first for diagnosis, and secondly for any necessary treatment; immediate clearance of one ureter only may be possible at first, but this may facilitate a later clearance of the other. Intravenous drip therapy in anuria is indicated only when it is certain that at least one ureter is functioning satisfactorily; irremovable bilateral ureteric blockage necessitates nephrostomy.

CASE HISTORY

The patient, a woman aged 26, was admitted to hospital on Feb. 19, 1943, with lobar pneumonia. She was given 2 g. of sulphapyridine on admission, 2 g. after four hours, and 1 g. four-hourly until Feb. 22, when the dose was reduced to 0.5 g. four-hourly, this dosage being maintained until the 24th. She had not had any sulphapyridine before admission, and while in hospital had received a total of 24 g.

Her progress was uneventful until Feb. 24, when she developed severe right renal colic, started to vomit, and was restless and depressed. Her urine at this stage contained a large number of red cells, and the sulphapyridine was consequently discontinued. She was kept under observation until the following morning, when it was found that her urinary output for the preceding 24 hours totalled only 2 oz., the urine was heavily blood-stained, her blood pressure had risen from 120/80 to 160/100, blood urea was 156 mg. per 100 c.cm., and she was vomiting fairly copiously. No urine was obtained on catheterization, and she complained of a continuous aching pain in her right loin. An intravenous sodium sulphate drip was begun, and she was cystoscoped.

Cystoscopy showed a normal bladder. The left ureteric orifice appeared normal, but no urine was seen coming from it. A ureteric catheter was introduced without difficulty, some blood-stained jelly-like material being dislodged from the lower end of the ureter in the process, whereupon urine immediately flowed from this ureter, both through and around the catheter. Protruding from the right ureteric orifice was a small blood-clot, completely obstructing the ureter, and attempts to pass a catheter into this ureter were unsuccessful, apparently owing to the obstruction offered by the clot. As the left ureter was functioning satisfactorily the patient was returned to bed for further observation, with the ureteric catheter in position.

On Feb. 26 she was passing urine in normal quantity, both through the catheter and per urethram, and consequently the intravenous drip was discontinued and the ureteric catheter removed. During the following three days the output of urine continued to be normal, and the haematuria gradually diminished. On March 1 she had another attack of right renal colic, and a further cystoscopy was performed with the intention of clearing the obstruction in the right ureter. This was done without difficulty, the obstructing substance being located in the last 2 in. of the ureter, and consisting of blood-clot only. Before the cystoscope was removed from the bladder it was ascertained that both ureters were functioning satisfactorily.

Thereafter the patient made an uninterrupted recovery, the haematuria ceased, her blood pressure and blood urea returned to normal, and intravenous urography on March 15 showed that both kidneys and ureters were functioning satisfactorily.

I wish to thank Dr A. P. M. Page, medical superintendent, for permission to publish this case and for his advice and help; and also Mr. T. M. J. d'Offay, who carried out the surgical procedures.

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