is quite pronounced—up to 50 mm. Hg systolic and 40 mm. Hg diastolic—and certainly sufficient to be of clinical importance in some patients.

The hypertensive effect is evident when the bladder distension becomes intolerable. There was some suggestion that blood pressure rises gradually as the tension in the bladder rises, even before any sense of discomfort or desire to micturate, but this came only from the pooled observations from the four catheterized patients, and was not substantiated by the blood-pressure measurements made before and after normal micturition. It can be concluded that the average behaviour with respect to retaining one's urine and passing it is not associated with any significant fluctuations in blood pressure.

The rise in blood pressure which accompanies gross distension of the bladder could depend on a number of factors such as anxiety and other effects of pain and discomfort, distension of the hollow viscus, and contraction of sphincters. The results of our experiments suggest that the latter may be an important factor, at least when conscious effort is required to prevent micturition. It is possible that contraction of the sphincters initiates reflex activity affecting the cardiovascular system, but it is also probable that the primary volitional effort aimed at the sphincters should spill over into autonomic pathways leading to cardiovascular centres. This would be similar to the mechanism invoked by those people who can voluntarily accelerate heart rate, raise blood pressure, and stimulate other activities controlled by the autonomic nervous system (Ogden and Shock, 1939; Whyte, 1966).

Summary

Blood pressure rose significantly (average 27/20 mm. Hg) in seven normal subjects and four patients when the bladder was distended to the maximum tolerable limit by oral fluid loading or retrograde filling (four patients) through a catheter. Pulse rate was unaffected.

There was a positive correlation between blood pressure and mounting bladder pressure for the combined results from the four catheterized patients, but this relation did not obtain in each individual.

There was no significant difference in blood pressures taken immediately before and after micturition when subjects followed their habitual practice in determining when to micturate.

Blood pressure rose significantly (average 17/12 mm. Hg) whenever subjects without distended bladders voluntarily contracted their sphincters. Pulse rate also rose.

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Multiple Sclerosis and Vaccination

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The purpose of this paper is to describe nine examples of onset or exacerbation of multiple sclerosis after vaccination or inoculation and to discuss the possible implications of these observations. The first five cases were seen in Newcastle and the remainder in Pruszkow. In five instances the onset of the neurological disease occurred after inoculation, in four (Cases 3, 4, 5, and 9) this was followed by exacerbation of established multiple sclerosis. The cases are summarized in the Table.

Multiple Sclerosis after Vaccination

Case No.	Age at Onset	Sex	Vaccinated Against	Period of Latency	Subsequent Clinical Course
1	23	F	Smallpox	48 hours	Remittent, mild
2	22	M	Yellow fever	Few "	" "
3*	19	M	Typhoid fever	12 "	" "
4*	26	F	" "	14 days	" moderate
5*	21	F	Smallpox	7 "	" mild
6	41	F	Rabies	48 hours	" moderate
7	13	F	Tuberculosis	7-14 days	" mild
8	31	F	Typhoid fever	14 "	" "
9*	30	F	" "	Few "	" moderate

* Exacerbations.

Case Reports

Case 1

In 1945, five years after primary vaccination, a previously healthy 23-year-old woman was revaccinated against smallpox. Within 48 hours she developed dragging of the left leg, clumsiness of the left hand, and dysuria, all of which cleared up within a few months. One year later, in 1946, she developed a left retrobulbar neuritis,

in 1949 the right eye was similarly affected, and in 1953 there was a recurrence affecting the left. Examination in 1957 revealed bilateral optic atrophy, peripheral blunting of sensation in the lower limbs, absent abdominal reflexes, and a right extensor plantar response. Disability was slight.

Case 2

In 1942 a 22-year-old man, who had received primary vaccination against smallpox, T.A.B., and tetanus toxoid inoculation six weeks previously without ill effect, was inoculated against yellow fever. This was followed within hours by progressive failure of vision in both eyes, more severe in the left, which recovered within a few weeks. A year later he had a mild attack of retrobulbar neuritis on the right. Between 1944 and 1951 he had about a dozen recurrent episodes of numbness on either side of the body, hemiparesis, and emotionalism. Examination in 1957 revealed left optic atrophy, left intention tremor, absence of the abdominal responses, slight ataxia of gait, and euphoria, with little disablement.

Case 3

In 1955, at the age of 45, 26 years after a right facial palsy and 18 years after a transient diplopia, a man was secondarily vaccinated

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against smallpox and also received a combined T.A.B. and tetanus toxoid inoculation. Within 12 hours of the injection fever, rigors, blurred vision, and diplopia developed and persisted for 48 hours. Two weeks later a further T.A.B./T.T. inoculation was followed by an identical but rather less severe disturbance. In 1956 he had two brief episodes involving weakness of the right leg and right hand of short duration, and later in the same year a third T.A.B./T.T. inoculation was followed by fever and blurred vision. Examination in 1956 revealed minimal disability, but there was nystagmus to the left, right facial weakness, dysarthria, intention tremor of the left hand, and an absent right lower abdominal reflex.

Case 4

During 1954–63 a 26-year-old woman had experienced four brief episodes of blurred vision and difficulty in focusing, dizziness, and clumsiness and paraesthesiae of one or both hands. In 1963 she developed a more disabling attack characterized by weakness of the right leg, frequency of micturition, and incoordination of all extremities, which cleared up entirely within three months. In 1965, within 14 days after her first T.A.B. inoculation, she developed sudden numbness of the right leg and severe vertigo. Examination at this time revealed marked pallor of both optic discs, nystagmus, and dysarthria. The tendon reflexes were bilaterally exaggerated and there was paresis of the right leg with an extensor plantar response. Vibration sense was absent in both legs below the knee, and voluntary movement of all four limbs showed marked incoordination. This acute episode cleared up within a few weeks.

Case 5

In 1951 a 21-year-old woman developed the first of several succeeding and usually autumnal attacks of numbness of the limbs, often asymmetrical, involving the lower more often than the upper extremities, and always clearing up in two to three months. In 1958 she developed a typical left retrobulbar neuritis and in 1960 an acute episode characterized by numbness of the right hand and left foot which cleared rapidly.

Seven days after primary vaccination against smallpox in 1963 she developed headache, nausea, vertigo, drowsiness, and mental confusion. She complained of feeling as though her body was tightly encased, continually drew up her legs as though in pain, and showed generalized spasticity with a marked increase in deep reflexes and extensor plantar responses. Generalized motor weakness became profound, but recovery began within four days and was rapid. Three months later clinical examination was virtually negative except for absent abdominal responses and a pale left optic disc. She has remained well since this time.

Case 6

In 1949 a 41-year-old woman was scratched by a cat, for which she received a series of injections of Polish antirabies vaccine containing animal nervous tissue. Less than 48 hours after the last injection she complained of blurred vision in both eyes, numbness initially of the legs and later of the trunk, weakness of the left arm and leg, and intermittent double incontinence. These symptoms began acutely but improved progressively during the succeeding month, leaving her symptom-free. In 1954 and 1955 she developed paraesthesiae affecting the face and body below the waist. In 1956 she had an acute attack of diplopia with marked weakness of both legs. Examination revealed enlargement of the left pupil, left facial weakness, increased deep reflexes in the left upper limb, an ataxic paraparesis with bilateral extensor plantar responses and loss of vibration sense in the lower extremities, and symmetrical intention tremor affecting both hands.

Case 7

A 31-year-old woman physician had been immunized with Danish B.C.G. vaccine in 1946 at the age of 13. Within a week or two after the immunization she noticed difficulty in differentiating colours, weakness of the right leg, and clumsiness of the right hand. These symptoms disappeared completely within a few weeks. In

1955 there was a similar episode. Six years later she noticed marked difficulty in walking; her right hand was ataxic and easily fatigued by writing. Examination in 1965 revealed temporal pallor of both optic discs, nystagmus, exaggeration of tendon reflexes in right upper and both lower extremities, with extensor plantar responses, absent abdominal reflexes, symmetrical intention tremor, and an ataxic gait.

Case 8

In 1954 a 31-year-old woman was inoculated for the third time against typhoid fever, and because of the long interval since her previous inoculation she received a double dose of vaccine. Within 14 days she developed retrobulbar neuritis on the left and one month later on the opposite side. In 1955 she noticed transient numbness of the left side of the face, left hand, and lower half of the body. Slight weakness of both legs occurred two years later. Examination in 1957 revealed pallor of the left optic disc, nystagmus, diminished superficial sensation around the lips, brisker deep reflexes on the right side, absent abdominal reflexes, and decreased vibration sense in the left lower extremity.

Case 9

In 1957 a 30-year-old woman contracted acute tonsillitis, followed within a week by transient weakness of the left upper and lower limbs. Four years later she was inoculated against typhoid fever, and within a few days developed left hemiparesis and disturbance of balance, which disappeared over a period of three months. In 1963 a subacute relapse occurred with impaired vision of the left eye, speech disturbance, and weakness in all extremities. Examination revealed pallor of both optic discs, slurred speech, paresis of the left upper and both lower extremities with diminished vibration sense, and bilateral dysdiadochokinesis.

Comment

Stovicek (1959), Palffy and Merei (1961), McAlpine *et al.* (1965), and various German authors have described the apparent provocation of multiple sclerosis by protective inoculation or vaccination against smallpox, typhoid and paratyphoid fevers, tetanus, poliomyelitis, and tuberculosis (B.C.G.), and after injections of antidiaphtheric serum and gammaglobulins. Zintchenko (1965) has reported 12 patients in whom multiple sclerosis first became evident after a course of antirabies vaccinations.

In most cases where data are adequate the onset of symptoms was acute or subacute. In three patients symptoms became apparent within 24 hours of inoculation, in 10 within 2 to 14 days, and in five after intervals ranging from 3 to 12 weeks. The relation between the injection and the subsequent neurological illness is more dramatic where the interval is short, though a very short interval raises difficult questions concerning the respective roles of delayed and immediate hypersensitivity in pathogenesis. On the other hand, a latent period is as characteristic of postinoculation neurological complications as it is of those that followed the exanthemata. Shoulder-girdle neuritis following serum administration usually appears after 7 to 10 days, and this period may be extended to 18 days at least, while the neurological complications of T.A.B. administration may be delayed for as long as 14 days, though they more often develop within three or four. The records of cases of multiple sclerosis occurring after inoculation do not confirm a relation between the nature of the injection and the duration of the latent interval, but the total number is insufficient to exclude such a possibility. Secondary or primary injections of vaccine may be incriminated. There is no information concerning any relation between the site of injection and the site of initial neurological symptoms.

Postinoculation multiple sclerosis usually appears to run a more benign course than the spontaneously arising disease, and this applied in our own cases. Whatever the exact relation

between the two phenomena it is tempting to suggest that this group of patients is suffering from "marginal" multiple sclerosis and that spared the gross insult of further vaccination they may maintain a precarious equilibrium with their disease temporarily disturbed by some other exogenous stress such as infection or fatigue.

The cases of Stovicek (1959) and Zintchenko (1965) evoke some reservations, since the intervals between B.C.G. or anti-rabies vaccination and the onset of multiple sclerosis was sometimes measured in years.

Discussion

A temporal relation between vaccination and the onset of multiple sclerosis does not in itself imply a causal connexion. However, the evidence as a whole, and especially the observations of Uchimura and Shiraki (1957) on the clinical and pathological characteristics of subacute encephalomyelitis after anti-rabies inoculation, support the suspicion that the vaccination has some aetiological significance.

If the rather improbable hypothesis of a relation that is nothing more than coincidental is discounted present knowledge suggests three possible explanations:

1. It could be argued that the inoculation introduces a specific organism—probably viral—which is the cause of multiple sclerosis. No such virus is known, nor can a viral aetiology for multiple sclerosis be excluded. It is, however, difficult to envisage a specific virus so ubiquitous as to be found in a wide variety of inoculated material but pathogenic to only a very occasional recipient and after a highly variable latent or incubation period. There are also many patients with multiple sclerosis who have never been vaccinated and have never received any kind of inoculation.

2. It might be maintained that the effect of the inoculation was quite non-specific, and that it acted merely as a trigger activating a latent asymptomatic pathological condition with which the patient was in a state of unstable equilibrium. This view has been put forward in the case of traumatic activation of multiple sclerosis (Miller, 1964) and devalues the role of the trauma or inoculation in favour of a pre-existing "constitutional" state. It appeals to our natural caution in matters of pathology and causation, since we have a reasonable reluctance to attribute serious recurring or progressive disease to a single minor event or insult. This explanation is attractive, but it must be admitted that it leans heavily on inference. There is no evidence whatever that individuals who develop either multiple sclerosis after vaccination or the commoner self-limited postvaccinal neuropathies and encephalomyelopathies were harbouring disease of any kind; most of them appeared to be quite healthy normal people. The postulation of latent disease is merely a *manœuvre* to make the facts less uncomfortable and to fit more plausibly within the conceptual framework of current pathological thinking. Furthermore, we know that a wide variety of sterile injections can in fact provoke disseminated neurological lesions in man and in healthy experimental animals where the postulation of a pre-existing pathological condition is untenable.

3. A possible explanation is that the inoculation or vaccination acts as a prime aetiological mover and is in fact the initiating "cause" of the disease. Such a view can be put forward only with trepidation, though it is quite compatible with the observed facts. The interpretation of these facts presents difficulties, but experimental evidence suggests the possibility that the toxic effect of the initial injection—which the delay between injection and succeeding illness suggests may itself involve sensitization—leads to the development of a state of hypersensitivity of the patient to the products of damage to constituents of the nervous system liberated and probably altered by the initial insult. After the acute episode the patient may be regarded as reaching a state of unstable immunological equilibrium which is susceptible to later disturbance by a variety of exogenous and even endogenous factors, as well as by the infrequent accident of exposure to further inoculation. But even this view is untenable without postulating a constitutional factor. After all, few vaccinated individuals suffer any neurological complication, and fewer still multiple sclerosis. Indeed, a prospective study by Sibley and Foley (1965) emphasizes the failure to evoke exacerbation in a group of patients with multiple sclerosis deliberately vaccinated against influenza. Similarly a streptococcal

sore throat occasionally evokes acute glomerulonephritis and much more rarely sets in train a succession of events which ends in chronic kidney disease. Here again only a small minority of those initially infected are involved, and the soil seems to be more important than the seed.

Recent Immunological Observations

Several recent immunological observations in relation to multiple sclerosis may be germane to this clinical situation, though their exact significance remains uncertain. Caspary *et al.* (1964) have shown, for example, that B.C.G. vaccination is followed by the appearance of titres of anti-brain antibodies in the serum of the normal subject twice as high as those commonly encountered in unvaccinated patients with multiple sclerosis. It seems that the antigens comprising B.C.G. vaccine may be similar to those extracted from normal brain and are probably more antigenically potent in stimulating antibody production. It is possible that the bacterial proteins injected in the course of vaccination against typhoid and yellow fever may also belong to the class of intermediate antigens "shared" by micro-organisms and cerebral white matter. Levine and Wenk (1963, 1964) and Miskolczy *et al.* (1963) showed that the adjuvant bacterial extract normally used to enhance the encephalitogenic activity of brain emulsions could be dispensed with if the animals had been previously injected with pertussis or influenza vaccine—in other words, the vaccine was apparently able to play the part of the adjuvant for some time after its injection. This observation may furnish a hint regarding the pathogenetic contribution of vaccination in the human neurological syndromes under discussion.

Can the analogy between the provocative role of vaccination and that of trauma be further pursued? It has been suggested (Miller, 1964) that the effect of painful injury in provoking the onset or exacerbation of multiple sclerosis may be related to circulatory changes in appropriate segments of the spinal cord reported by Field *et al.* (1951) after stimulation of the proximal end of a divided peripheral nerve. Such central changes might potentiate a latent morbid process already present in the cord or even excite pathological change *ab initio*. It seems improbable that a local reflex mechanism of this kind could explain the neurological complications of vaccination. Local reaction at the site of injection is often inconspicuous even when the procedure has evoked serious neurological disturbance; the latent period is characteristically longer; the neurological sequelae of serum injection more often than not follow evident somatic manifestations of serum sickness clearly attributable to a systemic pathological disturbance; and no relation is observed between the part injected and the location of initial neurological disturbance.

Finally, and more practically, what advice can be given to the patient with multiple sclerosis who inquires about the safety of vaccination or inoculation? It seems clear that, like pregnancy or infection, these procedures carry some risk of provoking an exacerbation of the disease; but many patients survive such trials unscathed, and it is rarely possible either to predict a deleterious outcome or to measure the risk. That vaccination and inoculation sometimes provoke exacerbation seems certain, and they are clearly better avoided by the patient except in circumstances that render the hazard preferable to the alternative. Such a patient can reasonably be advised to decline smallpox vaccination unless it is made imperative by epidemic conditions or the demands of foreign travel. Where there is a history of neurological disturbance in relation to previous vaccination common sense would advise against repetition of the procedure, but in this, as in many such connexions, patients are unpredictable. A few days before the present paper was submitted for publication the patient described as Case 5 above telephoned urgently asking us to confirm that a second vaccination against smallpox would be quite in order so that she could holiday in Switzerland: she

was advised to seek her pleasure in some less hygienically orientated milieu.

Summary

Nine cases are reported in which vaccination or inoculation apparently provoked the onset or exacerbation of multiple sclerosis, and the implications of these observations are discussed in relation to the aetiology and pathogenesis of the disease.

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Haemolysis in Chronic Renal Failure

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Anaemia often occurs in chronic renal failure, and is caused mainly by depression of the bone marrow but also in some patients by increased destruction of red cells. The object of this study was to determine whether increased red cell destruction is caused by the retention of products of protein breakdown or whether it is due to a reduction in renal function.

For this purpose the life span of the red cell has been measured by radioactive chromium ($T_{1/2}Cr$) in a series of patients with chronic renal failure. The dissociation between renal function and the retention of products of protein catabolism has been achieved by the use of a very low protein diet. As a result of this, blood urea levels only slightly raised above normal can be found in patients with advanced renal disease (Berlyne, Shaw, and Nilwarangkur, 1965).

The results suggest that increased red cell destruction is related to retention of products of protein metabolism rather than to the extent of renal damage.

Patients and Methods

Twenty-six red cell survival times were estimated on 25 patients with moderate and severe chronic renal failure. Two estimations were made on controls.

Patients were excluded from the series if there was external blood loss, or skin-bleeding, or if they had been transfused with blood less than seven weeks previously. Occult gastrointestinal bleeding was excluded in 17 patients by the estimation of faecal radiochromium activity (Veall and Vetter, 1958). No patient was haemodialysed, but two (Cases 14 and 20B) received a peritoneal dialysis a week before labelling of their red cells and three (Cases 21, 24, and 25) were dialysed shortly after labelling. No patient had any disease other than chronic renal failure, associated with reduced red cell survival. Six of the patients with reduced red cell survival times were under treatment with methyl dopa at the time of labelling (Cases 6, 14, 15, 18, 24, and 25).

Haematological Methods

Red Cell Survival Time ($T_{1/2}Cr$).—The red cells were labelled with ^{51}Cr by the method described by Veall and Vetter (1958). Gamma counting was done on 5-ml. aliquots of haemolysed whole blood. All samples and the background were measured

for at least 6,000 counts and at least five samples were taken at regular intervals during estimation of the $T_{1/2}Cr$. The radiochromium red cell survival time was taken as the time in days for the radioactivity in the blood to decline to 50% of the radioactivity of a sample taken 15 minutes after injection of the labelled red cells. Sample readings were corrected for radioactive decay but not for chromium elution, and were plotted against time on semilogarithmic paper. In those patients whose haemoglobin level was stable the haematocrit was used to correct sample readings for fluctuations in the blood volume (Veall and Vetter, 1958).

Red cell mass was calculated as described by Veall and Vetter (1958). **Haematocrit** was measured by centrifugation for 55 minutes in Wintrobe's tubes at 1,200 g. The result was corrected for trapped plasma (Chaplin and Mollison, 1952). **Haemoglobin** was measured by the cyanmethaemoglobin method.

Biochemical Methods

Serum sodium and potassium were measured by flame photometer, and serum chloride, creatinine, and blood urea were measured by autoanalyser. The serum phosphorus was measured by the method of Gomori (1942) and the plasma pH by the micro-Astrup method, arterialised capillary blood being used. Plasma osmolality was measured on a Knauer osmometer. Clearance values were calculated from the excretion of urea and creatinine over 24 hours and the results adjusted to a body surface of 1.73 sq. m. Urea clearance was accepted as a satisfactory measure of renal function in severe renal failure (Berlyne, 1966). All values given are the mean of several estimations.

As the blood urea concentration may vary greatly during estimation of the $T_{1/2}Cr$ a representative value was derived as follows. Serial urea values during the $T_{1/2}Cr$ estimation were plotted graphically and the resultant line was divided into 10 segments. The readings at the beginning and end of each segment were averaged and the mean of these averages is the figure given for the blood urea. In a few patients there were sufficient readings available for a simple average of all readings to give equal accuracy.

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