If vaccination were totally ineffective, the ratio between the vaccinated and non-vaccinated among patients admitted to hospital should be the same as the vaccinated to non-vaccinated ratio in the general population (Fig. 5). In the 0-4 age group, the ratio would be nine to one, but the actual ratio among the admitted cases in this age group was 1.17 to 1. A comparison between the expected ratio and the actual ratio of vaccinated to non-vaccinated patients seen is depicted graphically in Fig. 5. A decrease in value from the expected ratio represents the effectiveness of vaccination. Therefore, with the exception of the 20-39 age group, it seems clear that vaccination did offer protection against paralytic poliomyelitis. It is also noteworthy that 80.5% of the patients who recovered had a full course of vaccine, while the percentage of completely vaccinated people among those with a severe residuum was only 26%. One completely vaccinated individual died.

These results suggest that Salk vaccine does offer considerable protection against paralytic poliomyelitis.

SUMMARY

Analysis of 98 patients suffering from paralytic poliomyelitis who were treated at the University of Alberta Hospital revealed a relatively high proportion of severe disease in older patients. Some modifying effect of previous vaccination was evident, although 42 of these 98 patients had received three or more injections of Salk vaccine.

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Cerebral Embolism from Nonbacterial Thrombotic Endocarditis

E. M. ASHENHURST, M.B., B.Ch., M.R.C.P.[Edin.],
and G. CHERTKOW, M.D., F.R.C.P.[C], *Saskatoon, Sask.*

STERILE vegetations composed of fibrin, platelets and blood cells are occasionally found at necropsy on the heart valves of patients with chronic wasting disease. This condition is known as nonbacterial thrombotic endocarditis. The most commonly associated disease is carcinoma. In a large series of 78 patients, MacDonald and Robbins[1] noted the presence of carcinoma in 36%. A more recent report[2] describes concurrent malignant disease in 85% of 33 patients. Adams[6] has stated that, in the patient with a known carcinoma, the occurrence of apoplexy more often proves to be due to aseptic embolism from nonbacterial thrombotic endocarditis than to tumour emboli or metastases.

It has been suggested in the past that valvular lesions of this variety were without appreciable clinical significance.[3, 4] Subsequent observations have made this point of view no longer tenable. It is a well-established fact that embolus formation can occur. Cerebral embolism has the greatest clinical significance and usually contributes directly to the patient's death. Furthermore, an embolus from a peripheral source may be the initial manifestation of an occult carcinoma[1, 2, 5, 6] rather than the final event in advanced or disseminated malignancy. It must be stressed that, when embolization occurs as the initial manifestation, cachexia may be entirely lacking. Such a case is reported here. The occurrence over a lengthy period of numerous attacks of transient cerebral ischemia in this patient is thought to be of interest, and a description of this case may contribute to an understanding of the pathophysiology of this form of cerebral vascular disease.

From the College of Medicine and University Hospital, University of Saskatchewan, Saskatoon, Sask.

CASE REPORT

The patient, a 49-year-old married housewife, was first admitted to hospital in March 1959, with a history of vaginal bleeding of three months' duration. Examination revealed a carcinoma of the cervix, considered clinically to be Stage 1 (International Classification). From biopsy examination epidermoid cancer, Grade III, was diagnosed. She was treated by insertion of radium and external cobalt irradiation. At subsequent examinations no evidence of local recurrence of the tumour was discovered.

In February 1960, she was seen by her physician because of dizzy spells which had first appeared in

November of the previous year. These had been recurring with a frequency of two to three times weekly since December 1959. These episodes tended to occur mainly in the forenoon and were not clearly related to alterations in posture except on one or two occasions. The attacks would last from seconds to one or two minutes. One major component was unsteadiness of gait; only once or twice were they accompanied by objective vertigo. There was no associated nausea, tinnitus or hearing impairment. Her only other complaint was of visual disturbances affecting the left eye exclusively. Once again, these episodes were of brief duration and consisted of two distinct varieties: either a central scotoma or, less frequently, a complete temporal field loss. Several attacks of visual loss might occur within a single 24-hour period. Since January 1960, she had observed recurrent linear hemorrhages beneath the nails, at times accompanied by soreness and warmth of the finger pulp of the terminal phalanges. The patient stated that the episodes of unsteadiness and visual loss were closely related to the appearance of fresh crops of subungual hemorrhages. She did not have bleeding from other areas, or purpura. She was treated with nicotinic acid, and from February until May 1960, she had only four or five further attacks. During this period she was afebrile. Detailed hematological and coagulation studies were normal. A single blood culture was negative.

On May 9, while working in the kitchen, she suddenly developed incoordination of the right arm, accompanied by numbness and "pins and needles" sensations in both arms and inability to talk. Her tongue felt thick and too large for her mouth. She knew what she wanted to say, but could not make any sound. The whole attack lasted about two minutes. Afterwards she felt perfectly well and was able to resume her work. She was admitted to hospital in June for further investigation.

On examination, apart from the presence of linear hemorrhages under the finger and toe nails, no abnormality was noted. No cardiac murmurs were heard. Hematological values, blood cultures, an electroencephalogram and radiographs of the skull were normal. Urinalyses showed persistent microscopic hematuria. A definite diagnosis was not made.

Her symptoms continued unchanged and she again consulted an ophthalmologist in June 1960, because of frequent episodes of blurred vision in the left eye. Ophthalmodynamometry showed no significant difference in retinal artery pressures.

The final hospital admission was on July 1, 1960. She had suddenly lost consciousness in the morning. One hour later she was conscious and able to talk, although disoriented and confused. Neurological examination revealed left homonymous hemianopia, left facial weakness and left hemiparesis. All modalities of sensation were impaired on the left side. By the following day, she had become more difficult to arouse, and showed the syndrome of explicit verbal denial (nosoagnosia) of her hemiplegia. On July 5, a right carotid arteriogram (Fig. 1) demonstrated occlusion of the middle cerebral artery near its origin. Signs of increased intracranial pressure and tentorial herniation appeared, and the patient died on July 6.

Postmortem examination was performed. The heart weighed 255 g. No abnormalities were noted on the tricuspid, pulmonary or aortic valves. On the inner circumference of the mitral valve, and very close to the edge of the valve leaflets, were three separate clumps of vegetations (Fig. 2). These vegetations were quite friable and moderately firmly attached to the valve. Sections showed that they were composed of a homogeneous pale pink material suggestive of fibrin and platelet clot. No bacteria were present. Examination of the pelvic organs showed no evidence of recurrent tumour. However, the para-aortic lymph

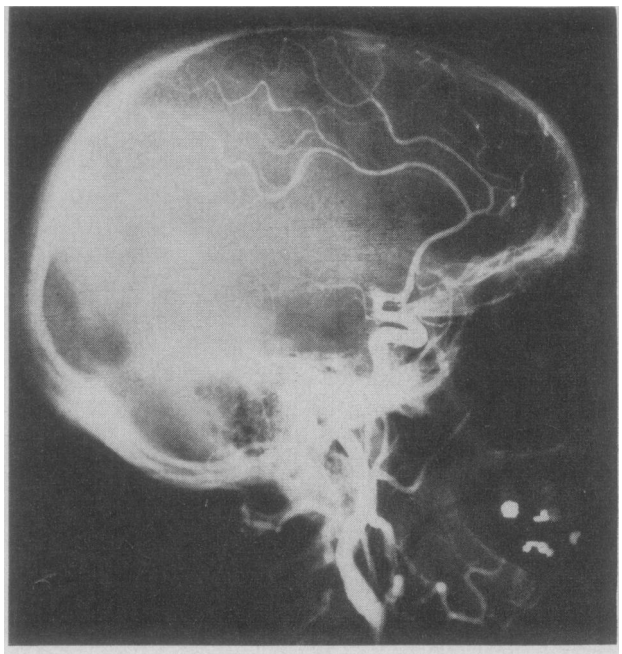

Fig. 1a.

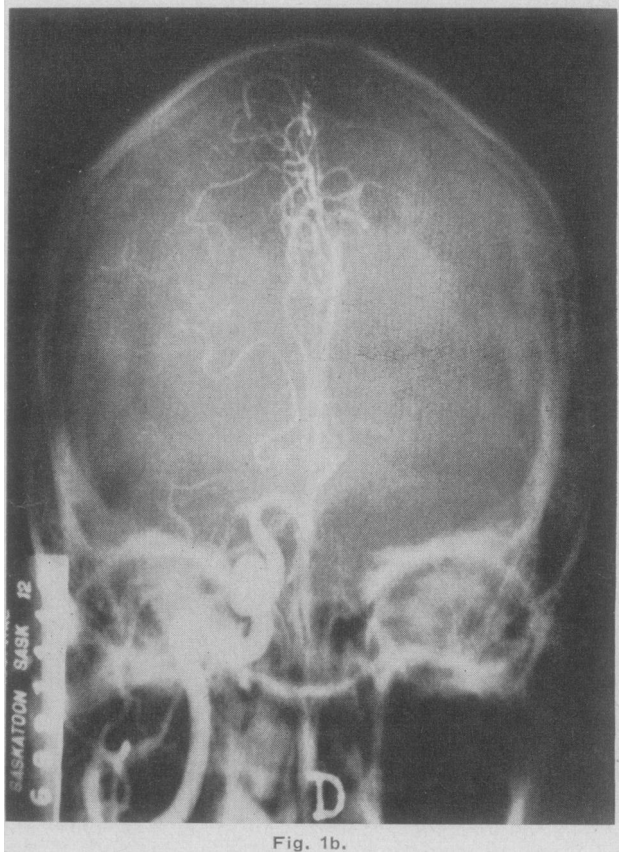

Fig. 1b.

Figs. 1a and 1b.—Right carotid arteriogram showing occlusion of the middle cerebral artery.

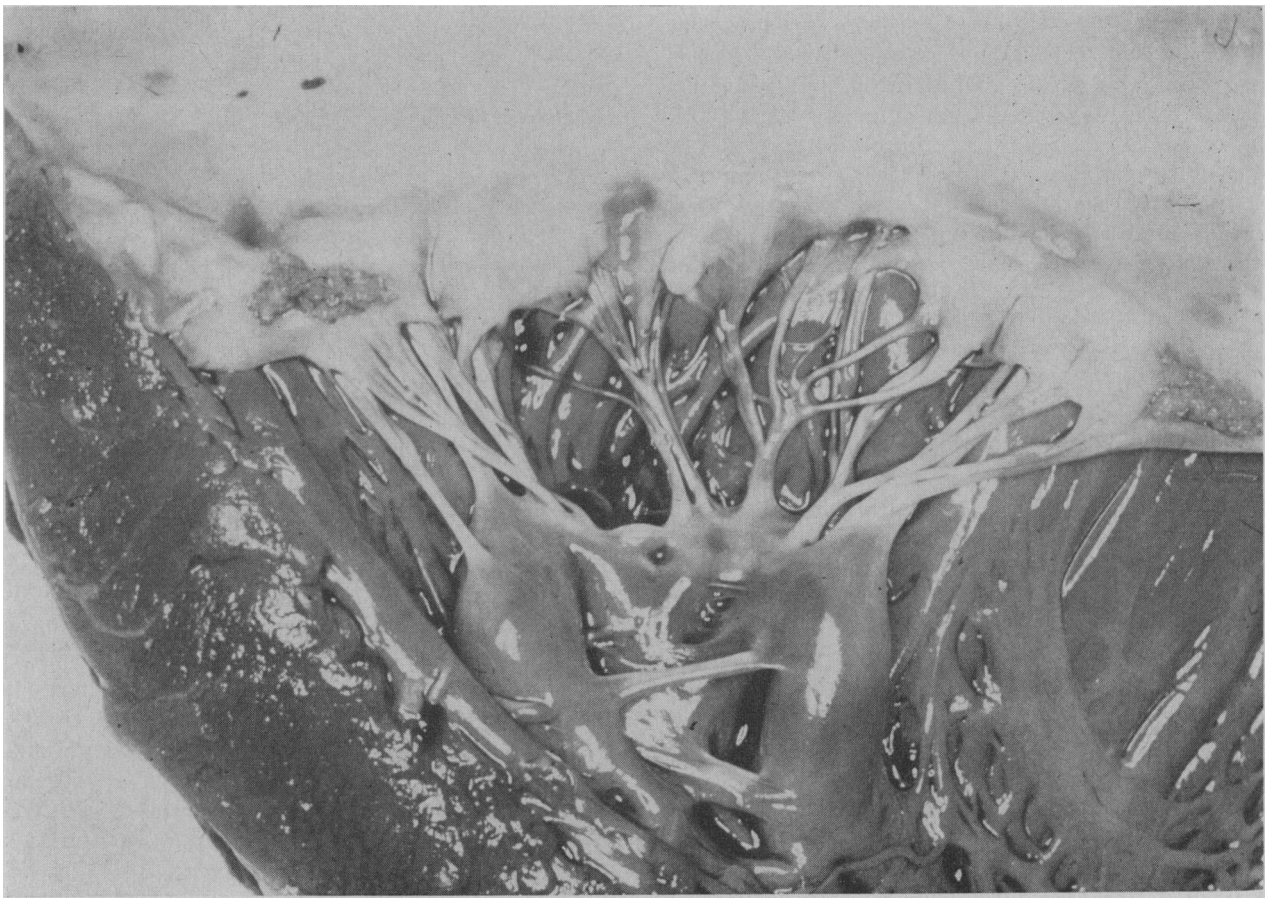

Fig. 2.—Vegetations on mitral value.

nodes and the local perilymphatic tissues were extensively infiltrated by anaplastic tumour. Comparison with the original biopsy of the cervix demonstrated this to be basically the same lesion, but more anaplastic.

Fibrin thrombi were noted in middle-sized arteries in the spleen and kidneys, with infarction of the latter organs. The right middle cerebral artery was occluded by embolus with ischemic infarction of the right cerebral hemisphere in the distribution of this vessel. There was also ischemic infarction of the occipital cortex in the distribution of the distal right posterior cerebral artery. There was uncal herniation on the right side. No other cerebral lesions were observed.

The pathological findings were typical of thrombotic nonbacterial endocarditis with systemic emboli and residual epidermoid carcinoma of the cervix in the retroperitoneal lymph nodes.

COMMENT

This is a further example of nonbacterial thrombotic endocarditis occurring in the presence of a clinically occult carcinoma. The true diagnosis was not recognized during life. The association of transient monocular blindness with occlusive disease of the internal carotid artery is well known, and this diagnosis was entertained for a time. However, the other symptoms, dizziness, ataxia and the attack of anarthria with bilateral paresthesiae, were thought to represent brain-stem vascular insufficiency. With evidence of multiplicity of lesions and the association of splinter hemorrhages in the limbs with persisting microscopic hematuria, arterial embolism appeared to be the only possible explanation of all the clinical manifestations. Repeated negative blood culture and the absence of fever or anemia seemed to exclude subacute bacterial endocarditis. We were falsely reassured by the absence of a cardiac murmur. It has been noted in previous reports of nonbacterial endocarditis that murmurs may be entirely lacking or, if present, fail to show any change in character throughout the illness.

Although there was no evidence of recurrence of the previously treated cancer, this possibility should have been more seriously considered and might have led to the correct diagnosis.

DISCUSSION

One purpose of reporting this case is to draw attention again to a combination of diseases not widely recognized; namely, carcinoma, thrombotic nonbacterial endocarditis and multiple arterial embolism. It would seem that this condition is not excessively rare. Our second and major object is to analyze the neurological component of this patient's illness and to relate it, in a general way, to the concept of transient cerebral ischemia.

The mechanism of transient ischemic attacks is incompletely understood. Two separate hypotheses have received considerable attention in recent years. First, it has been suggested that these episodes

represent transient failure of blood supply to an area of brain already compromised by vascular narrowing, this failure being secondary to a temporary fall in the systemic blood pressure. The fact that such attacks may be reproduced by hypotensive drugs, passive tilting of the patient and compression of the carotid arteries in the neck would suggest that this explanation is valid. The integrity of neural functioning during periods of normotension would be largely dependent on collateral circulation. While some patients with ischemic attacks fulfil the above criteria, it is general experience that others do not. That there must be other explanations for transient cerebral ischemia has become increasingly apparent.

The objections to the theory of hypotension may be briefly stated. Not infrequently one can reproduce neither an attack nor electroencephalographic changes by substantial reduction of the systemic blood pressure. More often than not, spontaneous attacks cannot be related to alterations in body posture. Ischemic attacks may occur in patients where disease appears to be localized to a single vessel, e.g. the internal carotid artery, and where collateral circulation might be considered adequate.[21] In some situations, transient ischemic attacks cease when thrombosis takes place, e.g. monocular blindness in internal carotid artery disease.[16] Finally, any consideration of the pathophysiology of these attacks must take account of the response of these symptoms to anticoagulant therapy. The dramatic effect of anticoagulants in this clinical situation has been repeatedly observed.[8-10] Denny-Brown[7] has recently analyzed the problem posed by what appears to be two distinct and different responses to anticoagulants in transient ischemic attacks. He states, "In our experience the effects of anticoagulation in patients with demonstrable insufficiency and known reproducible hypotensive mechanisms have been less effective." It has been proposed that, where a hypotensive mechanism has not been demonstrated, distal embolization from an atherosclerotic plaque might best explain the picture of intermittent cerebral ischemia.[7, 21]

There can be little doubt that recurrent cerebral embolism accounted for the neurological symptoms of the patient described in this report. The numerous attacks of brief duration with rapid and complete resolution are identical with those seen in cerebrovascular insufficiency. We would like to stress also the remarkable way in which successive attacks reproduced an identical neurological deficit. Amaurosis partialis fugax (temporary blindness occurring in attacks) had occurred on scores of occasions and was always confined to the left eye. The similarity of this symptom to blindness due to carotid artery disease is most striking. Apart from one attack of anarthria and bilateral paresthesiae, the remainder of the symptoms, comprised of dizziness and ataxia, recurred in a stereotyped fashion until the final episode of middle cerebral occlusion. These facts attain some importance when the objections to the theory of recurrent embolism are considered. Fisher[17] has said, "Emboli, in general, are very damaging to brain tissue so that one might escape one small attack unscathed, i.e. a reversible attack, but I think it unlikely that several successive emboli would enter exactly the same vessel and repeatedly produce the same type of transient attack." The same objections have been raised more recently by Millikan.[18] This case demonstrates that, indeed, repeated cerebral embolization of a symptomatic variety may occur without apparent cerebral damage. Furthermore, this is an example of a proximal source of emboli (mitral valve) producing repeated and identical symptomatology. The tendency for cerebral emboli to be recurrent in the same hemisphere has been observed by Wells.[22] Little is known of the hemodynamic mechanisms which might determine selective vulnerability of this nature. It may be that anatomical variations in the cerebral arteries, both in their extracranial and intracranial courses, have some influence on the distribution of emboli derived from the heart. With a more distal source of embolus formation, as in the carotid or basilar artery, it would be expected that repeated emboli should produce similar symptoms and signs with each attack.[21] In attempting to explain the frequency of a symptom, such as transient monocular blindness, other factors must be taken into consideration. The nature of the embolic material and its size are probably of importance. Platelet emboli from an atheromatous plaque would be most likely to enter a vessel of the calibre of the retinal artery. The functional importance of this vessel and the fact that it is an end artery would ensure a recognizable clinical deficit from embolic occlusion.

Evidence of this nature has been slow to accumulate. Platelet embolization of distal vessels from proximal occlusive disease has been photographed in the experimental animal.[15] Meyer[20] has recently described a patient with extracranial carotid artery disease in whom he believes this mechanism was operative. Pathological proof of the occurrence of embolism from the site of vertebral artery occlusion has been documented.[23] In an earlier study of bilateral loss of vision from cerebral infarction, Symonds and Mackenzie[11] concluded, "We believe . . . that in most, if not all, cases in which there is vertebral or basilar thrombosis the infarction of the occipital lobes results from emboli derived from the clot." These authors point out an analogous situation which follows compression of the subclavian artery by a cervical rib. There is initially thrombus formation within the artery followed by signs of circulatory failure in the fingers owing to the cumulative effect of small emboli.[12, 13] Atherosclerosis with arterial embolism may account for some cases of so-called Buerger's disease,[14] and provides a somewhat parallel situation in the vessels of the lower limbs.

We believe that the present case provides further support for the theory of recurrent emboli as a cause of transient cerebral ischemic attacks. While the source of emboli is quite unusual, the clinical picture of recurrent attacks is identical with that observed in carotid and basilar-vertebral occlusive disease. It seems justifiable to extrapolate our observations to the general problem of transient cerebral ischemia and cerebral atherosclerosis.

SUMMARY

A further case of nonbacterial thrombotic endocarditis and occult carcinoma is described. Analysis of the clinical picture, which was one of recurrent cerebral embolism, shows a striking similarity to the syndrome of transient cerebral ischemic attacks. Transient monocular blindness was a prominent symptom. It is suggested that this case lends support to the theory that, in some instances, transient ischemic attacks represent the result of recurrent embolism from distal sources.

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Clinico-Laboratory Studies of Alpha-ethylthioisonicotinamide (TH 1314)

D. G. GRAY, M.B., Ch.B.,* E. J. HAMILTON, B.Sc.† and
L. EIDUS, M.D.,† *Ottawa, Ont.*

THE FORMATION and spread of resistant strains after antibiotic treatment of chronic diseases result in therapeutic failure and public hazard, and this is one of the reasons for continued search for new antibiotics. The need for new effective drugs to combat tuberculous disease is clearly shown in recent statistics dealing with the occurrence of resistant strains in 149 Koch-positive patients with previous treatment, and 183 new cases without previous treatment.[1] In 35.5% of the Koch-positive treated cases, the strains exhibited a total loss of susceptibility to one of the generally used antibiotics (streptomycin, INH, and PAS) and, in 14.1%, a complete resistance to all three antituberculous compounds. Approximately 10% of the strains isolated from new untreated patients displayed complete resistance against one of the aforementioned drugs.

In alpha-ethylthioisonicotinamide (TH 1314), we gained an antituberculous drug which is as active as streptomycin *in vitro* and effective against INH-resistant and streptomycin-resistant strains.[2] Another advantage of TH 1314 is its effectiveness against a number of unclassified mycobacteria, generally resistant to the majority of antituberculous compounds.[2-5]

Laboratory experiments concerning the behaviour of TH 1314 in the host organism[2, 6] showed that TH 1314, administered intravenously into rabbits, is rapidly and widely distributed through the body. Its relative distribution volume is 0.86 mg./ml., representing an 86% distribution. Furthermore, the tissue concentration of TH 1314 in the different organs (lung, liver, kidney and spleen) was very similar to the serum level, so that the latter is indicative of the organ concentrations. Similar results were obtained when TH 1314 was administered subcutaneously into mice and guinea pigs.[6, 7]

The comparison of TH 1314 with isonicotinylhydrazine (INH),[7] which has a chemically similar structure but a different bacteriological action, showed that the distribution of INH is less extensive (62.5%) but its elimination from the body slower. TH 1314 has a half-life of 35 minutes, while that of INH is 54.6 minutes. Furthermore, the total clearance of TH 1314 (48.34 ml./min.) was approximately twice that of INH (25.49 ml./min.).

*Royal Ottawa Sanatorium.
†Biologics Control Laboratories, Laboratory of Hygiene, Department of National Health and Welfare.