Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies

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Abstract

Objective—To evaluate the effect of intravenous high dose human immunoglobulin (IVig) therapy on the clinical course and autoantibody titres of patients with neurological paraneoplastic syndromes.

Methods—Twenty two patients with paraneoplastic encephalomyelitis and sensory neuronopathy syndrome associated with anti-Hu antibodies (18) or paraneoplastic cerebellar degeneration (PCD) with anti-Yo antibodies (four), were treated with 1–26 (mean 5·9) cycles of IVIg. The Rankin scale was used to evaluate the response.

Results—The only serious toxicity was one case of haemolytic anaemia. Twenty one patients were evaluable for therapeutic response. One patient, with subacute sensory neuronopathy (SSN), improved for at least 15 months, 10 remained stable (eight with anti-Hu and two with anti-Yo antibodies), and 10 deteriorated (eight with anti-Hu and two with anti-Yo antibodies). In seven of the 10 patients who stabilised, the syndrome had already made a plateau when the treatment started but three patients (one with anti-Hu and two with anti-Yo antibodies) who had still been progressing stabilised for six, eight, and more than 48 months, including one patient with SSN who achieved stabilisation when the neurological dysfunction was only moderate (Rankin scale = 3). Another patient with SSN and initial stable response worsened when IVIg was reduced and improved when it was increased. No significant predictive factors of outcome could be identified but improvement or stabilisation was more frequent in patients with isolated involvement of the peripheral nervous system (62%) than in patients with evidence of CNS damage (37%) at the onset of treatment. Stabilisation in patients with CNS involvement was only achieved when the neurological dysfunction was already severe (Rankin scale > 3). The titres of autoantibodies did not change significantly.

Conclusion—Treatment with IVIg at the doses given in the present protocol was not effective in paraneoplastic CNS syndromes associated with antineuronal antibodies. The role of this regime in the treatment of SSN should be further evaluated.

Keywords: immunoglobulin treatment; paraneoplastic neurological syndromes; antineuronal autoantibodies; Rankin scale

Specific autoantibodies against neuronal antigens are found in serum and CSF of patients with paraneoplastic syndromes of the nervous system. The best characterised are the paraneoplastic encephalomyelitis/sensory neuronopathy syndrome with anti-Hu antibodies and small cell lung cancer and paraneoplastic cerebellar degeneration (PCD) with anti-Yo antibodies and breast or ovarian cancer. Anti-Hu and anti-Yo antibodies are directed against antigens shared by the primary tumour and neurons suggesting that an autoimmune mechanism is responsible for the neurological syndrome. There is no recognised treatment. Treatment of the tumour is often not effective in arresting the progressive course of the disease and in many instances the tumour is not detected at the onset of paraneoplastic syndromes. To date, immunosuppressive treatments, including corticosteroids or plasmapheresis, have not been useful, with a few exceptions. In this study, we evaluated the effect of intravenous human immunoglobulin (IVIg), which has been a successful treatment in several autoimmune diseases.

Patients and methods

Twenty two patients (nine women and 13 men) aged 35 to 78 (mean 59) years, with PCD with anti-Yo antibodies (four) or paraneoplastic encephalomyelitis/sensory neuronopathy syndrome with anti-Hu antibodies (18) received IVIg between 1990 and 1994 (table). Of 18 patients with anti-Hu antibodies, five had multifocal CNS involvement and 13 had no CNS involvement when the treatment began. Nine of the 13 patients had a subacute sensory neuronopathy (SSN) and four a sensorimotor neuropathy. In addition, seven of the 13 patients with neuropathy also presented signs of dysautonomia. Four patients had intestinal pseudo-obstruction, two orthostatic hypotension (one of them also had areflexic mydriasis), and one impotence. The four patients with PCD had an isolated cerebellar syndrome. No patient started the IVIg treatment in the month after the onset of the neurological dysfunction and only four did so in the second month (table). The median delay between development of paraneoplastic symptoms and IVIg was five (range 2 to 24) months. The neurological syndrome was stable when IVIg treatment started in 11 patients.
### Clinical features of patients treated with IVIg

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/ Age</th>
<th>Tumour(s)</th>
<th>Antibody type</th>
<th>Delay(c) PNS tumour (months)</th>
<th>Clinical picture</th>
<th>Delay(f) IVIg (months)</th>
<th>IVIg (µg)</th>
<th>Tumour(h) treatment during IVIg (months)</th>
<th>RS at onset (i)</th>
<th>Effect(j) of IVIg on PNS</th>
<th>Survival after IVIg (months)</th>
<th>Cause of death</th>
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<tbody>
<tr>
<td>1</td>
<td>M, 71</td>
<td>SCLC</td>
<td>Hu</td>
<td>17+</td>
<td>Brainstem(d)</td>
<td>18</td>
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<td>TX refused</td>
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<td>2</td>
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<td>Hu</td>
<td>0-25+</td>
<td>Lambert-Eaton</td>
<td>2</td>
<td>1</td>
<td>CDDP/ VP16</td>
<td>3</td>
<td>PD</td>
<td>2</td>
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<td>3+</td>
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<td>3</td>
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<td>3</td>
<td>PD</td>
<td>3</td>
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<tr>
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<td>ADR/VP16/ CPM</td>
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<td>4</td>
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<td>PD</td>
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<td>SSN(e)</td>
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<td>12</td>
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<td>Hu</td>
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<td>SMN(e)</td>
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<td>7</td>
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<tr>
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<td>2+</td>
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<td>Limbic(d)</td>
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<td>NA</td>
<td>SSN(e)</td>
<td>12</td>
<td>26</td>
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<td>24</td>
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<tr>
<td>16</td>
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<td>Yo</td>
<td>1-</td>
<td>PCD(e)</td>
<td>2</td>
<td>5</td>
<td>CDBCA</td>
<td>4</td>
<td>Stable</td>
<td>8</td>
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<tr>
<td>17</td>
<td>F, 78</td>
<td>Breast</td>
<td>Yo</td>
<td>8-</td>
<td>PCD(e)</td>
<td>8</td>
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<td>Pulmonary embolism</td>
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<tr>
<td>18</td>
<td>F, 43</td>
<td>Breast</td>
<td>Yo</td>
<td>6+</td>
<td>PCD(e)</td>
<td>3</td>
<td>2</td>
<td>None</td>
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<td>PD</td>
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<td>Neuro</td>
</tr>
<tr>
<td>19</td>
<td>F, 73</td>
<td>Breast</td>
<td>Yo</td>
<td>4+</td>
<td>PCD(e)</td>
<td>5</td>
<td>1</td>
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<td>SCLC</td>
<td>Hu</td>
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<td>2</td>
<td>13</td>
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<td>7+</td>
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<td>5</td>
<td>ADR/VP16/ CDDP/ CPM, RT</td>
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<td>12+</td>
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<tr>
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<td>Hu</td>
<td>10+</td>
<td>SMN(e)</td>
<td>8</td>
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<td>ADR/VP16/ CDDP/ CPM, RT</td>
<td>3</td>
<td>Stable</td>
<td>11+</td>
<td>Alive</td>
</tr>
</tbody>
</table>

(a) Tumour: SCLC = small cell lung cancer; SCC = small cell cancer; LCLC = large cell lung cancer; No = no tumour found. (b) No histology. (c) Delay between the occurrence of the paraneoplastic neurological syndrome (PNS) and discovery of the tumour: + the PNS precedes the tumour; − the PNS follows the tumour; NA = not appropriate. (d) Brainstem = brainstem encephalitis; Limbic = limbic encephalitis. (e) SSN = subacute sensory neuropathy; SMN = sensorimotor neuropathy; PCD = paraneoplastic cerebellar degeneration. (f) Delay in PNS/IVIg = Delay between the occurrence of PNS and the onset of IVIg. (g) Number of IVIg cycles. (h) CDDP = cisplatin; ADR = Adriamycin; VP16 = etoposide; MTX = methotrexate; CPM = cyclophosphamide; CDBCA = carboplatin; 5 FU = 5-fluorouracil; RT = radiotherapy. (i) Rankin scale at onset. (j) Effect of IVIg on paraneoplastic neurological syndrome. PD = progression. (k) Clinical evolution after IVIg courses.

(50%). Stable disease was defined as the absence of progression of the neurological syndrome in the month before the onset of treatment.

**NATURE AND TREATMENT OF THE PRIMARY TUMOUR**

A tumour was found in 20 patients. In 16, the neurological syndrome preceded the tumour diagnosis (mean time 7-3 (range 0–31) months). The neurological syndrome occurred after the tumour diagnosis (mean time 4-4 (range 1–4) months) in four patients (two with PCD and two with paraneoplastic encephalomyelitis/sensory neuropathy syndrome). In patients with anti-Hu antibodies, the tumour histology was small cell cancer (12 patients), large cell lung cancer (one), prostate adenocarcinoma (one), and ovarian dysgerminoma (one). Histological confirmation was not obtained in one patient with a mass lesion on chest radiography. No tumour was found in two patients with anti-Hu antibodies after a total follow up of three and more than 29 months. In patients with anti-Yo antibodies, the tumours found were breast (three) and ovarian (one). Seven patients received treatment for the tumour before IVIg. In three of them the paraneoplastic neurological syndromes appeared despite the tumour treatment. In the other four, they were known at the time of tumour treatment but none improved and only two stabilised. Nine patients had treatment of the tumour during IVIg therapy (table).

**THERAPEUTIC PROTOCOL**

Twenty two patients were treated with IVIg. Patients received IVIg, 0.5 g/kg/day for five days. Treatment was repeated every four weeks for three months. IVIg was continued for six months or more in stable or improving patients (0.5 g/kg/day for one day, monthly). Neurological impairment was evaluated by a
modified Rankin scale.\(^1\)\(^,\)\(^10\) (0 = asymptomatic patient; 1 = non-disabling symptoms which do not interfere with lifestyle; 2 = minor disabling symptoms, which lead to some restriction of lifestyle but do not prevent totally independent existence; 3 = symptoms significantly interfere with lifestyle or prevent totally independent existence; 4 = moderately severe disabling symptoms which clearly prevent independent existence with total support for basic daily activities; 5 = severe disabling, totally dependent requiring constant attention day and night; 6 = death from neurological symptoms). Symptoms were considered improved or deteriorated if there was a change of at least 1 point in the Rankin scale. Stabilisation was defined as no change of Rankin scale after 3 courses of IVIg.

The detection of anti-Hu and anti-Yo antibodies was done by indirect immunoperoxidase on frozen sections of normal human brain cortex or cerebellum, and confirmed by western blot analysis.\(^9\)\(^,\)\(^11\) Serum and CSF anti-Hu and anti-Yo titres were defined as the reciprocal value of the highest dilution that demonstrated neuronal nuclear or Purkinje cell staining. Antibody titrations were done monthly before each treatment.

Results
TOLERANCE
Patients received 1–26 cycles of IVIg (mean: 5.8). Tolerance was good in 19 patients. Three patients had side effects of IVIg: one had transient headache at each cycle, one had a transient episode of fever, malaise, and cyanosis but the IVIg could be continued and one (patient 18, table) had a severe haemolytic anaemia requiring discontinuation of IVIg after two courses.

THERAPEUTIC EFFECTS
Twenty one patients were evaluable for therapeutic response. One patient (1, table) refused further treatment after one course. One patient (20, table) with a subacute sensory neuronopathy (SSN) improved. In this patient, who also received antitumour treatment, symptoms were progressing when the treatment began. He could not walk alone at the onset of treatment but after one course, he became able to walk easily and even to ride a bicycle and to go hunting. He remains improved 15 months later. Ten patients were considered stable (five SSN, two sensorimotor neuropathy, one paraneoplastic encephalomyelitis, two PCD). However, seven of them were already stable at the onset of IVIg. The three patients who were progressing (17, 16, 7, table) stabilised after the first course of IVIg and remained so for 6, 8, and more than 48 months with IVIg. Among them, two patients had PCD with severe cerebellar dysfunction (Rankin scale of 4 and 5) whereas the third patient with a SSN remained stable with a moderate deficit (Rankin scale of 3). An unusual course was observed in one patient (14, table) with a SSN who had stable sensory symptoms and a Rankin scale of 1 before initiation of therapy. She was stable during the first three cycles of IVIg and therefore fulfilled the criteria for stabilisation. However, she developed a dysautonomia (subocclusion) when the dose of IVIg was reduced to one treatment per month. A new cycle of five days treatment was restarted and the dysautonomia improved. A second deterioration with increased sensory ataxia occurred 10 months later after slow reduction of the IVIg doses. She improved again after an increased dosage. Twenty nine months after the onset of treatment she still had a Rankin scale of 1. Finally, 10 patients deteriorated during IVIg (three with paraneoplastic encephalomyelitis, two with sensorimotor neuropathy, three with SSN, and two with PCD). One of them (2, table), with SSN and severe orthostatic hypotension died suddenly from unknown reasons two months after the first cycle. He was considered a treatment failure despite a clear improvement of the orthostatic hypotension during this period because we could not rule out a dysautonomia as the cause of death.

We did not identify significant predictive factors of response or stabilisation including the delay in the onset of IVIg, the degree of disability before IVIg, or concomitant treatment of the tumour. However, 62% (8/13) of patients with symptoms restricted to the peripheral nervous system improved or stabilised whereas none of the patients with CNS involvement (paraneoplastic encephalomyelitis or PCD) improved and only 37.5% (3/8) of them stabilised. In all patients with CNS involvement stabilisation was achieved when there was already severe neurological dysfunction (Rankin scale > 3). Median survival was six months for the entire group. Fourteen patients died, seven from neurological disease, four from tumour progression, one from pulmonary embolism, one from suicide, and one had a sudden unexplained death.

The serum titres of the antibodies did not change significantly during the IVIg treatment although there was a trend toward reduction of the titres in five evaluable patients (17200 (SD 13682) before, 11600 (SD 11696) after one course, 8400 (SD 4979) after two courses, 9200 (SD 4381) after three courses). Titres in CSF were not measured.

Discussion
Human immunoglobulins have been used with success in several neurological diseases with a presumed or proved autoimmune basis such as chronic inflammatory demyelinating polyneuropathy,\(^1\)\(^,\)\(^10\)\(^,\) dermamyelitis syringomyelitis,\(^4\) or myasthenia gravis.\(^1\)\(^,\)\(^3\)

This is the first study to evaluate the effect of IVIg therapy in a series of patients with paraneoplastic neurological syndromes and antineuronal antibodies. The study was designed as an open preliminary trial looking for a clear positive result that had an impact on the degree of disability of the patients. Although we recognise that these trials are not the best to evaluate a given treatment, it is highly unlikely that a double blind randomised
Intravenous immunoglobulin (IVIg) treatment can be designed in these disorders due to their low frequency.

In the present study, improvement was only seen in one patient but stabilisation occurred in 10 (47.6%). The patient who improved also received concomitant antitumour treatment. It is therefore possible that antitumour treatment was in part responsible for neurological improvement. Although there are a few reports of regression of paraneoplastic neurological syndromes after treatment of the primary tumour alone and one report of spontaneous improvement, two reasons make us believe that IVIg therapy was of some benefit: (1) neurological improvement after treatment of the tumour is very rare in patients with paraneoplastic neurological syndromes and circulating autoantibodies. In a review of 71 patients with the Hu syndrome, Dalmau et al could not find a single case of improvement after treatment of the primary tumour. In addition we also found no case of improvement in a previous study of plasmapheresis and antineoplastic treatment in 16 patients with paraneoplastic neurological syndromes with antineuronal antibodies. (2) Four of our patients had already received antitumour treatment before IVIg at a time when they were neurologically symptomatic, without improvement of paraneoplastic neurological syndromes.

Interpretation of stabilisation is difficult. Paraneoplastic encephalomyelitis and PCD are characterised by neuronal loss and therefore a stabilisation of the disorder may be considered an effective response to the treatment. Of the 10 patients who experienced stabilisation, seven were already stable before IVIg treatment, suggesting that they had either an indolent form of the disease or spontaneous stabilisation unrelated to the treatment which occurs sometimes in PCD patients. Nevertheless, in one of the three patients who were progressing when IVIg was started, the SSN has remained stable for more than four years.

Analysis of our data suggests that the type of neurological involvement at the onset of treatment may have an influence on the outcome. Indeed, improvement or stabilisation with a moderate (Rankin scale ≤ 3) degree of dysfunction in the setting of neurological progression at the onset of IVIg therapy, was only seen in two patients with SSN. In addition, another patient with SSN apparently became "IVIg dependent", as she deteriorated at each reduction of the IVIg dose with a return to her previous condition after increased dosage. We previously showed that the development of CNS symptoms is associated with the occurrence of an intrathecal synthesis of antineuronal antibodies, which rarely exist in patients with pure SSN. Because the high molecular weight (146 kDa) of IgG prevents entry into the CNS through the blood-brain barrier, it could be speculated that IgG could not reach the target in patients with CNS symptoms. However, patients with stiff man syndrome and antineglutamic acid decarboxylase antibodies improve after IVIg when the cause of the neurological deficit is thought to be a pathological involvement of the spinal cord interneurons. Intra-lesional or intrathecal injection of local anaesthetics in patients with SSN did not improve their condition, suggesting that the spontaneous stabilisation observed in some patients with SSN may be the result of a breakdown of their spinal cord interneurons, which are thought to form a myelinated layer below the inner plexiform layer on the ventral aspect of the spinal cord. It may be that IVIg therapy induces regression of the spinal cord interneurons that are thought to be responsible for the spinal cord symptoms in patients with SSN.

The mechanism of action of IVIg in autoimmune diseases is unclear. We did not find a significant effect of the treatment on the titre of serum autoantibodies even though there was a trend to a progressive reduction of the titre after three courses of IVIg. This feature suggests that in paraneoplastic neurological disorders the action of IVIg is not mediated by anti-idiotypic antibodies or down regulation of antibody production. However, the lack of consistent reduction in the titre of autoantibodies in the present series does not necessarily explain the modest clinical results. Previous studies of IVIg treatment in myasthenia gravis and in the Lambert-Eaton myasthenic syndrome did not show a correlation between the clinical response and the titre of autoantibodies. In conclusion, IVIg therapy at the doses given in the present study seems not to be effective in patients with paraneoplastic neurological syndromes affecting the CNS. The modification of the clinical course in three of the nine patients with SSN (32%) after IVIg therapy suggests that the treatment should be further evaluated in this subgroup of patients with paraneoplastic neurological syndromes.

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Doctors' remedies

As the last of these extracts was written over 70 years ago, it might seem that their message has dimmed; far from it. Medicine (and surgery) can still be applied inappropriately, prolong life unreasonably, and create new disorders to replace those for which it was first used.

Jonathan Swift, 1726, Gulliver's travels

For nature (as the physicians allude) having intended the superior anterior orifice only for the intromission of solids and liquids, and the inferior posterior for ejections; these artists ingeniously considering that in all diseases nature is forced out of her seat; therefore to replace her in it, the body must be treated in a manner directly contrary, by interchanging the use of each orifice, forcing solids and liquids in at the anus, and making evacuations at the mouth.

Laurence Sterne, 1759-67, The life and opinions of Tristram Shandy, gentleman

The stroke at the Prince of Physicians, with which he began, was no more than a short insult upon his sorrowful complaint of the ars longa,—and vita brevis—life short, cried my father,—and the art of healing tedious! And who are we to thank for both, the one and the other, but the ignorance of quacks themselves, and the stage-loads of chymical nostrums, and peripatetic lumbar, with which in all ages, they have first flattered the world, and at last deceived it.

Mark Twain, 1894, Pudd'nhead Wilson

The doctor asked for a few sheets of paper and a pen, and said he would write a prescription; which he did. It was one of Galen's; in fact, it was Galen's favorite, and had been slaying people for sixteen thousand years. Galen used it for everything, applied it to everything, said it would remove everything, fromwarts all the way through to lungs—and it generally did. Galen was still the only medical authority recognised in Missouri; his practice was the only practice known to the Missouri doctors, and his prescriptions were the only ammunition they carried when they went out for game. By and by Dr Clapppool laid down his pen and read the result of his labors aloud, carefully and deliberately, for this bat- tle must be constructed on the premises by the family, and mistakes could occur; for he wrote a doctor's hand—the hand which from the beginning of time has been so disastrous to the apothecary and so profitable to the undertaker... "There," he said, "That will fix the patient; give his hyman a dipperful every three-quarters of an hour..."—"While he survives," muttered Luigi...—

During Monday, Tuesday, and Wednesday the twins grew steadily worse; but then the doctor was dismissed south to attend his mother's funeral, and they got well in forty-eight hours.

H G Wells, 1900, Tono Bungay

Close at hand was the doctor with one of those cruel and idiotic injection needles modern science puts in the hands of these half-educated young men, keeping my uncle flickeringly alive for no reason whatever.

Marcel Proust, 1923, Remembrance of things past

The captive

Nature scarcely seems capable of giving us any but quite short illnesses. But medicine has developed the art of prolonging them. Remedies, the respite that they procure, the relapses that a temporary cessation of them provokes, produce a simulacrum of illness to which the patient grows so accustomed that he ends by making it permanent, just as children have regular fits of coughing long after they have been cured of the whooping cough. Then the remedies begin to have less effect, the doses are increased, they cease to do any good, but they have begun to do harm thanks to this lasting indisposition. Nature would not have offered them so long a tenure. It is a great wonder that medicine can almost rival nature in forcing man to remain in bed to continue taking some drug on pain of death. From then on, the artificially granted illness has taken root, has become a secondary but a genuine illness, with this difference only, that natural illnesses are cured, but never those which medicine creates, for it does not know the secret of their cure.