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Subacute myelo-optic neuropathy and clioquinol

An epidemiological case-history for diagnosis

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Meade, T. W. (1975). *British Journal of Preventive and Social Medicine*, **29**, 157-169. **Subacute myelo-optic neuropathy and clioquinol: an epidemiological case-history for diagnosis.** Between about 1955 and 1970, some 10 000 Japanese were diagnosed as having subacute myelo-optic neuropathy (SMON), a new disease characterized by abdominal and neurological manifestations, the former nearly always preceding the latter. Circumstantial evidence obtained in 1969–70 suggested that SMON might have been caused by clioquinol (CQL), a gastro-intestinal disinfectant, and led to the suspension of further sales of CQL in Japan. However, several inconsistencies for the CQL theory of SMON have now emerged; first, CQL had been widely used in Japan for nearly 20 years before SMON occurred. Secondly, the SMON epidemic began to subside several months before CQL sales were suspended. Thirdly, a large proportion of SMON patients—probably about one-third and possibly more—had not taken CQL within six months of the onset of the disease (the modal interval between first taking CQL and the onset of SMON being about three weeks, and more than 100 days in only 4% of SMON patients); of the remaining two-thirds or so, many had taken CQL as part of the treatment of the first (that is, abdominal) symptoms of SMON itself. Fourthly, there was no dose-response relationship. Finally, SMON rarely, if ever, occurred outside Japan. CQL could, however, have been involved in the causation of SMON as an optional enhancer of some other necessary cause; the history of post-war environmental pollution in Japan is compatible with this hypothesis. Over-readiness to accept postulated toxic effects of medicines and chemicals as proven is likely to do at least as much harm as good to individual and community health.

The Disease, and a Suspected Cause

During the mid- and late 1950s, doctors in Japan were consulted by increasing numbers of patients with an unusual combination of alimentary and neurological complaints. The common clinical picture was of abdominal pain and/or diarrhoea, followed within a few days or weeks by painful dysaesthesiae; in addition to the predominantly sensory disturbances, upper and/or lower motor neurone signs occurred in just over 50% of cases, and visual disorders due to optic neuritis in about 28% (Sobue *et al.*, 1971). The disease was called subacute myelo-optic neuropathy, or SMON. Table I summarizes Kono's (1971) list of SMON's 'cardinal' and other symptoms; of particular importance is that the abdominal symptoms nearly always preceded the neurological. Case-fatality from SMON itself is hard to assess because the disease was very often associated with other conditions, many having a poor prognosis; but it is likely that not more than 5% of SMON patients actually died of the disease itself. On the other hand, probably 90% of patients were left with dysaesthesiae, and 50% with limb weakness, visual impairment, or both; 10 to 15% were completely disabled (Kono, 1971). By the time the epidemic was over, some 10 000 Japanese were said to have developed SMON, a figure of the same order as the world wide total of thalidomide-deformed children. The main epidemiological features of the disease are summarized in Table II; these have not been seriously contested by the protagonists or antagonists of the hypothesis on aetiology with which this review is concerned.

TABLE I
'CARDINAL' AND OTHER SYMPTOMS OF SMON

'Cardinal'	1. Abdominal, preceding neurological in most cases 2. Neurological (a) Acute or subacute onset (b) Sensory disturbances predominate, mainly in lower part of body
Other	Include motor, visual, psychological and sphincter disturbances

For full details, see Kono (1971)

TABLE II
MAIN EPIDEMIOLOGICAL FEATURES OF SMON

Female incidence about twice that of male incidence (2·6 and 1·2/annum per 100 000 population of all ages)
Incidence maximum in summer months
Incidence maximum in seventh and eighth decades
Majority of patients from professional rather than labouring classes
Frequently associated with other diseases (see also Table IV)

See Kono (1971 and 1973)

Subacute combined degeneration (SCD) of the cord is the main neurological differential diagnosis of SMON; multiple sclerosis has also to be considered. In addition to pernicious anaemia, SCD may, of course, be associated with a number of intestinal disorders resulting in impaired vitamin B_{12} adsorption—such as blind loops, strictures, and anastomoses. Coeliac disease, lead, mercury, arsenic, and thallium intoxications also give rise to both abdominal and neurological manifestations, so that SMON was by no means unique in these respects. Neurologists are in general agreement that SMON exhibiting all its neurological features, visual, motor, and sensory, was a distinct and real clinical syndrome, but it is clear that in its less complete forms it was not easily distinguishable from other causes of peripheral neuropathy and myelopathy. Since these incomplete forms (for example, abdominal symptoms and dysaesthesiae) accounted for most cases, opportunities for misdiagnosis were frequent, a fact with obvious implications for epidemiological studies.

For virtually the whole course of the epidemic, which ran from 1955 to 1970, SMON was regarded as probably being an infectious disease (Ogata and Jitsunari, 1970). The main points in favour of an infective aetiology were a regular summer peak in incidence, and claims that the disease clustered in individuals drinking faecally contaminated water from the same source. Various workers (see Kono, 1971) claimed to have identified or isolated microbiological pathogens. The newness of the disease, its predilection for the elderly rather than the young, and the absence of expected clinical and pathological features of infective disease (for example, in the cerebrospinal fluid) were reasons against the infective theory.

In 1963, a greenish colouration of the tongue was noticed in some SMON patients (Tsubaki, Honma, and Hoshi, 1971a). Although this observation was thought to be of some possible relevance to the aetiology of SMON, it did not receive much further attention at that time. In February 1970, however, Takasu, Igata, and Toyokura (1970) reported on greenish faeces, and in May 1970 Igata, Hasegawa, and Tsuji (1970) on greenish urine in SMON patients; the green colour was found to be due to the iron chelate of clioquinol (CQL), a gastrointestinal disinfectant agent which had until then been generally thought not to be adsorbed from the gut. The presence of a chelate of CQL in urine demonstrated, however, that the preparation could be adsorbed, and this being so, it was at least possible that CQL was neurotoxic. (David *et al.* (1933) had recorded the urinary excretion of Vioform many years previously.)

After further investigations, including the demonstration that many SMON patients had recently taken CQL, a public announcement to the effect that CQL was probably the cause of SMON was made early in August 1970, and on 8 September 1970 the Japanese government suspended all further sales of the preparation (except for its very occasional use in exceptional circumstances such as the rare childhood disorder acrodermatitis enteropathica in which CQL is said often to be life-saving).

CQL is the generic name for a group of iodinated hydroxyquinolines; in the West, it is chiefly used (under the brand names Entero-Vioform and Mexaform) for the prophylaxis and treatment of 'traveller's diarrhoea', although the evidence that it is effective for these purposes is equivocal, at best. In other parts of the world, however, the main use of CQL is in the treatment of amoebiasis. Having been available for many years, CQL has never been subjected to formal clinical trials, but the view of many physicians in countries where amoebiasis is endemic is that the preparation is effective in the treatment of the disease; furthermore, it is cheaper than other amoebicides such as metronidazole. Neurotoxic reactions (possibly dose-related) to huge doses of CQL have been described (Gholz and Arons, 1964), but these are not the same as SMON.

To date, it has not been suggested, nor is there any evidence, that some CQL preparations cause SMON while others do not, or that substances

other than CQL (such as different emulsifiers, contaminants, or degradation products of CQL) were responsible. Clioquinol (CQL) is therefore used here in its generic sense, without implying other substances with which CQL may be mixed or contaminated, or to which it may be degraded (see later). Until the suspension of sales in 1970 nearly 200 CQL-containing preparations were available in Japan although most contained only small amounts of CQL. Over-the-counter sales of CQL probably accounted for one-third or even one-half of total sales.

Reason and Emotion in the SMON Controversy

Two misconceptions which have so far substantially clouded the issue when considering the epidemiological evidence for and against CQL as the cause of SMON need to be considered.

First, the fact that CQL sales were suspended in September 1970 is not proof that the preparation caused SMON. CQL sales were suspended for very good reasons of public health. A *prima facie* case that SMON might be caused by CQL had been made, and clearly needed to be answered. Since the therapeutic value of CQL was not such that there was any obvious likelihood of the sales suspension doing more harm than good, the decision to prohibit further sales was clearly prudent and correct. The scientific question of the nature of the association between CQL and SMON is, however, quite separate from the issue of the suspension of sales and has to be judged on different grounds from the practical reasons for the latter. Secondly, the therapeutic value or otherwise of CQL, although certainly relevant to the decision to suspend sales, is irrelevant to the question of whether the preparation caused SMON. It is clearly illogical to base an assessment of the *harmful* effects of a preparation on a belief that its *beneficial* effects may be limited. Yet it has often been assumed, both in Japan and elsewhere, that the sales suspension of a 'useless' preparation is evidence that CQL caused SMON.

Reactions to the CQL theory for SMON have to be interpreted against the background of the Japanese experience of environmental pollution; from the radiation of the atomic bombs onwards, pollution in Japan has run at levels of an almost different order of magnitude compared with the rest of the world. Mercury poisoning caused the notorius Minamata disease, and cadmium was responsible for Itai-Itai (ouch!—ouch!) bone disease. Asthma and bronchitis attributable to petrochemical pollution of the atmoshere, and Kanemi rice oil disease consequent on contamination of edible oil with polychlorobiphenyl derivatives are other examples, although they by no means exhaust the list (Ui, 1972). In addition, Japan was not only one of the earliest countries to license thalidomide but also virtually the last to withdraw it. That the Japanese approach to SMON was to assume that it was caused by CQL unless proved otherwise was therefore largely understandable, especially as there are said to have been 10 000 victims, in contrast for example, to perhaps 800 Minamata disease patients.

However, CQL had been used on a large scale for some 20 years before the SMON epidemic started; this, and analogy with approaches to the investigation of alleged adverse effects of other medicines, suggest that it is more appropriate to seek proof that CQL caused SMON, than that it did not. Clearly, this point is arguable, and neither the positive nor the negative can be established with absolute certainty; but to assume guilt in the absence of proven innocence carries potentially dangerous implications which are discussed later.

In the following review of the epidemiological evidence for and against the CQL hypothesis of SMON, the data discussed are chiefly those of the Japanese investigators who believe a cause and effect relationship between CQL and SMON to have been established.

Historical and Time-Sequence Data

Fig. 1, from Kono (1973), shows the sales of CQL in Japan from the mid-1930s and the numbers of SMON cases occurring each year. The unbroken line in Fig. 2, from Kono (1971), shows the monthly

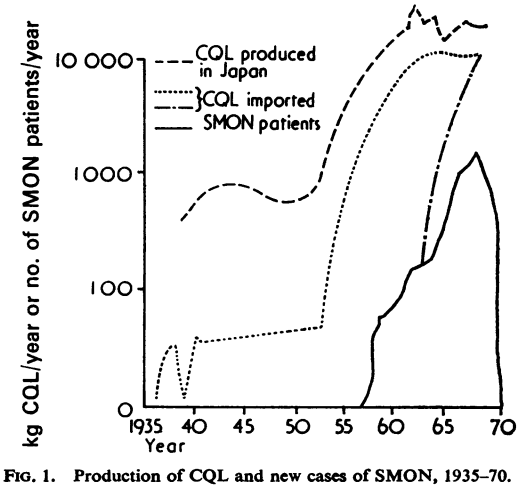

FIG. 1. Production of CQL and new cases of SMON, 1935–70.

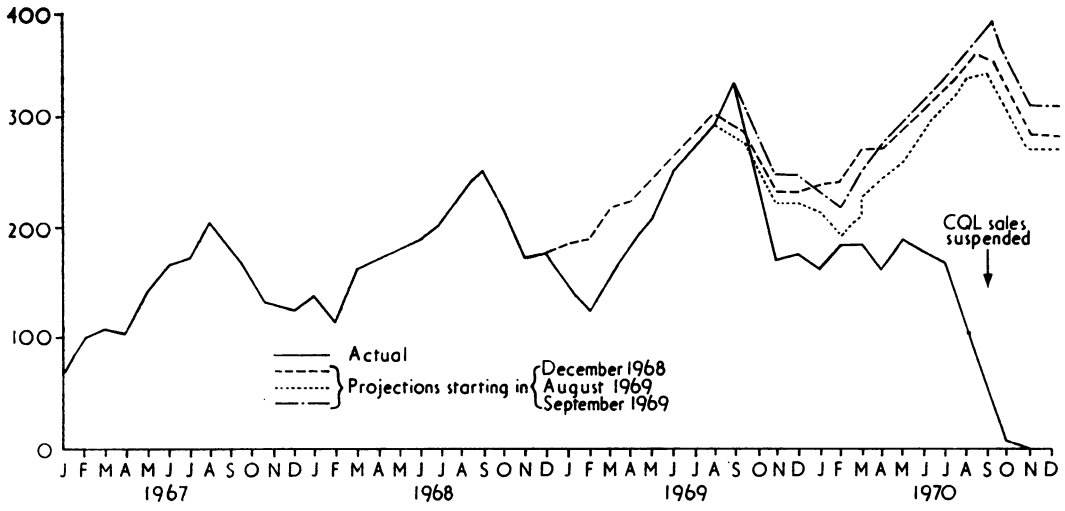

FIG. 2. New cases of SMON monthly; actual and projected, 1967-70.

numbers of new SMON cases in 1967–70. (The broken lines in Fig. 2 show projections, to be discussed later).

Two obvious questions are raised by Figs 1 and 2. First, why was there apparently no SMON before the mid-1950s in spite of substantial CQL sales? Secondly, why did the decline and disappearance of the SMON epidemic antedate the suspension of CQL sales?

The first question is difficult to answer because no sustained attempt was made to investigate how real the apparent rise in SMON incidence was, at any rate until about 1972, well after the 15-year epidemic was over. The ease with which incomplete forms of the SMON syndrome can be confused with other diseases makes it important to try to establish whether:

1. SMON was a new label applied to a condition that had already been occurring for some considerable time (that is, had SMON been underdiagnosed before the mid-1950s?)
2. Unfamiliarity with a genuinely new disease starting in the 1950s resulted in its underdiagnosis until, say, the early 1960s
3. SMON was overdiagnosed in the later stages of the epidemic
4. The figures can be taken at their face value

Only one of these possibilities has received any real attention; a series of papers (Katahira, 1972; Katahira and Nakae, 1973; Katahira and Sonoda, 1972; Takasu *et al.*, 1973) has recently claimed that SMON did occur in the pre-war period. The most detailed of these (Takasu *et al.*, 1973) reported findings in 703 typhoid patients admitted to hospital in 1937–38, of whom 30 were given CQL. Of these 703 patients, 16 were found to have dysaesthesiae of the lower limbs; 'SMON was suspected in one case, and it was possible to make a diagnosis of SMON (or it was impossible to deny a diagnosis of SMON) in the remaining 15. In six of these cases, it was difficult not to admit a diagnosis of SMON but there is some possibility that these six did not have the disease'. It was found that CQL-takers were admitted for nearly three times as long as non-takers; accordingly, only the 56 CQL non-takers admitted for more than 70 days were studied further. Four of the 30 CQL takers and four of the 56 CQL non-takers had dysaesthesiae (that is, were possibly SMON cases); the other eight (of the 16 possible SMON cases) fell into the group of CQL non-takers admitted for less than 70 days.

It is uncertain whether any of the 16 possible SMON cases really had SMON and certainly very doubtful for at least six. Of the 16 'cases', 12 had apparently not taken CQL. After several stages of selection, it is difficult to be convinced that like was compared with like. Finally, neurological complications may occur in typhoid itself. This investigation, therefore, failed to demonstrate convincingly that SMON was a real clinical entity in Japan before the second world war (or that it was caused by CQL);

the same is true of the other studies. Indeed, Katahira and Nakae (1973) identified 20 reports between 1929 and 1938 of side-effects of CQL, none of which described neurological symptoms or signs. However, some underdiagnosis of SMON in the early days of its recognition is likely to have occurred, just as some overdiagnosis probably occurred later. These uncertainties, however, do not provide a firm basis for other studies.

Fig. 2 suggests that the peak of the SMON epidemic may have passed by mid- or late 1969, that is, a year before the sales suspension, and that it had almost certainly passed by March or April 1970, that is, several months before the announcement in August 1970 of CQL's alleged toxicity and the suspension of sales in September 1970. The broken lines of Fig. 2 give three projections of the monthly numbers of new SMON cases that might have been expected had the trend established in each previous 2-year-period continued. Thus, one projection starts at the end of December 1968 (based on incidence figures for January 1967—December 1968), one at the end of August 1969, and one at the end of September 1969. Each projection gives similar results; together they indicate that the observed numbers of new SMON cases began to be fewer than expected in about September/October 1969. The usual interval between starting CQL and the onset of SMON was about three weeks and in only 4% of SMON patients was it more than 100 days (Tsubaki *et al.*, 1971a), so some change in CQL-taking habits in August/September 1969 seems to be indicated if the CQL theory of SMON is correct. (More detailed statistical analyses than those on which the projections in Fig. 2 are based could be performed, but are probably unwarranted given the non-specific nature of the incomplete, although commonly occurring, SMON syndrome, and the lack of uniform diagnostic criteria for epidemiological purposes (referred to in more detail in a later section). Moreover, the three projections in Fig. 2 are in close agreement with the calculations of the SMON Research Committee (1972) in Japan.)

From the data in Tsubaki *et al.* (1971a) on the interval between the start of CQL administration and the appearance of SMON it is also possible to estimate how quickly SMON should have disappeared after a total suspension of sales, on the assumption that CQL was the only cause of the disease. New SMON cases would have been expected in some numbers for a period of four months after the suspension; what was observed from June to October 1970, in terms of the *rate* of development of new cases (see Fig. 2), would have been expected had there been a *total* sales supension in June 1970, that was immediately and completely complied with, on *all* CQL sales, over-the-counter as well as medically prescribed. Even if all doctors had stopped using CQL completely by June 1970, over-the-counter sales were still presumably made until September 1970 and would have been expected to result in the development of new cases until January 1971, almost certainly in larger numbers than actually accurred; these numbers would have been determined by the pre-June proportion of over-the-counter to total CQL sales, said to be between 30 and 50%. Experiences at the time (late 1960s) that certain types of pressurized aerosols were implicated as a cause of sudden death in asthmatics (see Fig. 2 of Doll (1973)) indicate that doctors may, indeed, not only be aware of possible adverse effects before they are finally made known publicly, but also that they are likely to modify their practice accordingly. There is, however, no evidence that any Japanese doctor knew about and communicated the possibility of CQL as the cause of SMON in August/September 1969, which would have been necessary to explain the smaller than expected numbers of new SMON cases in September/October 1969 on the basis of advance information within the profession.

In summary, some decline in SMON incidence before September 1970 would not be incompatible with the CQL theory of the disease, although the onset of the decline may have been sufficiently long before the green urine report and the sales suspension to raise serious doubts about this theory. The *rate* of the abrupt decline that was actually observed can, however, be explained only if a very large proportion, perhaps most, of the lay public, as well as doctors, had advance warning *and* took appropriate action; this inconsistency is separate from the question of when the peak of the epidemic was passed.

In some areas of Japan, SMON did not apparently appear until well into the 1960s, and the disease

TABLE III

SMON IN TODA/WARABI, 1963–69

Year	Confirmed/Suspected	Unconfirmed	Total
1963	2	0	2
1964	18	21	39
1965	3	2	5
1966	6	1	7
1967	6	3	9
1968	2	1	3
1969	1	2	3
Total	38	30	68

waned and virtually disappeared long before the green tongue/urine reports, let alone the suspension of CQL sales. 'It was about the autumn of 1963 that SMON cases first appeared' in Toda/Warabi (SMON Research Committee, 1972); SMON cases by year of onset in this area of Japan are shown in Table III. It seems clear that the local SMON epidemic reached its peak in 1964 and that by 1968–69 it had almost entirely subsided. Another local inconsistency of this sort occurred in Okayama prefecture (SMON Research Committee, 1972) where no SMON was reported until 1967, although CQL had been in use for many years, as elsewhere in Japan.

Comparative Studies

The Japanese studies in which SMON patients have been compared with non-SMON patients for their previous CQL intake, or in which CQL-takers have been compared with CQL non-takers for their subsequent SMON experience, form perhaps the most crucial part of the epidemiological evidence available. These studies are unusually difficult to evaluate, mainly because little information is available on how far appropriate methods have been considered or adhered to, and the lack of much of the control or comparative information that is essential in this particular case, and also because of the very unusual, perhaps unique, situation in SMON that its alleged cause was also often used in its treatment.

The SMON Research Committee's first nation-wide study (1970) was mainly concerned with identifying and characterizing patients with SMON; it included 4280 patients (62·4% 'firm' SMON; 37·6% 'suspected'). The 'standards for diagnosis' in this survey were not really standard; the different ways in which the disease was viewed by different workers, and the varying diagnostic details used by three doctors involved in the study are in fact explicitly referred to. Definitions of physical signs were not given. There is little or no information on response rates or completeness of data. However, a regional study in Okayama reported in the same volume gave the results summarized in Table IV; it is not clear how the individuals without SMON were selected, but previous histories of several disorders, including gastrointestinal conditions, were found in substantially higher proportions of SMON patients than the non-SMON individuals; (a more intensive study of the SMON patients than those without it could be a partial or complete explanation for the differences shown). Sobue *et al.* (1971) reported similar findings.

The Committee reported also on further nation-wide studies (1972) in which it dealt with the CQL-taking of SMON patients. The Committee called for details on all SMON patients in designated cities and all prefectures who had attended or visited various medical institutions from 1967 to 1971. A detailed study appears to have been made only on patients whose intake of CQL before or after the development of neurological symptoms was recorded—that is, it seems where a definite note was lacking that CQL had or had not been taken, these SMON patients were not included in further studies. Before 1970 there was no reason why CQL non-usage should have been specially noted; for the SMON patients where CQL was said not to have been taken there must have been definite information to this effect. The CQL-taking part of the survey questionnaire was apparently revised in the course of the work.

Table IV

COMPARISON OF PAST MEDICAL HISTORY OF 60 SMON PATIENTS AND 3107 INDIVIDUALS WITHOUT SMON

Disease	A 60 SMON patients		B 3107 non-SMON individuals		A%/B%
	No.	%	No.	%	
Appendicitis* ..	27	45·0	507	16·3	2·8
Chronic gastritis ..	12	20·0	114	3·7	5·4
Allergic diseases ..	11	18·3	127	4·1	4·5
Gastroptosis ..	9	15·0	131	4·2	3·6
Abortion**.. ..	8	13·3	133	4·3	3·1
Tuberculosis ..	6	10·0	140	4·5	2·2
Rheumatism ..	6	10·0	92	3·0	3·3
Diarrhoea/enteritis ..	4	6·7	52	1·7	3·9

*Figures of 50% for A and 12% for B also quoted
**Women only
Kono (1973) also reports frequent occurrence of SMON in diabetes and cancer, and after laparotomy

TABLE V
CQL-TAKING WITHIN SIX MONTHS BEFORE ONSET OF NEUROLOGICAL SYMPTOMS OF SMON

	Never Ingested	Apparently not Ingested	Ingestion Confirmed	Unknown/ Uncertain*	Total
No.	269	189	1381	617	2456
%	14·6	10·3	75·1	—	100**

*There is obviously an inconsistency between the inclusion of this category in the table and indications elsewhere (see text) that the studies were confined only to those whose recent CQL-taking history was known
**Of those whose CQL-taking histories were known

Although 9249 patients were eventually identified in the studies reported on in 1972, only 2456 were included in the main analyses of CQL-taking, which are summarized in Table V. How the 2456 patients were selected is not clear, and the authors of this part of the report had serious reservations as to how representative the group was. Some prefectures did not return any questionnaires although they often had hundreds of SMON cases. If any conclusions can be drawn from this study, it is clear that even in those patients where CQL ingestion status was known, 25% had probably not ('Never' and 'Apparently not') taken CQL. If the groups for whom there was no CQL information are also considered these figures could be even higher. It has already been pointed out that the CQL-taking studies appear to have included only those whose CQL intake was definitely recorded; it thus becomes difficult to attribute the SMON patients with no apparent history of CQL-taking to inaccurate recording or recall of CQL intake at a later date.

Estimates of the proportions of SMON patients who did not take CQL vary considerably. They range from only 4% in the 171 hospital patients studied by Tsubaki, Honma, and Hoshi (1971b) through the figures just discussed, to about 50% in the series collected by the Japanese Ministry of Health and Welfare (1973). In the latter, 'not taking chinoform' (CQL) was defined as no history of the preparation having been taken for six months before the onset of SMON (although it might have been taken more than six months before or at any time after the onset), a definition which seems reasonable in view of the data of Tsubaki *et al.* (1971a) on the distribution of intervals between starting CQL and the onset of SMON. The particular value of the six cases in the Ministry series with clinical onsets between February and July 1970 (after the 'green tongue/urine' reports) and especially of the 17 cases with onsets between October 1970 and September 1972 (after both the 'green tongue/urine' reports and the sales suspension) is that they must have been investigated especially thoroughly with every expectation of positive CQL-taking histories, and yet, no such histories were elicited. It is difficult to accept that serious mistakes over both the diagnosis of SMON and the taking of CQL were made in these patients, and there is thus strong evidence for believing that SMON does occur without CQL; the 17 CQL non-taking cases described after October 1970 constitute about 50% of the total of 30 or so new SMON cases apparently reported after this date.

The observations so far described on the CQL-taking histories of SMON patients were uncontrolled; conclusions drawn from them rest on the assumption that the proportions of SMON patients who took CQL are 'exceedingly high compared with the rate of administration of other drugs' (Kono, 1971). Certainly, it may sometimes be concluded from uncontrolled observations that a preparation caused a disease; thalidomide is the outstanding example. However, CQL-taking in SMON patients is almost certain to have been a frequent occurrence for at least two reasons. First, the fact that a high proportion of SMON patients had had previous gastrointestinal disease makes it more likely that they would have taken CQL (and other preparations) than individuals without SMON. Secondly, CQL is not only the postulated cause of SMON, it may frequently be its unintentional or intentional treatment; in fact, Takasaki (1967), Kusui (1969), and Shibata and Osawa (1970) described its use in the actual management of the disease. In the 752 cases of SMON studied by Sobue *et al.* (1971), chronic abdominal disorders

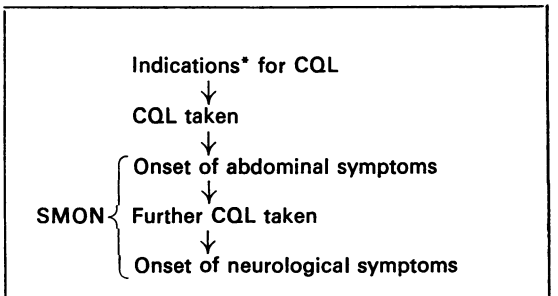

FIG. 3. Course of events and onset of SMON, assuming SMON caused by CQL.

(diarrhoea and pain) occurred in 84%, and in 87·4% of these, the abdominal symptoms *preceded* the neurological. Consequently, as Fig. 3 illustrates, any studies that simply measure CQL-taking in SMON patients over a short period of time, without distinguishing CQL taken for an initial bout of diarrhoea or abdominal pain from CQL taken after the onset of the abdominal symptoms of SMON itself, are virtually guaranteed to find a spuriously high proportion of patients with a history of CQL-taking. The most striking features of SMON are the neurological ones, and results in the Japanese studies of SMON patients have so far been almost exclusively presented in terms of CQL-taking before the onset of the *neurological* component of the disease without allowance being made for the crucial importance of the intervening onset of its abdominal symptoms. Very few attempts have been made to deal with this difficulty, but in one group of 255 patients 42% had taken CQL before the onset of the prodromal abdominal symptoms (9% during the course of chronic abdominal disorders); 47% took it after the onset of the abdominal symptoms of SMON and 11% had not taken it at all (Sobue and Ando, 1970). In these terms, at least 58% of the patients had not taken CQL before the onset of SMON.

Several studies have described the subsequent SMON incidence in groups of CQL-takers and non-takers; four appear to show a higher incidence in those who took CQL than in those who did not, and their results are summarized in Table VI. If the apparent differences between CQL-takers and non-takers could be interpreted at face value, they would provide compelling evidence for the CQL theory of SMON. There are, however, several reasons why they cannot be so interpreted, at any rate without further information.

TABLE VI
ONSET OF SMON BY CQL ADMINISTRATION

Authors	Year	Administration of CQL	Developed SMON	Did Not Develop SMON
Yoshitake and Igata	1970	Yes	34 (43·6)	44
		No	0	77
Kuratsune *et al.*	1971	Yes	5 (4·3)	110
		No	0	217
Aoki *et al.*	1971	Yes	17 (3·2)	515
		No	4 (0·1)	3782
Tsubaki *et al.*	1971b	Yes	29 (11·0)	234
		No	0	706

Percentages are given in parentheses

First, the proportions of CQL takers who then developed SMON range widely, from 3·2 to 43·6%. This in itself suggests that there may have been differences in the methods used, or between CQL-takers and non-takers, that may have had a bearing on the results.

Secondly, each of the studies says very little about its methods or sources of material, or (most important of all) to what extent the CQL-takers and non-takers were comparable in other respects. A reconsideration of the main epidemiological characteristics of SMON patients (Table II) raises the possibility that if the CQL-takers in the four studies referred to in Table VI were (to take an extreme example, for illustrative purposes) elderly women from professional backgrounds with frequent histories of other illnesses associated with SMON, and the CQL non-takers were young men in labouring occupations with few previous illnesses, a higher incidence in the former than the latter would be virtually guaranteed for reasons that might very well have little or nothing to do with CQL-taking, which could simply be yet another 'marker' or characteristic of those prone to SMON. It is presumably likely that the CQL-takers in the studies referred to in Table VI tended to conform to the first sterotype described; the characteristics of the CQL non-takers in these studies are, however, largely unknown. Yoshitake and Igata (1970) accept that some factor other than CQL may have been responsible for their findings (Table VI).

At least one paper (Hino, 1972) claimed no excess of SMON in CQL-takers compared with non-takers although, again, methods were not specified. The study of Takasu *et al.* (1973) on possible SMON in typhoid patients (already discussed) can also be interpreted as demonstrating no excess of SMON in CQL-takers.

Since the four studies summarized in Table VI were certainly reported, and presumably carried out, after the CQL hypothesis for SMON was advanced, and as there is nothing to suggest that SMON diagnoses were made independently of information on CQL-taking, it may very well have been that SMON was in some cases diagnosed partly, perhaps even mainly, because it was known patients had taken CQL.

DOSE-RESPONSE RELATIONSHIP

Since adverse reactions to medicines can be idiosyncratic or allergic as well as dose-related, the absence of a dose-response relationship is not necessarily evidence against the CQL hypothesis of SMON. The presence of a clear dose-response

relationship would, however, be in favour of the hypothesis. It is sometimes claimed that the onset of SMON did not follow the relatively low doses of CQL recommended outside Japan, for example, by the British Committee on Safety of Medicines (1973), which suggested that courses of treatment should not exceed 7·5 g in total, separated by intervals of at least four weeks. Data of Tsubaki *et al.* (1971a) show, however, that while 20–29 g total was the modal dose in this series of 171 patients, 15 patients had taken less than 10 g. In one of the SMON Research Committee reports (1971) 62 out of 508 CQL-takers who developed SMON (there were also 102 cases who had not taken CQL) had taken less than 10 g (mean 52 g). The report explicitly concluded that there was no dose-response relationship.

To establish a graded dose-response relationship for the *incidence* of SMON, data on CQL dosages for a comparison population are needed (as well as for SMON patients). Three of the studies summarized in Table VI (Aoki *et al.*, 1971; Kuratsune *et al.*, 1971; Tsubaki *et al.*, 1971b) are apparently the only sources of such information, and none supports a dose-response relationship. Data on CQL doses in SMON patients do not support a dose-response relationship for *severity* of SMON.

Aggregated regional and countrywide data on CQL sales and SMON incidence provide little or no useful information on dose-response relationship.

International Data

It is not certain how many cases of SMON (if any) have occurred outside Japan. The world literature and case reports have been reviewed by independent experts (Rose, 1974). In brief, there may be some 20 patients whose diagnoses are compatible with SMON, although this is not to say they definitely had SMON. Even if there were 100 such cases, however, the numbers would be trivial compared with those in Japan, both absolutely and relatively, bearing in mind the numbers of people in the rest of the world who have taken CQL. The following countries had *per caput* sales in 1969 of Entero-Vioform and Mexaform equal to or higher than Japan:

Libya	0·66
Switzerland	0·61
Lebanon	0·48
Belgium and Luxembourg	0·44
Morocco	0·41
Holland	0·36
Italy	0·35
Mexico	0·29
Norway	0·27
Sweden	0·27
Australia	0·27
Western Germany	0·25
Brazil	0·23
Greece	0·23
Egypt	0·19

The figure for Japan itself was 0·18

These figures (Ciba-Geigy, 1974) are sales in grams per person, based on the total populations of the countries concerned, and this general picture is not materially altered if sales of CQL in forms other than Entero-Vioform and Mexaform are taken into account.

It has been suggested that national CQL sales figures in Japan are misleading, when compared with similar figures for other countries, because dosage differed in Japan by being at high levels and for long periods—that is, a great deal was given to relatively small numbers of patients. There are no objective data by which to judge this possibility, but dosage patterns in Brazil, for example, are said to be very similar to those in Japan. Dosage levels and durations in the *Japanese Pharmacopoeia* do not differ markedly, if at all, from schedules in other pharmacopoeias.

Only one possible case of SMON in a Japanese outside Japan (he was on holiday) has been reported, although it is reasonable to assume that many ex-patriate Japanese have taken CQL. (CQL is not generally available in the USA, but there are other Japanese communities in countries outside Japan, such as Brazil.) A genetic predisposition to SMON in the Japanese thus seems improbable.

There are, however, examples of chemicals which fit the SMON time sequence better than CQL, being very much more heavily distributed in Japan than in other countries at the relevant times. FAO data show eight times the use of mercurial fungicides per agricultural km^2 in Japan in 1961—65 than, for example, in the USA, and large differences in the late 1960s between the heavy use of benzene hexachloride (BHC), DDT, aldrin, and dieldrin per agricultural km^2 in Japan and their lighter use in India, the USA, and other countries, (Food and Agricultural Organization 1971–72). Concentrations of mercury in various foods in Japan greatly exceeded those in the USA in the 1960s (Smart, 1968; Goldwater, 1971), and total BHC levels in human fat in the late 1960s and early 1970s in Japan were more than 20 times the figures in the USA and UK (Doguchi, 1973). Furthermore, most if not all these substances were introduced after the war and their usage in Japan declined sharply in the late 1960s as concern over their potential

hazards began to mount. The SMON epidemic conforms to time sequences of this sort considerably more logically than to that of the availability of CQL. The time lag between the marked decline in the use of organomercuric fungicides in 1965 and of chlorinated hydrocarbons in 1968—69, and the virtual disappearance of SMON in 1970 could be explained by the time taken for food treated with with these compounds to grow, be harvested, marketed, and consumed, and for toxic levels to accumulate. It is not suggested that the specific compounds named were the cause of SMON, but they are examples of how the use and subsequent control of other environmental pollutants in Japan could fit the rise and fall of SMON incidence.

One hypothesis for SMON in which CQL might have played a causal role and which would explain the apparent inconsistencies discussed is suggested by these considerations. The necessary cause of SMON might have been an environmental agent —for example, a medicine, virus (compare the pre-CQL theories about SMON), or chemical— that was much more widely distributed in Japan, and in higher concentrations, than in other countries. This agent might have appeared in Japan in the early 1950s and disappeared in the late 1960s. The agent would have been able to cause SMON on its own, but, in combination with CQL, its potential for doing so would have been greatly enhanced; CQL on its own, however, could not have caused SMON except in very rare circumstances. People suffering from the diseases listed in Table IV might have been particularly susceptible to this agent (there are clinical examples, such as herpes in leukaemia, consistent with this suggestion).

An explanation along these or similar lines would account for:

1. The absence of SMON before about 1955.
2. The fact that the decline in the SMON epidemic antedated the sales suspension.
3. The CQL non-takers among the SMON patients.
4. The virtual absence of SMON outside Japan.

Apart from the indirect evidence on levels of environmental pollutants in Japan already discussed, there is no real evidence for or against this theory. Nevertheless, interactions between two or more factors as the possible cause of some environmentally determined diseases should not be overlooked, although these interactions are obviously likely to be more difficult to investigate than instances where only one factor is involved; the epidemiological study of possible interactions is, indeed, in its infancy. Which agent is 'causative' in these circumstances, especially where both are necessary, is something of a philosophical question. In the case of a two-factor hypothesis for SMON, CQL could be an enhancer of a necessary cause but probably not the necessary cause itself.

It is theoretically possible that SMON was the result of the contamination of CQL with something else. However, SMON occurred in some patients who had taken Japanese preparations, and in some who had taken imported preparations; there is no evidence or reason for believing that the same contaminant was mixed with, and later excluded from, both Japanese and imported preparations. (The same general argument applies to CQL degradation products.) In addition, the full SMON syndrome is a specific clinical entity, which is not characteristic of known toxic substances. A contamination explanation for SMON thus seems unlikely.

Conclusion on SMON

It would be unreasonable to take an absolutely rigid view about all the inconsistencies in the CQL hypothesis for SMON and to conclude that, so long as even one remained, the hypothesis could not be accepted. The thalidomide episode demonstrated that phocomelia sometimes occurred in those with no apparent history of having taken the preparation; in the case of sudden deaths in asthma, the eventual decline in mortality probably preceded any formal warnings. Reasons have, however, been given for doubting that similar inconsistencies in the case of CQL and SMON can reasonably be explained within similar margins of tolerance; in addition, the SMON controversy is characterized not simply by one or two serious inconsistencies but by a series—the apparent absence of SMON until long after the introduction of CQL, its decline before CQL sales were suspended, a large proportion of SMON patients who did not, apparently, take CQL, no dose-response relationship, and the virtual absence of SMON outside Japan. (Finally, although outside the scope of this review, there are at present no convincing data from animal experiments.)

Wider Implications of the SMON Controversy

It would be easy to set SMON on one side as a strange disease, confined to one country, and caused by a 'useless' medicine the precise role of which in the SMON epidemic requires no further definition than it has already received. Yet the SMON controversy could prove something of a water-shed in the study of the adverse effects of medicines. Contemporary reactions to suggestions that a preparation may have adverse effects are partly,

perhaps largely, conditioned by the fact that these claims have so far usually been substantiated—for example, chloramphenicol in aplastic anaemia, thalidomide in phocomelia, aerosols in asthma deaths, and oral contraceptives in thromboembolic disease. By contrast, several more recent episodes have been much less easy to resolve than these earlier ones. The nature of the relationship between postoperative jaundice and exposure to holothane is hotly disputed (see Inman and Mushin, 1974 and subsequent correspondence); the demonstration that halothane affects liver function, as assessed by changes in serum enzyme levels, (Wright *et al.*, 1975; Trowell, Trowell, Peto, and Crampton Smith, 1975) strengthens, but by no means settles, the case. Whether tolbutamide causes rather than prevents arterial complications in diabetics is another controversial issue (Feinstein, 1971). Data on the relationship between reserpine and breast cancer (Armstrong, Stevens, and Doll, 1974; Heinonen *et al.*, 1974; Boston Collaborative Drug Surveillance Program, 1974) have stimulated much critical discussion about appropriate study methods and a growing realization of difficulties of interpretation that may arise in this and similar cases. The *prima facie* case that reserpine is involved in the aetiology of breast cancer remains strong, although in an inquiry in which both the breast cancer patients and the subjects with whom they were compared came from the same defined population, Mack *et al.* (1975) found no association, and have thus introduced a substantial element of doubt. The SMON epidemic shows signs of being assimilated into the case-law of undisputed cause and effect associations (Lawson and Wilson, 1974) although it is perhaps the best available example of these much more open and unresolved episodes.

The continuing production of powerful therapeutic agents carries with it the virtual certainty of further unwanted reactions, while inquiries such as the Boston Collaborative Drug Surveillance Program (1974) will ensure that many of these reactions are detected, as indeed they should be. Associations that may at first sight seem to be of a causal nature, but eventually prove not to be, will almost certainly also come to light under modern conditions of surveillance. There is a great deal to be lost by failing to distinguish true from spurious adverse effects. A central concern in the halothane debate, for example, has rightly been that the value of this generally accepted and widely used anaesthetic should not be compromised by allegations of toxicity that may be unfounded. Many fear that the use of other anaesthetics, consequent on anxieties of possible litigation in the event of jaundice after halothane, could be against the best interests of thousands of patients undergoing surgery.

Over-ready acceptance of the possible adverse effects of medicines is only one aspect of a wider debate about the costs and benefits not only of medicines but of other substances. There are signs that the outcome of this debate could be to the detriment of useful advances in the fields of community health and clinical medicine. Environmental hysteria, rather than objective appraisal, characterized much of a recent campaign against DDT which, had it been successful, would almost certainly have cost many lives. The 1958 Delaney Amendment to the Food, Drug, and Cosmetic Act in the United States (reviewed in Preventive Medicine, 1973) and insistence on inappropriate and uniformative toxicological testing in animals (*Lancet*, 1973) are other examples of measures that are probably more likely to delay progress than prevent harm. Over-caution in prescribing may sometimes have disastrous consequences; in amphotericin pharmacophobia, Symmers (1973) reported on five patients who died because amphotericin was withheld, although it was obviously indicated. Wade (1974) used the examples of chloroform, cyclamates, oral hypoglycaemic agents, and oral contraceptives to show how either the nature or manner of a decision about possible adverse effects may have undesirable consequences.

It is only necessary to compare modern with earlier methods of treatment in diseases as different as leprosy and hypertension to appreciate the advances that pharmaceutical research and development have brought about. The conquest of many other diseases, including under-nutrition, depends *inter alia* on further advances of a similar kind. There is, however, an increasing number of obstacles to further progress (Spinks, 1974; Weatherall, 1974); one of these could easily turn out to be over-eagerness to accept scientifically unsubstantiated allegations of adverse effects, especially if 'guilty until proved innocent' is the starting-point. This view is not by any means to argue for the unmonitored use of new compounds but it does argue, among other things, for very searching investigations in the study of alleged side-effects. It is possible to define at least four purposes to which the results of such studies may be put. The first is the decision whether or not to restrict the use of a medicine, and considerations of its clinical value are clearly relevant here. The second is to make a scientific evaluation of the probability that the agent is the cause of the unwanted effect, and here neither its clinical value nor decisions about its continued use

are to the point; this evaulation may provide valuable information on the aetiology and prevention of other diseases, which makes it especially important that it should be entirely objective. Doll (1971) has rightly pointed out that different study techniques are necessary in different circumstances; it may therefore not be useful to try to draw up routine methods or criteria by which to judge the likelihood of a cause and effect relationship. However, the case against a medicine should be able to command fairly general agreement before it is finally accepted as such. The third use depends very much on the second and is the fair and swift compensation of those affected, where cause and effect have been shown to be reasonably likely. Fourthly, the pharmaceutical industry will have to decide what further research and development it will or will not pursue. These are fairly distinct issues, and the balance of evidence could be used to make different decisions under different headings—for example, a medicine could be withdrawn from use under the first, while the scientific and legal questions remained unresolved. However, therapeutic progress in the future stands to suffer if decisions against the further use of medicines under the first heading become, or are made to become, the basis for decisions under the other three. SMON has provided an excellent opportunity to review and re-assess all the scientific and social implications of the whole field.

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*denotes original in Japanese