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An Approach to the Modeling of the Tolerance Mechanism in the Drug Effect. II: On the Implications of Compensatory Regulation

A. PEPER*, C. A. GRIMBERGEN*, J. W. KRAAL†, and J. H. ENGELBART†

* *Laboratory of Medical Physics, University of Amsterdam, Meibergdreef* 15, 1105 *AZ Amsterdam, The Netherlands and* † *Department of Analgesiology of the Academic Medical Centre, Meibergdreef* 9, 1105 *AZ Amsterdam, The Netherlands.*

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In the previous paper (Peper *et al.*, 1987: *J. theor. Biol.* **127,** 413), a model of drug tolerance was developed based on the assumption that the decrease of drug effect after repeated administration of a drug is caused by the involved regulations in the organism adapting themselves to the presence of the drug. In the present paper, the behaviour of the model is studied with respect to the dose-response relation, the drug effect in dependent and non-dependent subjects and withdrawal symptoms. Computer simulations demonstrate the model to be highly sensitive to sudden changes of drug dose. Dependent on the open loop gain of the adaptive mechanism, a sudden decrease of drug dose might result in an effect opposite to the common drug effect. In the model, the rate of decrease of drug dose necessary for optimal drug withdrawal appears to be determined by the same mechanism as the rate of increase of dose necessary for a constant effect at the commencement of treatment. The behaviour of the model suggests the degree of drug dependence in an addicted subject to depend on the extent to which non-somatic factors are involved in the process of initiation of the adaptive mechanisms.

1. Introduction

In the previous paper (Peper *et al.*, 1987), a short survey was given of processes which can be responsible for the decreasing effect of drugs upon an organism after repeated administration (drug tolerance). In the mechanisms described, drug tolerance is attributed to processes which compensate or counteract the drug action. Apart from the increasingly effective suppression of the drug effect, the working of these antagonistic processes is in the existing models of drug tolerance not described as being influenced by the actual presence of the drug. However, if processes which counteract the drug effect remain active during the intervals between drug administration, substantial reactions must occur (e.g. effects opposite to the common drug effect) in the intervals when the drug action has ceased and the corrective vector itself is not compensated by the drug action. Large reactions can often be observed in the organism during the intervals between drug administration. However, in the existing models, both the frequent administration of drugs and the sporadic use of drugs would have to be followed by equally large reactions. In reality, this is not the case if drugs are administered infrequently, the organism is not affected very

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much in the intervals, although tolerance to the drug in question might be high. The proposed drug opposing processes must therefore be assumed to be acting mainly during the presence of the drug. This implies that a drug selective mechanism must be present which "recognizes" a drug and activates the relevant processes.

In the previous paper (Peper *et al.*, 1987) a model was developed, based on the above-described assumptions. It was proposed that, in many cases, the effects of drugs upon a living organism originate from the disturbance the drugs evoke in regulated processes in that organism. This disturbing action was attributed to the drugs interfering with the transfer of information between the regulated processes and their regulations, rather than to a disturbing effect of the drugs on the regulations themselves. The model developed was also based on the assumption that the decrease of drug effect after repeated administration is due to the disturbed regulations adapting themselves to the presence of the drug. Adaptive behaviour implies that a living entity adapts itself to the consequences of disturbing influences from its environment. From the model, it can be learnt that adaptive behaviour for an organism implies a negative reaction if the disturbing factor is withdrawn. If, on the other hand, an environmental change appears to be permanent, it will, in time, become the normal situation for the organism. This implies that no fixed reference exists for adaptive processes in the organism, which has important implications for the form of the model. In the present paper, the behaviour of the model is studied with respect to the dose–response relation, the drug effect in dependent and non-dependent subjects and withdrawal symptoms. The relevance of the model to clinical practice will be discussed.

2. Form of the model

In Fig. 1, a block diagram is shown of the model developed in the previous paper (Peper *et al.*, 1987). The diagram can be divided into two parts: the process part with the process regulation and the adaptive regulator part. The process is regulated by the primary regulation. The primary regulation bases its regulation on the level of the primary reference and on information it receives from the process output via the feedback path. Disturbances of the functioning of the process are assumed to be caused by disturbances in the transfer of this information. The effect of a

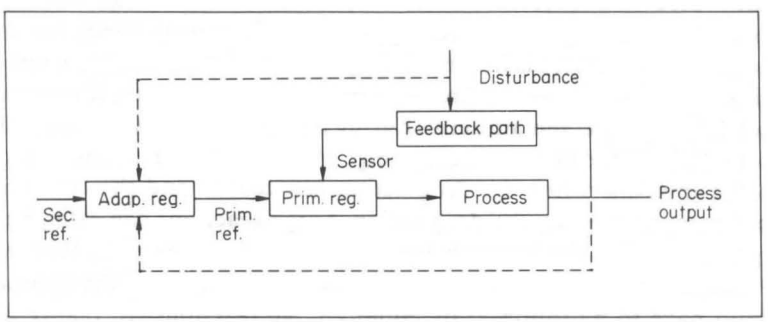

FIG. 1. Block diagram of the model (Peper *et al.*, 1987).

disturbance is counteracted by the adaptive regulator by an adjustment of the primary reference. The adaptive regulator bases its regulation on information from the process output and the disturbing stimulus.

In the model, the adaptive regulator is an additive (or compensatory) regulator. Another kind of regulation capable of effecting a decrease of response after repeated stimulation is multiplicative regulation (Lang & Ham, 1955; Aseltine *et al.*, 1958; Truxal, 1961). In a compensatory adaptive mechanism, the magnitude of the response to a stimulus depends on the difference between the stimulus magnitude and a reference level. The decrease of response is effected by a readjustment of the reference level in the direction of the stimulus magnitude. In a multiplicative mechanism, the response depends on the ratio of stimulus magnitude and reference signal. A decrease of response results here from an increase of the magnitude of the reference signal.

There were some strong points in favour of the use of a compensatory adaptive mechanism as a basis for the model. A practical advantage of the compensatory adaptive regulation is it being a linear system. The multiplicative adaptive regulation is essentially a non-linear system and consequently more difficult to analyze.

Another consideration is the transient response of the two types of regulators. The effect of a transient on a multiplicative regulator manifests itself only in a disturbance of the *magnitude* of the transferred signal (Lang, 1955; Truxal, 1961). On the other hand, the effect of a transient on a compensatory regulator is a disturbance of the *level* of the output signal (Chestnut & Mayer, 1951), an effect closely resembling the after effect or rebound mechanism in drug administration.

Another important consideration is that a compensatory adaptive regulator reacts to a change of the magnitude of the stimulus rather than to the magnitude of the stimulus itself (Peper *et al.*, 1987). In a multiplicative adaptive regulator, the response is a function of the magnitude of the stimulus and adaptation to a strong stimulus also implies a low gain to a weak stimulus. After adaptation to a strong stimulus, the weak stimulus is therefore strongly attenuated and loses its disturbing effect. In the latter kind of adaptation, the withdrawal effect in drug dependence is difficult to describe, while it follows naturally in a compensatory adaptive regulation as will be demonstrated. In a compensatory adaptive regulation, a non-changing stimulus magnitude results in a low response of the system, whereas changes in the stimulus magnitude cause large responses to occur. This appears to be in accordance with biological reality: changes in the environment seem to be highly significant for a living organism. In fact, it can be argued that the adopted compensatory form of the model not only gives a good description of the biological mechanism of drug tolerance, but also that the biological regulation itself is compensatory (Jaffe & Sharpless, 1968; Martin, 1968; Kalant *et al.*, 1971). The examples given in the present and previous paper demonstrate that many of the characteristics of drug tolerance can be simulated with the model.

3. Constant Drug Effect

In the previous paper (Peper *et al.*, 1987), the behaviour of the model during repeated stimulation with a stimulus of constant magnitude (constant drug dose)

was studied. In clinical practice, it is not the drug dose, but the drug effect that is of primary interest. Because the drug effect decreases with time as the involved regulations adapt themselves to the drug's action, the dose must be increased with time to maintain the drug effect at the desired level. In the long run, the drug effect is determined by the regulation error of the adaptive regulation of the process involved. Once adaption has been reached (drug tolerance), a constant drug dose will yield a constant drug effect. In the previous paper, the relation between the open-loop gain of the regulation loop and the regulation error, and the effect of these parameters upon the regulation, was discussed. Simplifying the case, it can be stated that a regulation without error suppresses disturbances completely. It is the deviation from this ideal situation—caused by factors such as time lag of the regulation or an insufficient open-loop gain—which allows disturbances to influence the process output. Consideration of stability suggests the open-loop gain to be small in fast biological processes (Peper *et al.*, 1987) and the regulation error large. In Fig. 2 the implications of a constant drug effect are elucidated with the result of a computer simulation (see the appendices of the present and previous paper). The magnitude of the stimulus (drug dose) has been adjusted during the simulation to maintain a nearly constant effect in the process output (drug effect). After an initial increase, the magnitude of the stimulus settles at a level at which the regulation error of the adaptive regulation yields the desired effect. Note the relatively large undershoot of the signal below zero during the interval between drug administration, representing the rebound phenomenon following drug action (Jaffe, 1968; Seevers & Deneau, 1968; Kalant *et al.*, 1971; Snyder, 1977). The relative magnitude of these

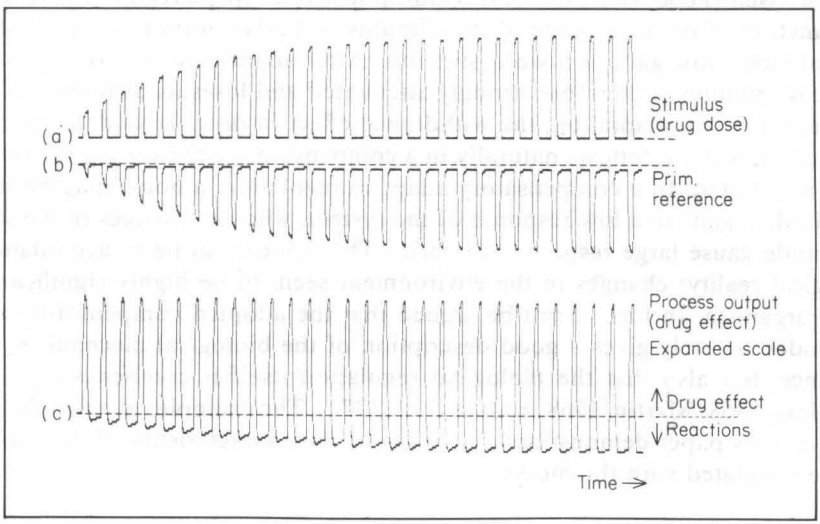

FIG. 2. The result of a computer simulation showing dose-response relation for constant drug effect. (a) Stimulus (drug dose). (b) Primary process reference. (c) Process output (drug effect). The magnitude of the stimulus has been adjusted during the simulation to maintain a nearly constant effect in the output of the model. For clarity, the scale of the output signal has been expanded in this and the following figures.

reactions is determined by the repetition rate of drug administration as described in the previous paper. In the simulation of Fig. 2, the ratio of stimulus time and interval between the stimuli is 1:2, which provides a clear picture of the described effects.

4. Dose–response Relation

The degree of compensation of a stimulus by the adapting mechanism is not determined by the magnitude of that particular stimulus, but by the average magnitude of the past stimuli. The described regulation suppresses disturbances only effectively in a non-changing situation, the complete adjusted regulation being "switched on" during the stimulus. The regulation appears to be based on anticipation rather than on knowledge of the stimulus magnitude. That this might be a sound description of the biological process of drug tolerance follows from the following consideration: if on a change of drug dose the organism would be able to determine the magnitude of the necessary compensation instantly, the decrease of drug effect at the commencement of drug treatment would not have to occur. In addition, the quantity of a (slowly dissolving) drug can only be known to the organism after complete dissolvement of the drug, whereas the compensatory mechanism of the organism has to begin its action at the onset of the drug action to obtain an effective compensation. This also demonstrates that the drug quantity can only be an indirect factor for the adaptive mechanism: it determines the level of compensation during the learning process when the organism pursues optimal suppression of the drug effect. Apparently, a change of magnitude of the stimulus necessitates a renewed learning of the organism. The consequence is that a change of drug dose is followed by a period of imperfect compensation.

In the model, this manifests itself in large changes of the magnitude of the disturbances in the process output on small changes of the stimulus magnitude. Figure 3 shows a computer simulation of the effect of small changes of the stimulus magnitude after adaption has been reached. In the model, a decrease in the stimulus magnitude of 20% nearly results in an extinction of the disturbance in the process output. When the adaptive regulation adapts itself to the new situation, the magnitude of the disturbance in the process output settles at a proportionally decreased level (-20%). If the stimulus magnitude is increased to the level it would have been at without intervention, a comparable *increase* of the disturbance magnitude in the output signal results.

The ratio between the steady-state effect in the process output on the one hand, and the initial effect of a sudden change of the stimulus magnitude on the process output on the other, depends on the open loop gain of the adaptive regulation loop. In a regulated system, an additive disturbance with a magnitude D results in a disturbance of the output of a magnitude $D/(1+G)$, in which G is the open-loop gain of the regulation loop. The transfer of the process itself is taken to be unity because its real value does not change the essence of the argumentation. In the described adaptive process regulation, the effect of a disturbance is—after adaptation—determined in the same way by the open-loop gain. However, adaptation

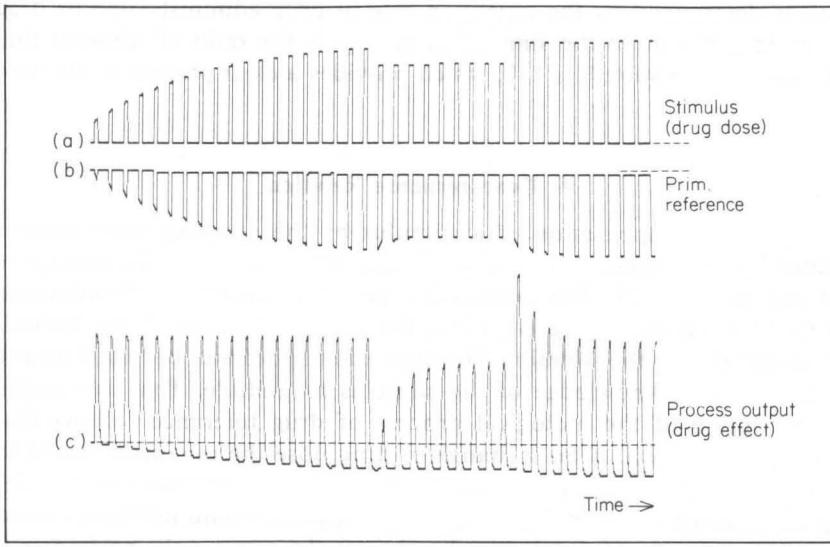

FIG. 3. The effect of small changes of the stimulus magnitude after tolerance has been effected. In the model, a decrease of the stimulus magnitude of 20% nearly results in an extinction of the disturbance in the process output (open loop gain is 4). After adaptation, the magnitude of the disturbance in the process output settles at a proportionally decreased level of −20%. An increase of the stimulus magnitude to the original level, results in a comparable increase of the disturbance magnitude in the output signal.

takes time, and initially the compensation of the disturbance will be zero. This implies that the magnitude of the initial disturbance of the process output on a change of stimulus magnitude will be equal to the magnitude of that change. Because the magnitude of the effect of a stimulus upon the process output after adaptation has taken place is a factor $1+G$ smaller than the magnitude of the stimulus itself, the initial effect of a change of the stimulus magnitude upon the process output is a factor $1+G$ larger than the steady-state effect of a stimulus. In the simulation of Fig. 3, the open-loop gain is low (4), but the gain can be higher or even lower in biological reality, depending on the form of the regulation and on its biological function (see paragraph 4 of the previous paper).

Translated to the physiological situation, a large open loop gain necessitates a large drug dose to obtain the desired drug effect. A large drug dose results in large initial effects on changes of the dose. Because the open-loop gain can be assumed to be coupled inversely with health and age (Mitchell *et al.*, 1970; Verveen, 1978, 1983), young and healthy subjects can be expected to need high drug doses to obtain the desired drug effect which consequently results in large initial effects on changes of the dosage. In aged or diseased subjects, small drug doses can be expected to yield the desired drug effect, while changes in the dosage will not lead to large changes of the drug effect.

An example from everyday life to illustrate these mechanisms is the strength of coffee as experienced by coffee drinkers of different age (Brezinova, 1974; Karacan *et al.*, 1977; Battig, 1985; Snel, 1988, in preparation). Following the argumentation

above, old people commonly drink weak coffee, which causes the same sensation as strong coffee does in young, healthy subjects. In the latter, the effect of the coffee will be effectively compensated by the adaptive regulation. A consequence of the high open-loop gain in young coffee drinkers will be that small changes in the strength of the coffee result in large changes of the experienced effect: coffee which is slightly less strong is experienced as very weak coffee, while this effect will be much less pronounced in elderly coffee drinkers.

If in the simulation, the stimulus magnitude is decreased more than 20% (i.e., more than $1/(1+G)$), the result will be a negative effect in the process output with a magnitude equal to the steady-state effect minus the magnitude of the change in the stimulus. This effect is demonstrated in Fig. 4. A step-wise decrease of the stimulus magnitude results—in a tolerant subject—in an increasingly negative effect, the maximum magnitude of the negative disturbance in the process output being the result of a maximum negative step in the stimulus magnitude. It is interesting to note that this effect agrees with the theory behind homeopathic therapy. In homeopathy, a small quantity of a drug is administered with the intention of evoking a reaction in the organism. Because a drug is chosen which induces—if given in high dosage—similar symptoms to those of the patient, the reaction is assumed to counteract the patients disorder.

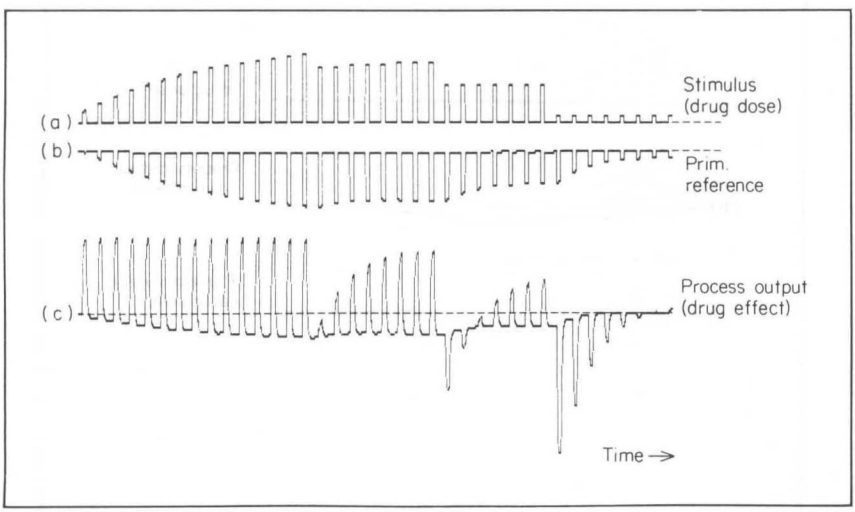

FIG. 4. In tolerant subjects, a step-wise decrease of the stimulus magnitude results in an increasingly negative effect, the maximum magnitude of the negative disturbance in the process output being the result of a maximum negative step of the stimulus magnitude.

5. Drug Dependence

If small changes of the magnitude of the stimulus result in such large disturbances in the process output of the model, an interruption of the stimulus might be expected

to be the cause of major effects. However, this is only the case if on interruption of the stimulus, the initiation of the adaptive regulation continues to take place. In the computer model, the selective fast regulation is activated at the onset of the on-going slope of the stimulus, which moment represents the time of administration of the drug. In reality, the initiation of the adaptive mechanism is likely to be a complex process in which the organism makes use of different kinds of information to learn about the occurrence of disturbances.

Primarily, the adaptive mechanism will be activated on the administration of a drug. If administered orally, the registration by the organism of drug presence and drug characteristics will be by gustatory and olfactory mechanisms and possibly also by direct-acting chemical senses. The specialized chemical senses in the mouth and nose are able to detect and to discriminate between very small quantities of chemical substances (Moncrieff, 1967). If the drug is administered intravenously, there are two ways the adaptive mechanism might obtain information about the presence of the drug: by chemical sensors which are sensitive for the drug in question, or by information from processes in the organism which themselves are disturbed by the drug.

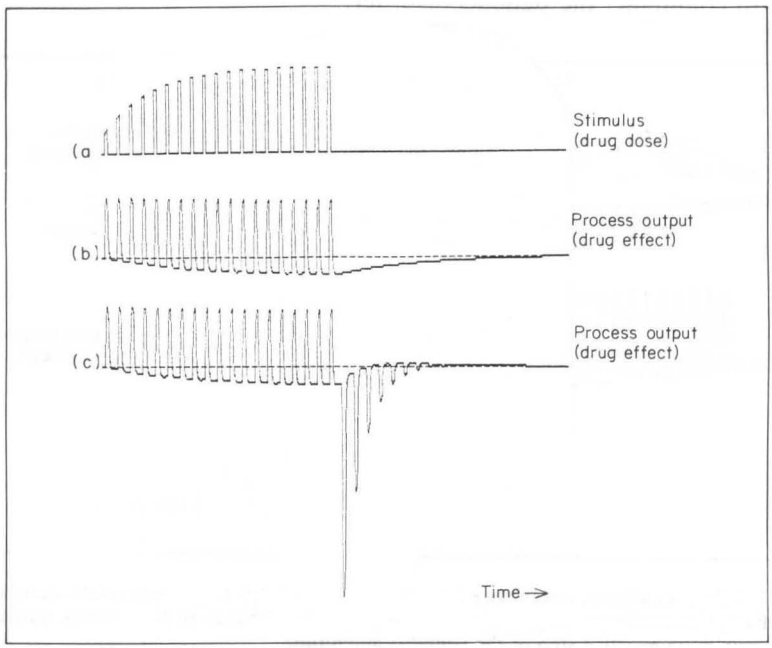

FIG. 5. The behaviour of the model if (after tolerance) the stimulus is interrupted. (a) The stimulus (drug dose). (b) The process output (drug effect). The negative effect in the process output decreases slowly in time when the adaptive regulation adapts to the new situation (non-dependence). (c) The process output if on interruption of the stimulus, stimulation of the adaptive regulation is continued (dependence). The compensatory component, now not compensated by the stimulus, causes large negative reactions in the process output to occur at the moment of the "expected" stimulus. The intensity of the reactions gradually decreases with time when the regulation adapts to the new situation.

There are other factors beside the physical presence of drugs which might be involved in the initiation of the compensatory process: time of administration, anticipation, circumstances (drug scene) etc. (Seevers, 1962, 1968; Kalant, 1971). The combination of direct and indirect stimuli for the initiation of the adaptive mechanism and the consequences of interruption of the direct stimulus are described by the theory of classical conditioning (Pavlof, 1906, 1927): an effective or unconditioned stimulus (drug), which elicits a response (compensatory component in the drug effect), is associated or paired with an otherwise ineffective or conditioned stimulus (time of day, location etc.). If after repeated pairing of the two kind of stimuli, the unconditioned stimulus is withheld, the conditioned stimulus alone can elicit the response, which, however, gradually declines if it is no longer combined with the unconditioned stimulus (Terrace, 1973; Kandel, 1976). In Fig. 5c, the behaviour of the model is shown if on interruption of the stimulus, the initiation of the adaptive regulation is continued. In normal functioning, the stimulus and the compensatory component nearly balance each other, their difference resulting in the output signal of the process (drug effect). If the stimulus is withheld but the initiation of the adaptive regulation is continued, the compensatory component will be generated at its regular time, but its effect will not be compensated by the stimulus. This will result in large—negative—reactions in the process output at the moment the stimulus is "expected". The intensity of these reactions gradually decreases in time when the regulation adapts to the new situation. This "side effect" of compensatory regulation provides a satisfactory description in the model domain of the reactions of a dependent organism to drug withdrawal. It might imply that the degree to which a subject is addicted to a drug, depends on the extent to which non-somatic factors are involved in the process of initiation of adaptive mechanisms.

6. Discussion

Compared with the severe reactions in the model on drug withdrawal in a dependent subject, the effect in a tolerant but not dependent subject appears to be very moderate (Fig. 5b). Nevertheless, its consequences may be considerable. The negative shift of the process output on drug withdrawal signifies the occurrence of antagonistic symptoms with respect to the drug effect and these are consequently in the "direction" of the disorder the drug was intended to counteract (Kalant, 1971). This implies that the negative reaction in the model to an interruption of the stimulus represents a worsening of the disorder of the patient after termination of drug treatment. Although the reaction will diminish in time as the organism adapts itself to the absence of the drug, an initial worsening of the symptoms will be a strong stimulus for the patient to proceed drug treatment.

In addition, in the case of a disorder due to a chronic shift of reference level of a process regulation (Verveen, 1978, 1983), it is doubtful if adaptation to abstinence will occur at all. A chronic shift of a reference level of a process in the organism indicates a certain malfunctioning of the involved adaptive regulation. In the model, the level of the reference value is determined by the adaptive regulation. The negative reaction in the process output on interruption of the stimulus originates in a further

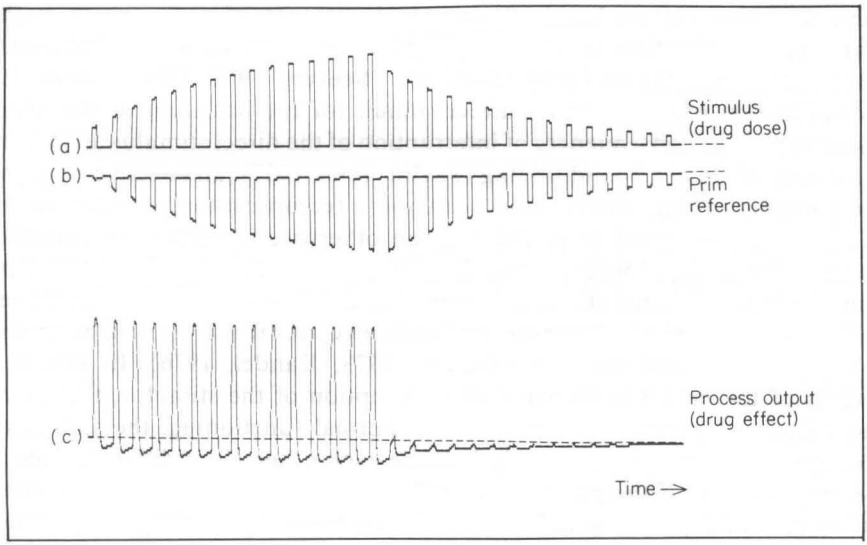

FIG. 6. In a dependent subject, the reactions which occur on drug withdrawal are kept minimal if the rate of decrease of drug dose equals the rate of increase necessary for a constant drug level at the commencement of drug treatment.

shift of this reference level (Peper *et al.*, 1987). Consequently, if the disorder was due to a chronical shift of the reference level, the extra shift after termination of a drug treatment might becomes chronic too and the effect of drug treatment of limited duration will then be a chronic worsening of the disorder.

In the model, drugs are supposed to be acting during a precisely described period of time and their action is assumed to be of constant magnitude during this time. In reality, the drug quantity varies largely during the time the drug is active in the organism and a precise time of action is difficult to define. The quantity of the drug in the organism at any moment is on the one hand a function of the dose and the frequency of administration, and on the other of drug metabolism and excretion. The integrative effect of the volume in which the drug is dispersed tends to decrease the fluctuations in drug quantity caused by repetitive drug administration. The frequent administration of small quantities of a drug will result in a nearly steady level of drug in the organism. As is demonstrated in paragraph 3 of the previous paper (Peper *et al.*, 1987), the net drug effect in this case is much smaller than the drug effect resulting from a fluctuating drug level. Slowly changing disturbances, like the drug effect resulting from a steady level of drug in the organism, are regulated by the slow adaptive regulation. Because the slow adaptive regulation is more effective than the fast adaptive regulation, compensation of the drug action will be large and the net drug effect will be small. If the drug effect is small, the drug quantity has to be high to obtain the desired result. Apparently, for a given drug effect the frequent administration of small doses of the drug results in a higher average drug quantity in the organism than the infrequent administration of large doses of that drug. This fact is of high clinical significance. Beside the obvious

disadvantage of a high average drug level in that it might result in large side effects, a high drug level also requires a high level of compensation of the involved adaptive regulations, which might in turn cause large reactions in the organism if drug administration is terminated.

If, in a dependent subject, drug administration has to be terminated, the customary method of preventing excessive reactions in that organism is a gradual lowering of the drug dose. This procedure is readily simulated in the model (Fig. 6). It appears that in the model, reactions are kept minimal if the rate of decrease of drug dose is made equal to the rate of increase necessary for a steady drug level at the commencement of drug treatment. This phenomenon is a consequence of the fact that for the adaptive mechanism, interruption of a stimulus is essentially the same disturbance, although in opposite direction, as the stimulus itself. This was discussed extensively in the previous paper (Peper *et al.*, 1987, paragraph 3). The rate of decrease of stimulus magnitude necessary for minimal drug action is the mirror image of the curve which represents the drug dose as a function of time necessary for a constant drug effect (Fig. 5). A possible clinical implication of the behaviour of the model in this respect is that, if the rate of increase of drug dose necessary for a constant drug effect can be determined accurately, drug withdrawal can be accomplished in a minimal period of time with minimal risk of reactions in the organism.

The model presented here, gives a description of several characteristics of the process of drug tolerance. Its form, a combination of two relatively simple regulations, must be regarded to be the minimum configuration able to describe the essential characteristics of drug tolerance (Peper *et al.*, 1987). The model is therefore necessarily only a first step in describing this highly complex mechanism. Drug tolerance develops differently for different drugs when different processes in the organism are involved. The model developed in this study is not intended to go into these differences. However, we hope that the general approach adopted can provide a basis for more detailed investigations on the modeling of the process of drug tolerance of the individual drugs.

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APPENDIX

The simulations in the previous paper (Peper *et al.*, 1987) were executed with a relatively simple computer program written in BASIC (see appendix to that paper). In the present paper, the simulations were performed with the help of a universal simulation program designed at the Twente University of Technology: TUTSIM (Meerman Automation, P.O. Box 154, 7160 AC Neede, The Netherlands). TUTSIM accepts input in the form of a block diagram. In Fig. A1, the block diagram of the model used for the generation of the figures is shown.

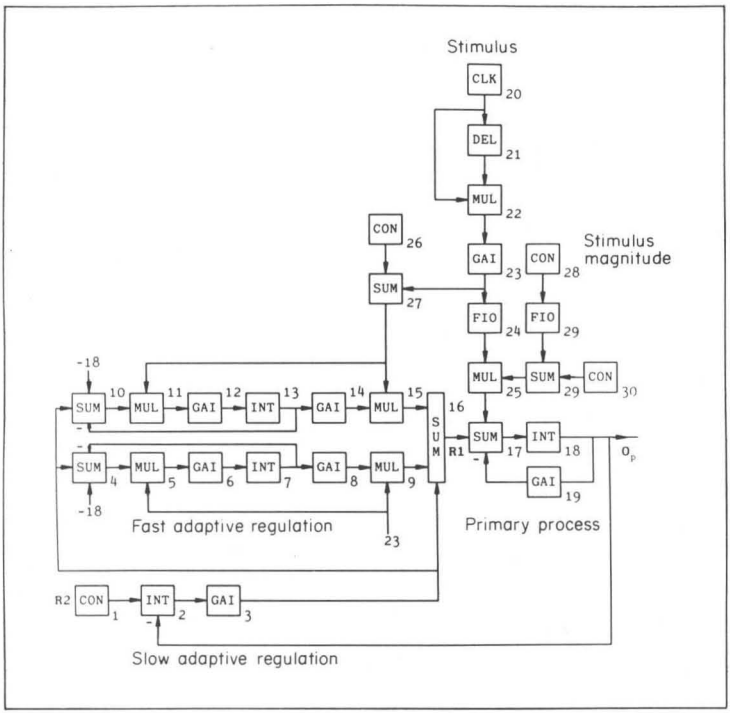

FIG. A1. A block diagram of the model (see appendix Peper *et al.*, 1987) used for the generation of the figures as implemented in the simulation program TUTSIM (see text). SUM represents a summation function, MUL a multiplier, GAI a gain factor, INT an integrator, CON a constant, FIO a first order low-pass filter, CLK a square wave generator and DEL a delay function. Block 1 represents the secondary reference; block 2 and 3 the slow adaptive regulation; block 4 to 15 the fast adaptive regulation; block 20 to 25 provides the stimulus; block 28 to 30 determines the magnitude of the stimulus in time; block 17 to 19 form the primary process (see Fig. 1).