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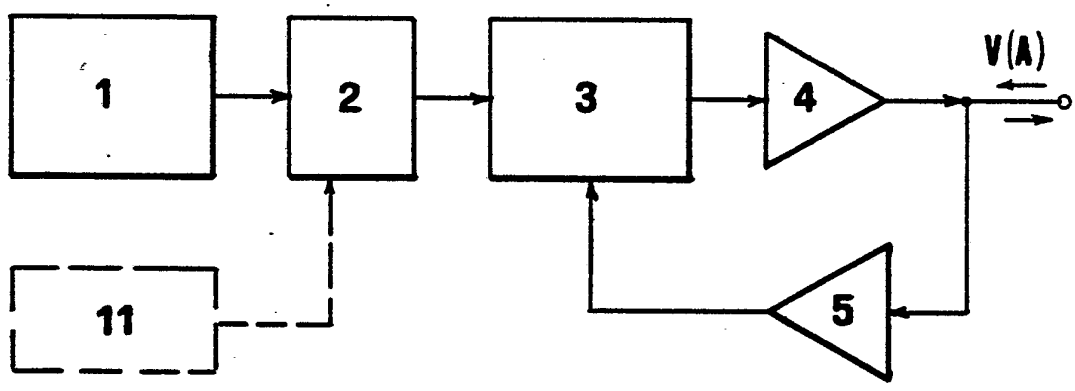
(54) Title: A PACEMAKER FEATURING A PARAPHYSIOLOGICAL, CIRCADIAN OPERATING CHARACTERISTIC



(57) Abstract

A pacemaker with a device (1) that varies the frequency emitted by a clock circuit (2) exploiting a function which simulates natural circadian variation in hearbeat as far as possible, and thus takes account of the body's biorhythmic behaviour. The function may take the form of a sine wave covering a 24-hour period, phased such as to exhibit maximum amplitude between 14.00 and 16.00 hours, and minimum amplitude between 02.00 and 04.00 hours.

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A pacemaker featuring a paraphysiological, circadian operating characteristic.

The invention described relates to a pacemaker in which paraphysiological operation is produced by virtue of the circadian design principle adopted.

Extensive observation at experimental and clinical level has by now established the existence of a circadian regularity in the heart's natural pacemaking system, traceable to the sinoatrial node.

More recently, observation has also confirmed that a circadian rhythm persists in heartbeat even in the event of total atrioventricular stoppage. Circadian rhythm is also manifest in variations of the normal atrioventricular sequence.

Even in transplant situations, the heart of a donor will retain circadian rhythm in its beat notwithstanding the absence of sympathetic connections.

The regular, natural pacemaking characteristic of the heart can undergo circadian variation resulting from disturbances such as a concentration of hydrocortisone and catecholamine, electrolytic changes, and above all, direct influence from the nervous system.

Whatever the age bracket into which a given subject may fall, dynamic ECG (Holter) will show a circadian variation in rhythm of the heartbeat, regardless of

whether the subject suffers from a heart condition or is 100% fit.

From the trends observed in monitoring heartbeat, it can be deduced, on average, that minimum levels are registered between 02.00 and 06.00 hours, whereas maximum levels occur between 14.00 and 16.00 hours. Dynamic ECG recordings are such that a curve may be plotted to represent heartbeat in the form of a sine wave covering the 24-hour circadian period.

It would not appear, from data furnished by literature currently available, that variation in heartbeat bears any relation either to age, in subjects of between 16 and 65 years of age, or to sex. Available data would seem to suggest, however, that the female sex registers a generally higher average heartbeat rate than does the male sex.

In the light of the chronobiological modulation thus produced in conjunction with alternating sleep and wakefulness, and with vital bodily functions, the object of the invention described herein is that of embodying a pacemaker that will permit of producing a circadian rhythm in heartbeat exogenously, and of ensuring that the circadian variation produced is commensurate with the overall pattern of endogenous biorhythmic factors normally influencing heartbeat, physical exercise excluded.

There are several models of pacemaker commercially available, in effect, that are not synchronized with spontaneous physiological atrial activity, such activity being either non-existent, or unreliable.

At all events, conventional pacemakers are designed to generate a minimum number of beats per minute, beneath which the rate must not drop.

Minimum bpm is fixed in VVI types, and is programmable at preset levels in externally controlled VVIM types. In DVI, VDD and DDD types, the disappearance or significant weakening of the atrial signal is compensated by emission of a fixed, preset bpm by the pulse generator; in this instance, however, bpm neither follows nor takes account of bioryhthm. The same disadvantage occurs with those types of pacemaker which vary heartbeat according to biological or metabolic parameters such as pH value, temperature and breathing; heartbeat is varied only when the individual expends physical or mental effort, whilst minimum bpm remains a fixed quantity that does not adapt to chronobiological requirements.

Recent work in the field shows that a fixed minimum (conventionally 60...70bpm) can constitute a hazard to the individual, especially during the night when reduced biological activity would dictate a lower heartbeat rate; this is particularly the case in patients suffering from disease of the sinoatrial node.

The invention as described and claimed herein overcomes the drawbacks aforementioned, setting forth a pacemaker which not only is sensitive to triggered physiological change, such as would be produced by physical effort, but also responds to biorhythmic variation in the state of the individual.

One of the advantages obtained with a pacemaker according to the invention consists in the fact that it can be embodied simply by connection of a sine wave pulse generator to the input of the clock of a conventional pacemaker; the signal produced by such a device, covering a 24 hour period and variable in amplitude, will thus be integrated with that of the clock generator.

The invention will now be described in detail by way of example, with the aid of the accompanying sheets of graphs and diagrams, in which:

fig 1 shows the natural curve traced by chronobiologically induced circadian variation in heartbeat;

fig 2 shows the stimulus curve, produced by a pacemaker according to the invention, relating solely to chronobiologically induced circadian variation in heartbeat;

fig 3 is the block diagram illustrating a pacemaker according to the invention;

fig 4 is a detailed block diagram of the block denoted 1 in fig 3;

fig 5 is the block diagram of a programmable pacemaker according to the invention.

The pacemaker disclosed is suitable for all current methods of producing cardiac stimulus, and is definable as paraphysiological, inasmuch as it takes account of circadian rhythm in an individual's heartbeat.

According to the invention, embodiment of a circuit that will reproduce the periodic, circadian type of

variation encountered in heartbeat, is made possible by virtue of the fact that such variation can be considered as a sine wave (fig 1).

Fig 3 is a basic block diagram of the pacemaker as described herein, which implements one of the simplest of cardiac stimulus methods, namely VVI and AAI, that is, ventricular or auricular 'on demand'. The pacemaker stimulates the ventricle (or the auricle), and is inhibited whenever the muscular depolarization signal, amplified by the block denoted 5, rises above the preset bpm dictated by a clock generator 2 and divider 3.

In a circadian pacemaker according to the invention, use is made of a VCO (voltage controlled oscillator) the clock frequency of which can be varied by application of a voltage. In pacemakers of sophisticated design, therefore, the input stage of the clock 2 may be in receipt of a signal representing variation in biological or metabolic parameters (pH value, or breathing &c.) from the block denoted 11. The sine wave signal, with its period of 24 hours, will thus vary the beats per minute between preset maximum and minimum levels, which are dictated by the sine wave generated by block 1 and the clock frequency emitted by block 2. Phase of the sine wave is adjusted such as to respond to the normal chronological conditions illustrated in the graph of fig 1.

An example of the method of producing a signal with periodic time of 24 hours is given in fig 4, which illustrates a digital generator.

The circuit of fig 4 utilizes digital filter technology, and produces a frequency F_0 that is tied to the clock frequency 6 by the formula: ($F = Rn\ F_0$), where F is the clock frequency 6 and n is the number of divider stages 7 utilized in the counter 18.

The network of resistances denoted R_1, R_2, ... R_{n-1} is calculated utilizing the formula:

$$\frac{R_n}{R_1} = \frac{\text{sen } k\pi/n}{\text{sen } \pi/n}$$

where k = 1, 2, ... n-1

Data given by way of example relates to a counter 18 (see fig 4) incorporating ten divider stages; clock frequency would be $F = 20\ F_0$ with $F_0 = 1/86400$Hz. The clock frequency may be produced by a quartz type generator giving a period of 4.12msec, and utilizing a 20-stage binary divider.

Resistances R_n would be geared to R_1, and calculated as follows:

$R_2 = 1.9R_1$; $R_3 = 2.618R_1$; $R_4 = 3.07R_1$; $R_5 = 3.23R_1$; $R_6 = R_4$; $R_7 = R_3$; $R_8 = R_2$; $R_9 = R_1$

The curve of the resulting sine wave will not appear continuous, but as a series of steps (fig 2) corresponding to the number of divider stages incorporated into the system; thus, the greater the value of n, the smaller the steps will become.

The curve illustrated reflects the example described above, where for each 24h/2n interval one produces a variation in bpm of $(F_{max} - F_{min})/n$, plus or minus according to phase.

With a periodic amplitude variation range of 20bpm and using ten stages, a variation of 2 beats every 72 minutes will be produced.

The option exists of employing an active integrating amplifier 10 to smooth out the steps and obtain more gradual variation. However, adopting a counter 18 in which 'n' is much higher, say, 30 stages, the steps would become so shallow that an individual would remain unaware of the variation in heartbeat between one step and the next.

Still referring to fig 4, the block denoted 9 amplifies and adjusts the sine wave of fig 2 in order to vary amplitude commensurately with the physiological characteristics of the individual.

It will be noted that the circuit in question can be integrated without difficulty adopting CMOS technology, by virtue of its digital operation.

Whilst the sine wave illustrated in fig 2 provides a sufficiently accurate approximation of the circadian rhythm in heartbeat, the effective curve can be approached yet further by varying the value of the resistances R_n, which may be achieved by calculation, where a mathematical equation representing the curve is made available, or by experimenting with the resistance settings on a trial-and-error basis.

The device thus embodied permits of engineering circadian rhythm exogenously adopting paraphysiological criteria simulative of natural bio-rhythm, and may be fitted to any type of pacemaker to the end of ensuring that an acceptable bpm is generated.

Fig 5 illustrates a development of fig 3, in which one has the standard programming options for cardiac stimulus parameters as already featured in programmable pacemakers: mean bpm is varied by the block denoted 14, and pulse width by the block denoted 15; amplitude of the signal fed into the circuit 20 producing the output pulses is varied by the block denoted 16; a block denoted 17 alters the sensitivity threshold. In addition, one has integration of the parameters which take account of circadian rhythm by incorporation of a device as in fig 4, signifying programming facilities governing start of the sine wave phase, via block 12, mean bpm $(F_{max} - F_{min})/2$, via block 14, and the maximum permissible variation $(F_{max} - F_{min})$, via block 13.

The implanted pacemaker can be programmed utilizing any of the methods currently employed; moreover, the identification code can remain the same as those already in use.

Bpm can be programmed by way of the pacemaker's VCO, and maximum permissible variation between F_{max} and F_{min} set by adjusting amplitude of the sine wave signal applied to the VCO trigger.

Phase can be adjusted at the moment of implanting a pacemaker according to the invention, for instance, by accelerating the clock frequency 6 (fig 4) until coincident with the value dictated by the sine wave at that particular instant.

Claims

1) A pacemaker, characterized in that it comprises a device (1) designed to vary the clock frequecy of the pacemaking signal according to a function simulative of the natural circadian rhythm in heartbeat.

2) A pacemaker, comprising a clock pulse generator and characterized in that it comprises a device (1) designed to supply a signal to the input of the clock circuit (2) that is variable according to a function simulative of the natural circadian rhythm in heartbeat.

3) A pacemaker as in claim 2, wherein the clock circuit (2) is a voltage controlled oscillator, and a voltage signal supplied by the device (1) is integrated with the signal produced by the clock circuit (2).

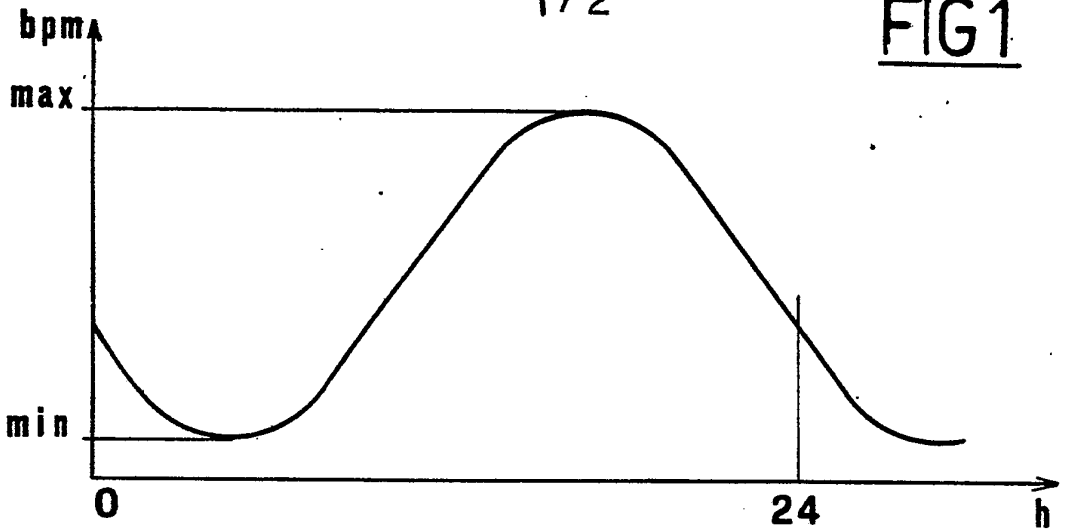
4) A pacemaker as in claim 3, wherein the output signal produced by the device (1) varies by distinct steps.

5) A pacemaker as in claim 4, wherein the device (1) is embodied as a digital pulse generator comprising a clock circuit (6), a signal divider (18) the stages (7) of which correspond in number to the steps that separate any two consecutive peaks of the output signal, and an amplifier (9) designed to permit of varying amplitude of the output signal generated by the device (1).

6) A pacemaker as in claim 5, wherein the device (1) further comprises an integrating amplifier (10) the purpose of which is to attenuate the discontinuous effect of stepped variation in the output signal produced by the device (1), thereby investing it with sinusoidal waveform.

7) A programmable pacemaker as in claim 3, wherein the output signal produced by the device (1) is programmable at the outset in respect both of the mean bpm generated and of its permissible variation.

FIG1



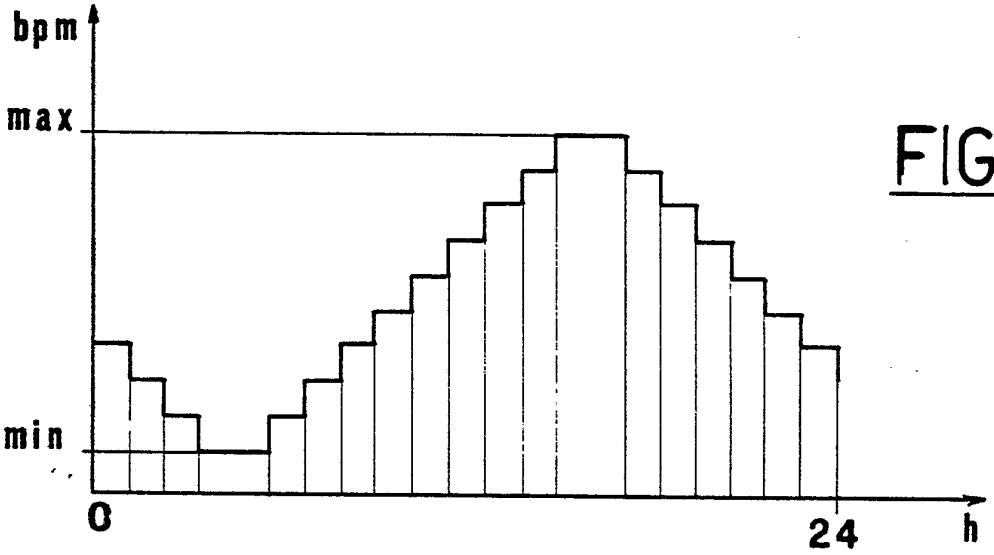


FIG2

FIG 3

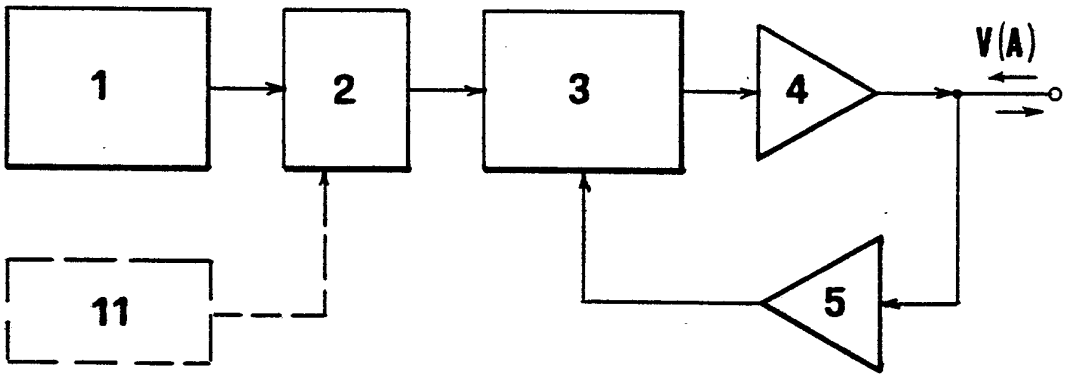


FIG 4

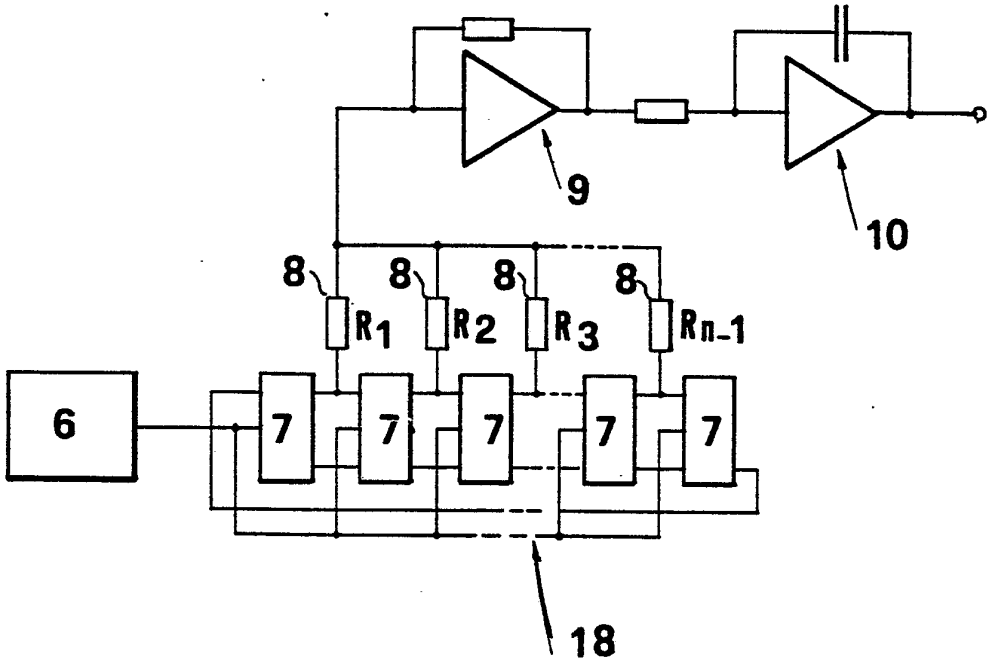
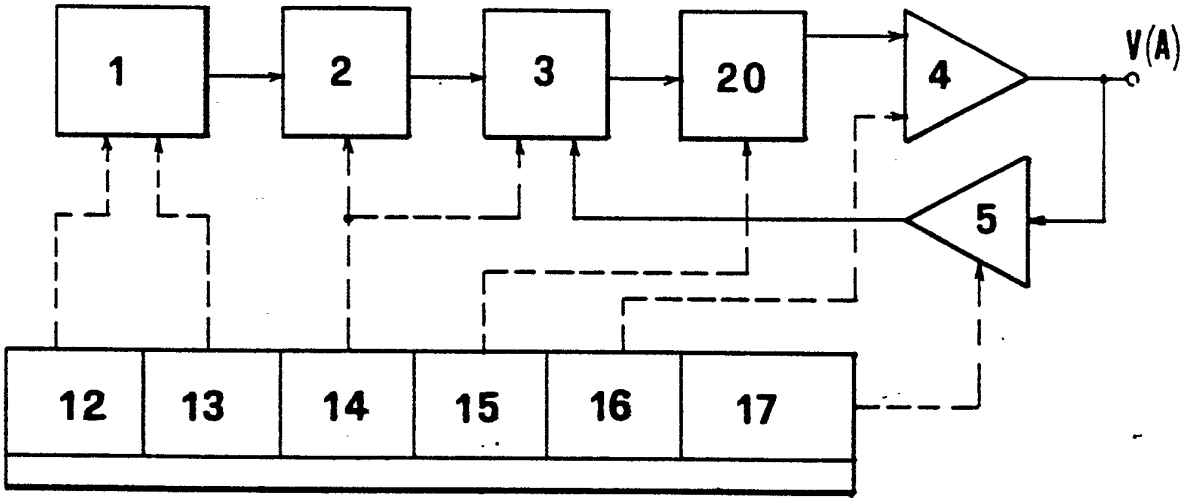


FIG 5



INTERNATIONAL SEARCH REPORT

International Application No PCT/IT 86/00039

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 N 1/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 N; A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A, 0080348 (MEDTRONIC, INC.) 1 June 1983 see abstract; page 1, lines 1-4; page 2, lines 23-29; page 6, line 19 - page 7, line 25; figure 3	1,2,7
A	--	3,4,6
Y	US, A, 4443218 (L.J. DECANT et al.) 17 April 1984 see abstract; column 1, lines 5-9; column 6, line 51 - column 7, line 3; column 8, lines 3-56; figures 1,2,5	1,2,7
A	-- Electronic Design, vol. 15, no. 5, 1 March 1967 (Rochelle Park, US) R.A. Griffis: "Generate time functions digitally", pages 59-61; see page 59, left-hand column, line 1 - right-hand column, line 27; figures 1,2	4,5
A	-- EP, A, 0059868 (WIRTZFELD et al.) 15 September 1982	./.

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1st September 1986	15 OCT 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	see abstract; page 1, lines 1-15; page 8, line 35 - page 9, line 9; page 11, lines 1-7; figures 10,11	1,4,7
A	EP, A, 0026476 (SIEMENS AG) 8 April 1981 see abstract; page 1, lines 7-13; page 3, line 20 - page 5, line 27; figure 1	1,2,5

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/IT 86/00039 (SA 13406)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/09/86

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0080348	01/06/83	US-A-	4428378	31/01/84
US-A- 4443218	17/04/84	None		
EP-A- 0059868	15/09/82	DE-A,C	3107128	09/09/82
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		AU-A-	6276480	09/04/81