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Chronic Hepatitis

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Mr. Chairman, ladies and gentlemen !

I would like to express my gratitude to the Medicine Society of Tokai University for the invitation to give lectures in your country. I feel especially honoured to be able to address myself to you in this very place. There has been a glorious tradition of relationship between German and Japanese medicine ever since the discovery of Salvarsan by Paul EHRLICH and HATA. German and Japanese medicine have exerted a thorough influence upon each other in the past, I could tell of many fine examples, and a lot of extensive cooperation between Japanese and German scientists is going on at present. In Germany we admire the progress of Japanese medicine and the marvelous discoveries that Japanese research has contributed recently to the future development of medical science. Everyday life in the clinic confronts us constantly with the progress that has been given to us by Japanese medicine in endoscopy by introducing glass fiber optics.

As I would like to speak about chronic hepatitis today, I have to point out at first that this disease has been presented to clinical medicine by reports of KALK and coworkers, published in Germany, after I had introduced the term " chronic hepatitis " in my monograph on hepatitis in 1951. Meanwhile the literature on chronic hepatitis has increased tremendously, thus providing us with many attractive and noteworthy problems concerning etiology, pathogenesis of clinical manifestations and treatment. Table 1 shows the pattern of chronic hepatitis.

Doubtless, acute viral hepatitis holds a special position concerning etiology since it has been acknowledged today that acute viral hepatitis might not heal under some circumstances and develops into chronic hepatitis. It is my personal belief that these are cases of hepatitis B exclusively. The incidence of transformation of acute viral hepatitis into chronic hepatitis has been reported to be 1—15% in the western literature. According to our collection of material that consists of hospitalized cases of acute hepatitis exclusively, 15% of the cases result in chronic hepatitis and 25% of these end in cirrhosis of the liver. Laparoscopy and needle biopsy have definitely

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contributed to the understanding of the formal genesis of posthepatitic chronic hepatitis. By means of these methods we were enabled to keep track minutely of the different stages of the development and course of such a process *in vivo*. In many cases of this pattern, persistence of Australia antigen attracts attention.

Table 1. Patterns of chronic hepatitis

Secondary chronic hepatitis (sequel of acute hepatitis)
Primary chronic hepatitis
Chronic hepatitis with autoimmune phenomena (lupoid hepatitis)
Chronic hepatitis with cholestasis
Non-specific reactive hepatitis
Chronic hepatitis in hemochromatosis
Chronic hepatitis in fatty liver
Chronic Granulomatous hepatitis
Chronic non-suppurative destructive cholangitis (primary biliary cirrhosis)
Chronic hepatitis in panarteriitis nodosa

On the one hand, there are cases of chronic hepatitis, where there is no acute viral hepatitis in the case history and where Australia antigen can not be found so that we have to discuss the possibility of a primary chronic onset of the disease. Therefore, the term " primary chronic hepatitis " has been used ever since. We do not know anything for certain about the etiology of these cases and naturally can not exclude that an acute stage might have taken place in the form of a non-realized non-icteric viral hepatitis. On the other hand, other etiologic factors are being discussed right now, such as mushroom poisons (Aflatoxin) or chemicals such as biphenyl found in table utensils and other environmental factors. Another group of chronic hepatitis patterns is characterized by autoimmune phenomena, i. e. by the effect of abnormal auto-antibodies. The most important example of these is the " lupoid " hepatitis. Chronically relapsing cholestatic hepatitis is characterized by clinical symptoms of obstructive jaundice accompanied by histologically visible intrahepatic cholestasis. Chronic hepatitis may also represent a sequel of a nonspecific reactive hepatitis and is to be understood as a monotonous reaction of the liver towards various injuries such germs, exogenous or endogenous toxins, products of proteinolysis, antigen-antibody complexes etc. The cause of this form of hepatitis could be infections, gastrointestinal affections, ulcerative colitis, carcinoma, rheumatic diseases or collagen vascular diseases. Chronic hepatitis related to fatty liver should be distinguished from the forms of chronic hepatitis mentioned before; this form was considered as a clear away inflammation in the past, but now we tend to believe that the same injury that causes fatty liver is capable of inducing chronic inflammation, as in chronic alcohol abuse for example. Chronic hepatitis develops in hemochromatosis due to a reaction of connective tissue with round cell infiltrations, cell necrosis and dissection of liver lobules caused by iron deposits in the form of hemosiderin; this chronic hepatitis may finally result in hemochromatotic cirrhosis.

A special form of chronic hepatitis is represented by granulomatous hepatitis which is seen now and then as a manifestation of sarcoidosis, but which may arise from a variety of other etiological factors such as infections including tuberculosis, Whipple's disease, infectious mononucleosis, reactions of hypersensitivity, cancer and, Crohn's disease and as a simultaneous phenomenon of other liver diseases such as viral hepatitis,postnecrotic cirrhosis,

primary biliary cirrhosis and, fatty liver. A very interesting phenomenon is the rather frequently observed coincidence of granulomatous hepatitis and chronic aggressive hepatitis ; the focus of interest is on the question of whether granulomatous hepatitis is the precipitating factor of the latter. Finally we have to include among the forms of chronic hepatitis the chronic, non suppurative, destructive cholangitis which ends in primary biliary cirrhosis in due time.

This form is now considered to be an autoimmune disease which seems to be settled by the detection of antimitochondrial antibodies. Because of the morphology, activity of the process and the clinical course, I have demanded as far back as 1912 that we should clearly distinguish between the stationary, prone to regression forms of chronic hepatitis and the progredient forms. Recently the stationary form is referred to as chronic persistent hepatitis and the actively progredient form as chronic aggressive or chronic active hepatitis.

The aspect of chronic hepatitis as seen through the laparoscope is sufficiently known. The surface of the liver is in these cases either smooth or delicate, sometimes coarsely granulated. The lobular substructure may be marked more than usual because of enlargening of portal triads ; the colour is greyish red to greyish brown, sometimes flamingly red. Scar formation is also detectable. Connective tissue can transform the liver margin to a hemlike appearance (plane wing phenomenon). For a couple of years we have especially emphasized the examination of the liver surface with a magnifying glass in chronic hepatitis. This is exceedingly interesting when ectatic lymphatic vessels which are a sign of mesenchymal activity can be detected. They can show either " dynamic " or " mural " lymph track insufficiency.

The histological findings are the basis of differentiation between stationary and progressive forms. Chronic persistent hepatitis is characterized by portal inflammation which at no time intrudes into the parenchyma on a large scale. Whereas chronic aggressive hepatitis appears as a proliferative lympho-histiocytic inflammation occurring in the portal triads, perforating the limiting layer and destroying the adjacent peripheral lobules. Proliferation of ductuli and fibrous enlargement of portal triads are soon to be seen. Liver cell necrosis completes the full picture. Destruction of normal parenchymatous structure and transformation with the appearance of pseudolobules is possible. The so-called " piece-meal " necrosis is characteristic. Here lymphocytes, plasma cells and macrophages are gathered in the portal regions and seem to inundate the adjacent parenchyma producing a fissured, piecemeal like margin of parenchyma. Inflammatory cells approach normal liver cells and destroy many hepatocytes. According to histological findings we can furthermore distinguish three different patterns of chronic aggressive hepatitis : first, subacute hepatitis with bridging (Tisdale) ; second, subacute hepatitis with multilobular necrosis (Wepler) and finally chronic cholestatic hepatitis (Siede).

The clinical picture of chronic hepatitis varies considerably. On the one hand there are patients with a lot of general and localized complaints and a vast amount of pathological findings and on the other hand there are patients with a moderate amount of complaints of a rather general nature which at first do not suggest a hepatic disease and where definitely patholog-

ical findings can hardly be detected. The clinical suspision of the existence of chronic hepatitis can be drawn only by evaluating the entire findings very often. The complaints given most often are the following :

1. Reduced efficiency, incapability of concentration, rapid physical and mental fatigue
2. Inclination for outbursts of perspiration, vertigo, collapse
3. Inappetence, nausea in the morning, occasional vomiting, belching, increased flatulence.
4. Meteorismus, discomfort after meals, dull pain in the hepatic region partly irradiating in the back, abdominal attacks.
5. Loss of weight
6. Deficiency of smell or taste
7. Intolerance of fat and alcohol, aversion towards nicotine
8. Frequent diarrhea, sometimes alternating with constipation.
9. Depressive tendencies
10. Difficulty in falling asleep and remaining asleep.
11. Decrease of libido and potency.
12. Tendency for allergic efflorescence and epistaxis.

A definite diagnosis is only possible by means of laparoscopy and needle biopsy. Among the essential findings in examinations of the patients, I could quote : often reduced strength and nutritional conditions, yellowish-brown complexion, subicteric appearence, reduced turgescence of skin, furry tongue and meteorismus. The liver is more or less enlarged and increases in consistency are moderate to considerable. There is a tenderness especially above the left lobe. Often the spleen is found enlarged and of slightly increased consistency.

As far as the clinical picture is concerned we can distinguish the common forms of chronic hepatitis from special forms characterized by marked morphological findings : in the cholestatic form the signs of intrahepatic cholestasis such as pruritus, increased jaundice, acholic feces, elevation of alkaline phosphatase and γ-GT are predominant ; in the forms with bridging and multilocular necrosis, signs of liver cell insufficiency with precomatous conditions are predominant.

A special position among the forms of chronic hepatitis is given to the so-called " lupoid hepatitis " which is also called " chronic active hepatitis " by English-speaking authors. Other synonyms are : chronic disease of the liver in young women with extreme hypergammaglobulinemia (Bearn), active juvenile cirrhosis (Sherlock), plasma cell hepatitis (Page) and progressive hypergammaglobulinemic hepatitis (Mielsher). The latter was described by Waldenström in 1950, and in 1956 was called " lupoid " hepatitis by Mackey and his team since in1955, Joske and King found a LE-cell preparation in the blood of the cases mentioned before. Lupoid hepatitis has to be distinguished from other forms of chronic hepatitis because of its clinical picture and the finding of special autoimmune phenomena.

Laparoscopy shows the picture of chronic aggressive hepatitis with focal isolated or diffuse flaming redness. In correlation with the severe mesenchymal reaction, extremely ectatic subcapsular lymph tracks have been observed almost regularly directly after the actively increased lymph production by the liver cells. Large fields of necrosis also exist, frequently with transition into scarification and adenoma-like regenerates. Shortly after that we

see the transition into postnecrotic cirrhosis. Histologically there will be extensive piece-meal necrosis and massive infiltration by plasma cells.

The disease starts either slowly progredient or, as it seems, following acute viral hepatitis.

The clinical picture is characterized by relapsing icteric episodes (Table 2) with arthralgias, efflorescences and fever. Amenorrhea is common in women. Besides the liver, other organs are involved due to deposits of circulating antigen-antibody-complexes. Polyarthritis, pleurisy, pericarditis, peritonitis, myocarditis, endocarditis, pancreatitis, retinitis, nephritis, pulmonary fibrosis and Hashimoto's thyroiditis have been observed (Table 3). The course is progredient.

Table 2. No. of icteric episodes in chronic " lupoid " hepatitis (98 patients)

No. of icteric episodes	No. patients
8	2
6	6
4	8
3	14
2	25
1	39
0	7

Table 3. Extrahepatic symptoms in 98 cases of so-called lupoid hepatitis

Exanthema	7	Infiltrates of lungs	9
Purpura	3	Pulmonary fibrosis	4
Arthralgia	62	Pancreatitis	3
Arthritis	21	Ulcerative colitis	2
Iritis	11	Parotitis	11
Retinitis	6	Lymphonodular swellings	8
Endocarditis	1	Thyroiditis (Hashimoto)	2
Myocarditis	12	Hemolytic anemia (Coombs test+)	2
Pericarditis	4	Sjögren's syndrome	1
Polyseritis	3	Multiple sclerosis	0
Mediastinitis	1	Polyneuritis	0
Serofibrinous pleurisy	13	Amenorrhea in young women	24
Serofibrinous peritonitis	16		
Glomerulitis	3		
Vasculitis	0		

Findings on examination are lupus-like face erythema, spider nevi, palmar erythema and extensive enlargement of liver and spleen. Especially remarkable laboratory results are highly accelerated blood sedimentation, the distinct increase of serum transaminases, with higher values for GOT than for GPT, and the extreme pathological retention of BSP. The serum protein pattern is characterized by hyperproteinemia up to 12g/100 ml and dysproteinemia of the hypergammaglobulinamia-type. Table 4 shows a typical course of the illness in lupoid hepatitis. Table 5 shows the laboratory findings in lupoid hepatitis in comparison with other forms of chronic hepatitis. Immunoelectrophoresis shows an isolated and extreme increase of immunoglobulin G. The hypergammaglobulinemia is caused by hyperactivity of lymphoid cells and plasma cells, characterizing the activity of the inflammatory process in addition to the abnormal immunological reaction.

The LE-cell preparation is positive in the blood of 25% of the patients. Positive AHG consumption test and immunofluorescence reaction are evi-

Table 4. Typical course of in lupoid hepatitis

1961		1962		1963			1968	1971	1974
September	November-December	March	May-July	August	March	September	June	May	May
Sojourn in Italy	Jaundice	Relapse of jaundice	Convalescent treatment in bad Mergentheim Continous deterioration 2. relapse of jaundice	Hospitalization Multiple spider nevi Palm erythema Hepatosplenomegaly Ascites Pancreatitis Exudative pleurisy Amemorrhea Arthritis	Laparoscopy : Postnecrotic Cirrhosis Histology : Chronic Aggressive hepatitis Plasma cell infiltration, Piecemeal necrosis, Transformation	No subjecive complaints No jaundice Considerable regression of spider nevi Hepatosplenomegaly	Well conditioned, Some isolated pale spider nevi Hepatosplenomegaly Needle biopsy : Considerable regression of inflammatory activity of chronic aggressive hepatitis Same findings as in stationary (=persistent) chronic hepatitis	Well conditioned Hepatosplenomegaly No spider nevi	Well conditioned Hepatosplenomegaly No spider nevi Palm erythema
BSR Serum proteins y-globulin Serum-bilirubin GOT GPT				127/138 mm 11, 4g/100 m*l* 55, 8 re*l*% 3, 1 mg/100 m*l* direkt 896 WrE 412 WrE Le cell preparation +++	BSR Serum-proteins y-globulin Serum-bilirubin GOT GPT HBS- antigen	7/15 mm 6, 83 g/100m*l* 19, 0 re*l*% 0, 4 mg/100 m*l* indir. 43 mu/m*l* 90 mu/m*l*	7/24 mm 6, 4 g/100 m*l* 17, 8 re*l*% 0, 47 mg/100 m*l* 11 mu/m*l* 10 mu/m*l*	7/25 mm 6, 4 g/100 m*l* 16, 0 re*l*% 0, 40 mg/100m*l* 13 mu/m*l* 9 mu/m*l*	9/16 mm 6, 4 g/100 m*l* 15, 6 re% 0, 44 mg/100 m*l* 14 mu/m*l* 8 mu/m*l* Negative
				Onset of prednisolone treatment 15 mg	Prednisolone 15 mg	Prednisolone 10 mg	Prednisolone 5 mg	Prednisolone 5 mg	Prednisolone 5 mg

Table 5. Laboratory investigations of chronic hepatitis

	Chronic persistent	Chronic aggressive	Chronic active (" lupoid ")
Bilirubin i. s.	Normal	Normal-3 mg/100 ml	Normal-12 mg/100 ml
GOT	Normal-50 mu/ml	30—80 mu/ml	100—300 mu/ml
GPT	Normal-50 mu/ml	30—80 mu/ml	80—200 mu/ml
AP	Normal	Normal to slightly elevated	Normal to moderately elevated
y-GT	Normal-40 mu/ml	Normal to Slightly elevated	Normal to highly elevated
GLDH	Normal	1, 0—4, 0 mu/ml	5, 0—15, 0 mu/ml
Blood sedimentation (first hour)	10—20 mm	15—30 mm	30—80 mm
Quick-test	Normal	Normal-70%	70—40%
Protein i. s.	Normal	Normal	up to 12 g/100 ml
y-Globulin	Normal-25 rel%	Normal-30 rel%	30—50 rel%
FE i. S.	Normal	Normal-80 y%	180—220 y%
BSP-test	Normal-15% ret.	15—30% RET.	Usually exceeding 50% ret.
Prontosil-test	Normal-120 mg	120—150 mg	Usually exceeding 160 mg
Card-green	Normal	Moderately pathological	Highly pathological Leukopenia Thrombopenia

dence of circulating antinuclear factors. Especially typical is the presence of antibodies against nuclei of both liver cells and smooth muscles. The lymphocytes must be immunological competent immunocytes since their antibody character can be shown by fluorescence-microscopic technigues. The transformation of lymphocytes also often shows positive results. Table 6 gives a synopsis of the immunologic reactions in lupoid hepatitis.

Table 6. Humoral and cellular immuno-reaction in chronic active (" lupoid ") hepatitis

Hypergammaglobulinemia
Y-globulins markedly increased
Immunglobulin G markedly increased
Circulating antibodies against nuclei (LE-cell phenomena)
Liver cell nuclei
Smooth Muscle
Cellular antigen-antibody-reaction
" piece-meal-necrosis
" killer-lymphocytes
Immunofluorescence tests
Transformation of lymphocytes in presence of autologous liver tissue

The significance of the circulating antibodies and of the tissue-bound immunological phenomena–as which piece-meal necrosis has been explained–is still being discussed. It has not been decided as yet whether they are primary autoimmune processes or whether these phenomena are to be considered as a secondary immunological simultaneous reaction to liver damage. It has been assumed that these immunological reactions in the sense of autoaggression are responsible of the autonomy of the process, i. e. of the so-called self-perpeptuation of chronic hepatic inflammation. This term, first introduced by Popper, tries to give an explanation of why the inflammatory process in many chronic hepatitis cases smoulders on without any discernible reason. The frequently rapid transition of lupoid hepatitis in cirrhosis of the liver is explained by the very extensive activation of fibroblasts with transformation of connective tissue fibers in collagenous fibrils as part of a mesenchymal reaction.

In this context it is very interesting that in rabbits active chronic hepa-

titis could be induced with human liver protein against which specific antibodies were directed. The concept of the autoimmune pathogenesis of lupoid hepatitis is supported furthur by the fact that it can be remarkably well influenced by Glucocorticoids.

In case of a primary viral infection of the liver in this disease we have to discuss the theory of whether the virus is capable of changing the liver cell proteins in such a manner that they are transformed into antigens. This could explain the clone theory of Burnet : in an anomaly of the antibody producing tissue, either genetically fixed or due to mutation, lymphocytes originate incapable of recognizing liver proteins that have been transformed by viral invasion as such (so-called forbidden clones) and these lymphocytes attack proper liver cells. Thus the problem culminates in the question of whether this disease is to be understood as a chronic autoimmune hepatitis caused by antibodies or a chronic hepatitis with antibodies.

Table 7. Incidence of various findings in chronic " lupoid " hepatitis (98 patients)

	%	no. of patients
Fever	72	98
Splenomegaly	79	98
Spider nevi	72	98
More than one relapse of icterus	48	98
Cholestasis	12	98
GOT exceeding 1	94	98
GPT		
GLDH elevated	88	49
B. S. P. test exceeding 25% retention	92	32
LE cells	31	98
AHG	98	98
Immunofluorescence test +	96	36
Hyperproteinemia exceeding 8 g/100 ml	88	98
Hypergammaglobulinemia exceeding 30 rel%	87	98
IgG increased	89	42
Positive RF-test	78	98
ASR	75	98
Plasma cells increased in sternal marrow	62	32
Australia antigen positive	25	8

Table 8. Characteristics of lupoid hepatitis

Onset like acute virus hepatitis or creeping course
Several relapses of jaundice
Higher incidence in young and in pre-menopause women
Fever, facial erythema, amenorrhea, arthralgia
Involvement of other organs : arthritis, polyserositis, carditis etc.
Intensive elevation of transaminases GOT>GPT
Abnormal immunological reactions :
hyperproteinaemia, hypergammaglobulinaemia
elevation of Ig G
LE cell phenomenon +, AHG test +
Immunofluorescence : antibodies against liver cell nuclei
antibodies against smooth muscle
Rheumatic Factor +, ASR reaction +
deosit of antigen-antibody complexes in liver tissue (T-lymphocytes)
Histology :
Aggressive chronic hepatitis with infiltrates of
plasma cells and with piecemeal necrosis
Multilobular necrosis with bridging
Evolution towards postnecrotic cirrhosis
Therapy successful with steroids

Table 7 shows the incidence of various findings in lupoid hepatitis. Table 8 gives a synopsis of characteristics of lupoid hepatitis.

Chronic hepatitis accompaning panarteritis nodosa is very interesting. This hepatitis has some special features : only moderately elevated serum-bilirubin below 5 mg% and in the course only slight elevated transaminases. In one patient Australia-antigen was detectable during the entire 3 years of observation. With regard to the context, several pathogenetic mechanisms are being discussed. Chronic hepatitis could be a substantial condition for the development of panarteritis nodosa providing immune complexes consisting of Australia-antibodies and complement.

In one patient tissue deposits of Australia-antigen in the vessel wall could be detected by means of immunofluorescence.

Due to the outstanding immunological features of a group of patients suffering from chronic hepatitis we can add an immunological classification to the etiological and morphological classification which I presented to you in my paper, according to our contemporary knowledge. We try to classify chronic hepatitis according to etiological points of view and immunological phenomena with respect the various antibody patterns and the distribution of etiological pattern-antigens such as the Australia-antigen (see Table 9).

Table 9. Chronic aggressive hepatitis

		HBs-Ag	auto-antibodies	Serum(IgG)	
1)	Non defined form	ϕ	ϕ	—	20%
2)	HB_s-Ag positive	+	rare SMA+	Ig G+	50%
3)	Lupoid hepatitis	ϕ	ANA++ SMA++	Ig G++	30%
3)	PBC associated	ϕ	AMA+ANA+SMA+	Ig M++	

We can differenciate into at least three groups, according to antibodies against nuclei, smooth muscles and mitochondria, as they appear in chronic hepatitis :

1). " Lupoid " hepatitis with antibodies against nuclei and smooth muscles.
2). chronic active (frequently cholestatic) hepatitis with heterogenous mitochondrial antibodies (Berg)
3). The classical primary biliary cirrhosis with homogenous mitochondrial antibodies.

The detection of these afore-mentioned immunological reactions on one hand and the possibility of Australia-antigen estimation on the other hand, offers an important differentiation of chronic hepatitis. In the majority of patients with chronic hepatitis, approximately two-thirds, either persistence of Australia antigen (42%) or immunological factors (26%) has been discovered so that one factor seems to exclude the other. In the other cases (32%) neither factor could be detected (see Table 10).

Tabl 10. Incidence of viral and autoimmune phenomena and distribution of sexes in 215 patients suffering from chronic active hepatitis confirmed by needle biopsy (Berg)

Group	Number of patients	♀ Sex ♂
Viral	90 (42%)	31/59
Autoimmune *	57 (26%)	54/3
Negative	68 (32%)	32/36

*Autoimmune : only cases with finding of ANA/SMA without AMA

According to this review and the afore-mentioned statements on the different forms of chronic hepatitis and its confirmed, possible or suspected causes we can conclude that this disease is actually a multi-etiological reaction syndrome. Prognosis of chronic hepatitis has to be considered under different aspects. It is mainly governed by its prospective potency to develop into a florid liver cirrhosis with all its consequences. This is true for a number of patients–the incidence reported varies depending on the author–suffering from chronic aggressive and to an extraordinary degree from " lupoid " hepatitis. The average expectation of life at the time of diagnosis for untreated lupoid hepatitis is five years.

Chronic hepatitis of fatty liver can either result in a stationary stage or gradually be transformed into so-called " fatty " cirrhosis. The course of latter depends upon whether alcohol abuse continues or is radically stopped. If acute alcoholic hepatitis occurs in such cases prognosis becomes considerably poorer. Prognosis of primary biliary cirrhosis is unfavorable. In contrast to the outlooks of the diseases mentioned before, prognosis of chronic persistent hepatitis and of unspecific reactive hepatitis is favorable on all accounts ; there is either complete recovery or at least no tendencies towards progression.

Prognosis of granulomatous chronic hepatitis is favorable as well provided that no complications occur ; if the disease is aggravated by coincidence with chronic aggressive hepatitis however, the general outlook is determined by the course of the latter.

At the end, I would like to underline that I am fully aware of the fact that my lecture has been rather incomplete with regard to many aspects of chronic hepatitis which have not been referred to. I do hope, however, that I have suceeded in drawing particular attention to the actual problems of chronic hepatitis which are still unsolved and controversial.